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Kinetic Resolution by Lithiation: Highly Enantioselective Synthesis of Substituted Dihydrobenzoxazines and Tetrahydroquinoxalines

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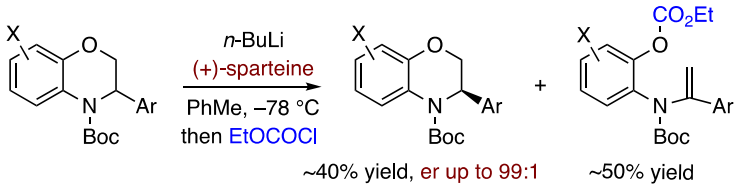

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Abstract Kinetic resolution provided a highly enantioselective method to access a range of 3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines using *n*-butyllithium and the chiral ligand sparteine. The enantioenrichment remained high on removing the *tert*-butoxycarbonyl (Boc) protecting group. The intermediate organolithium undergoes ring opening to an enamine. The kinetic resolution was extended to give enantiomerically enriched substituted 1,2,3,4-tetrahydroquinoxalines and was applied to a synthesis of an analog of the antibiotic levofloxacin that was screened for its activity against the human pathogen *Streptococcus pneumoniae*.

Key words ring opening, lithiation, kinetic resolution, heterocycles, enantioselectivity, elimination, antibiotics

Nitrogen-containing heterocycles are extremely common in pharmaceutical and agrochemical compounds. One class of such heterocycles are 3,4-dihydro-2*H*-1,4-benzoxazines that are represented in several important bioactive compounds including the antibiotic levofloxacin,[1] and in other compounds with a variety of activities such as androgen receptor modulators,[2] anti-arrhythmic agents,[3] and together with various 1,2,3,4-tetrahydroquinoxaline compounds as cholesteryl ester transfer protein inhibitors (Figure 1).[4]
The ability to prepare enantiomerically pure substituted 3,4-dihydro-2*H*-1,4-benzoxazines is therefore of importance and the development of methods to access such chiral derivatives is of interest in medicinal chemistry.[5] The most common approaches involve asymmetric reduction of 2*H*-1,4-benzoxazines using transition metal catalysts, organocatalysts, or enzymes,[6] or transition metal catalysed cyclization reactions with concomitant generation of a new stereocentre.[7] An alternative method involves kinetic resolution of the racemic dihydro-2*H*-1,4-benzoxazine on reaction with a chiral acid chloride,[8] or with an imine and a chiral phosphoric acid.[9]
In a continuation of our work on the kinetic resolution of 2-arylpiperidines,[10] 2-aryltetrahydroquinolines,[11] and 2-arylindolines,[12] we considered the possibility that this chemistry could be exploited for the formation of enantiomerically enriched 3,4-dihydro-2*H*-1,4-benzoxazines, particularly derivatives with an aryl group at the 3-position (adjacent to the nitrogen atom). Recently, we demonstrated that one enantiomer of *N*-Boc-2-aryltetrahydroquinolines preferentially undergoes lithiation in the presence of *n*-BuLi and the chiral ligand (+)-sparteine.[11,13] This provided high enantioselectivities (selectivity factor, S = 20)[14] to give the recovered starting material with enantiomer ratio (er) up to 98:2, together with the 2,2-disubstituted tetrahydroquinoline products from electrophilic quench (Scheme 1). Here we describe our work with the related *N*-Boc-3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines (X = O, Scheme 1) that has similarly led to very high enantiomer ratios through a kinetic resolution process. In addition, we have extended the chemistry to 2-aryl-

1,2,3,4-tetrahydroquinoxalines (X = N-Boc, Scheme 1).

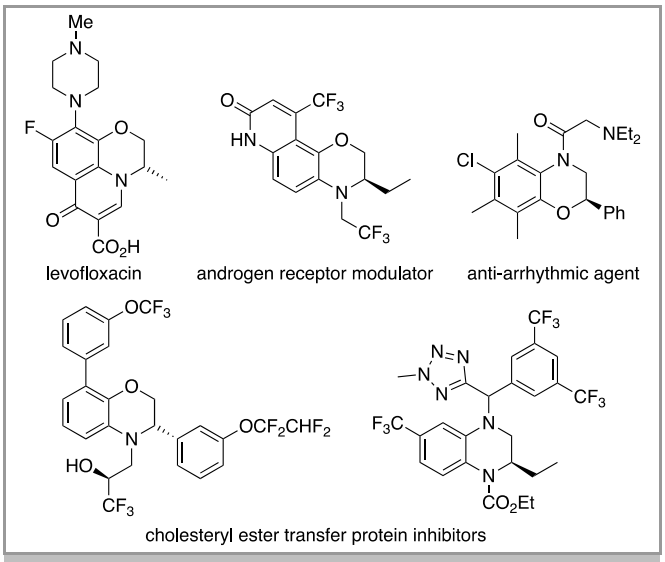
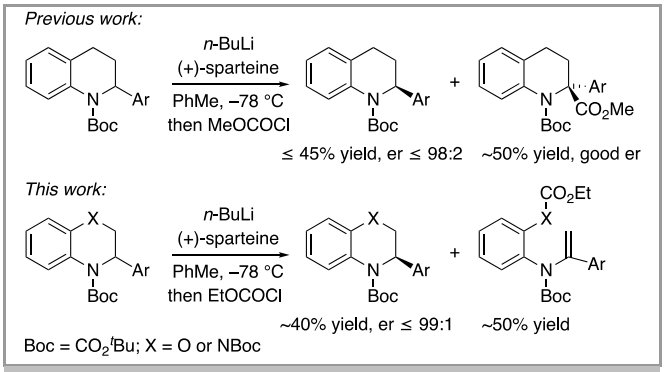
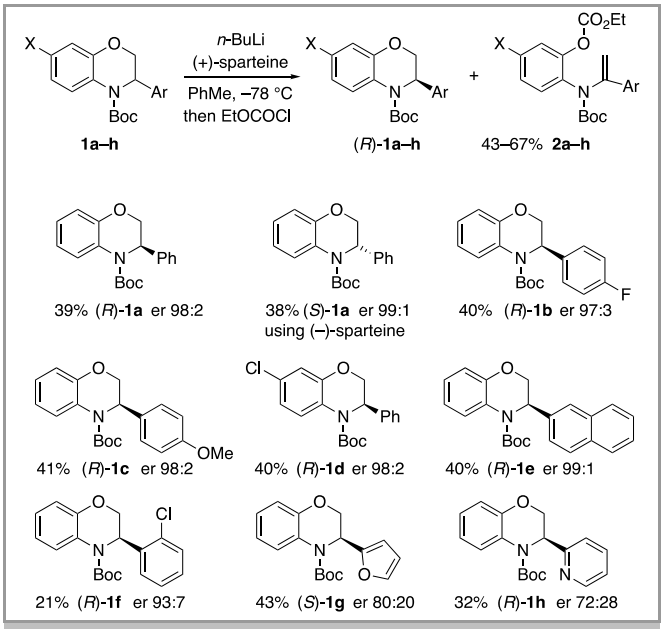


Figure 1 Bioactive chiral 3,4-dihydro-2H-1,4-benzoxazines and a tetrahydroquinoxaline



Scheme 1 Kinetic resolution of tetrahydroquinolines and substrates described in this paper

The racemic *N*-Boc-3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines **1a**–**h** with a variety of substituents were prepared from the corresponding 2-aminophenol by addition of the relevant 2-bromoketone followed by reduction of the imine with sodium borohydride and Boc protection of the nitrogen atom (Scheme 2).[15] Treatment of the benzoxazine **1a** with *n*-BuLi in THF followed by addition of MeOH, AcOH, or $NaHCO_3$ resulted in decomposition, presumably as the intermediate organolithium undergoes elimination to an unstable enaminophenol.[16] However, trapping with a chloroformate was successful and we found that addition of ethyl chloroformate gave the ethyl carbonate product (**2a**) that was easier to purify than the corresponding methyl carbonate. Therefore, EtOCOCl was used in the subsequent kinetic resolution experiments. We anticipated that lithiation would lead to the ring-opened products **2** but the recovered starting material would be enantioenriched due to the slower reaction of one enantiomer of the racemic benzoxazines **1** with the chiral base *n*-BuLi/sparteine.



Scheme 2 Synthesis and kinetic resolution of 3,4-dihydro-2*H*-1,4-benzoxazines

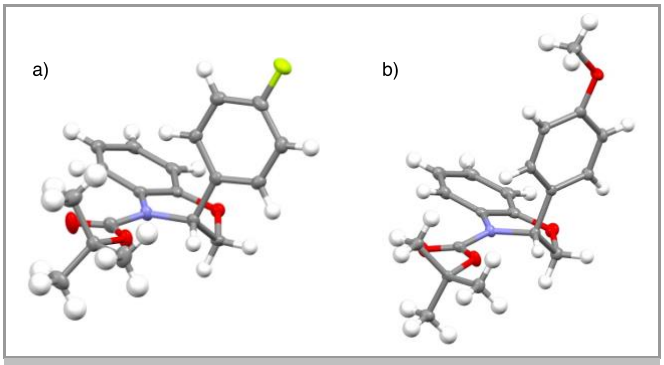
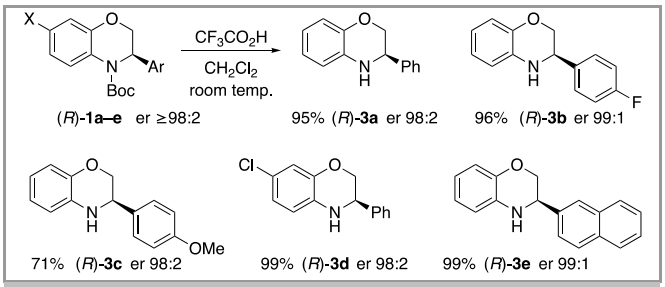


Figure 2 X-ray crystal structures of (a) (*R*)-**1b**, CCDC 2093628, (b) (*R*)-**1c**; CCDC 2093629

Optimization of the yield and enantiomer ratio for the recovered benzoxazine **1** led to the following reaction conditions in which, typically, 1.0 equivalent of *n*-BuLi was added to a mixture of the racemic benzoxazine **1** and 1.0–1.3 equivalents of the chiral ligand (+)-sparteine in toluene at –78 °C. After about 1 h, ethyl chloroformate was added and the mixture was warmed to room temperature and ethanol was added. The alkene products **2** were readily

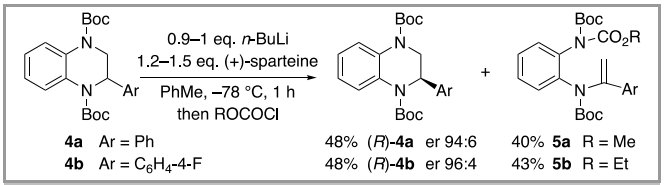
separable from the recovered benzoxazines **1** by column chromatography. These conditions gave about 40% yield of the benzoxazines **1** with high enantiomer ratios (Scheme 2). The parent benzoxazine **1a** (Ar = Ph) gave either enantiomer with excellent selectivity (er ≈ 99:1, S ≈ 20) on using (+)-sparteine or (–)-sparteine. Electron-withdrawing or electron-donating substituents on the 2-aryl ring were tolerated to give (*R*)-**1b** or (*R*)-**1c** and the absolute configurations of these two recovered benzoxazines were verified by single crystal X-ray analyses (Figure 2). The stereochemistry matches that expected for the use of (+)-sparteine in comparison to the use of this enantiomer for other lithiations.[10,11,17] The 7-chloro derivative **1d** and the 3-(2-naphthyl) derivative **1e** were both suitable substrates. The 3-(2-chlorophenyl) derivative **1f** gave lower selectivities although good enantioselectivity of recovered **1f** was possible at higher conversion. In addition, heteroaryl derivatives **1g** and **1h** resulted in lower selectivities of the recovered benzoxazines, perhaps due to coordination of the heteroatom in the heteroaryl group with the *n*-BuLi.

Removal of the *N*-Boc group was achieved under acidic conditions to give the amines **3a**–**e** (Scheme 3). In each case there was no loss of enantiopurity, as determined by chiral stationary phase HPLC. The absolute configurations of the 3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines **3a**–**e** matched those reported in the literature.[18]



Scheme 3 Deprotection to give 3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines

We then prepared the 1,2,3,4-tetrahydroquinoxaline **4a** by reduction of 2-phenylquinoxaline with sodium borohydride,[19] followed by double *N*-Boc protection. Kinetic resolution was carried out by addition of *n*-BuLi to a mixture of the racemic 2-phenyl-1,2,3,4-tetrahydroquinoxaline **4a** and (+)-sparteine in toluene, followed by electrophilic quench with methyl chloroformate (Scheme 4). The recovered (*R*)-2-phenyl-1,2,3,4-tetrahydroquinoxaline **4a** was isolated with high enantiomer ratio. The absolute configuration of the recovered tetrahydroquinoxaline (*R*)-**4a** was verified by single crystal X-ray analysis (see Figure 3). In the same way as the benzoxazines, the side product (**5a**) was the ring-opened compound. Likewise, kinetic resolution was carried out with the 4-fluoro derivative **4b**, which gave the recovered (*R*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoxaline **4b** with high enantioselectivity.



Scheme 4 Kinetic resolution of 2-aryl-1,2,3,4-tetrahydroquinoxalines

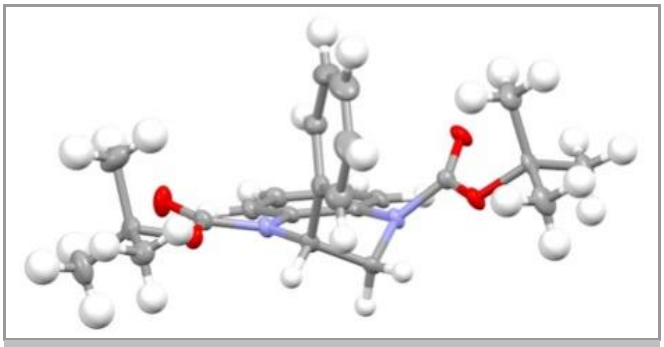
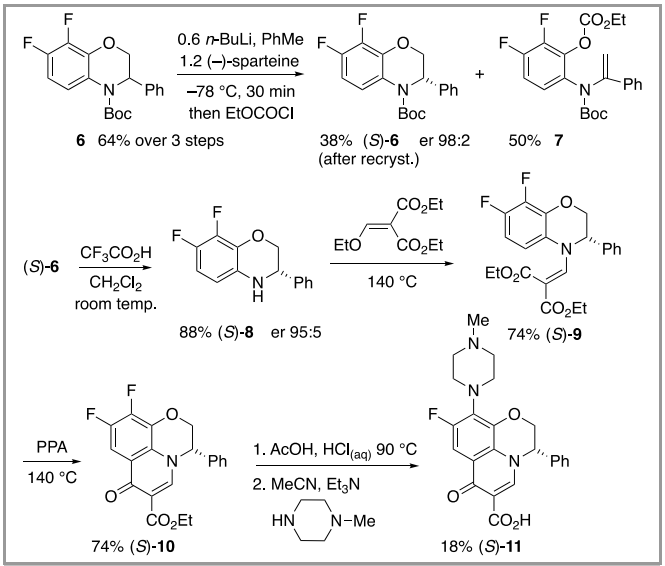


Figure 3 X-ray crystal structure of (*R*)-**4a**; CCDC 2093630

The antibiotic levofloxacin contains a 3,4-dihydro-2*H*-1,4-benzoxazine in which a methyl group is located at position C-3 (Figure 1). The (*S*)-(–)-enantiomer is more active than the racemic compound (ofloxacin).[20] We were intrigued by the possibility that our methodology could provide access to the (*S*)-enantiomer of analogs of levofloxacin with an aryl group at C-3. The racemic benzoxazine **6** was prepared from the known aminophenol and its kinetic resolution was tested (Scheme 5).[21] Treatment of (±)-**6** with *n*-BuLi and (–)-sparteine gave the desired recovered (*S*)-**6** (49% yield, er 85:15) that was recrystallized from CH_2Cl_2–hexane to give the recovered (*S*)-**6** with 38% yield and excellent enantiomer ratio (er 98:2). Removal of the Boc group gave the amine **8** with only a small loss of enantiopurity.

Amine (*S*)-**8** was converted to the diester **9** and hence the ketone (*S*)-**10**. Hydrolysis of the ester and S_NAr reaction gave the analog (*S*)-**11** of levofloxacin.[22] We were not able to determine the enantiomer ratio of products **9**–**11** but the desired analog **11** latter had a specific rotation, $[\alpha]_D^{23}$ –68 (0.2, DMSO).



Scheme 5 Preparation of levofloxacin analog (*S*)-**11**

Levofloxacin, together with the phenyl analogs (*S*)-**11** and (±)-**11** were tested for their bioactivity using a strain of *S. pneumoniae* (D39 D*cps*).[23] The compounds (10 mg·mL^{-1} in DMSO) were added to a culture of the cells (final concentration 10 mg·mL^{-1}) and incubated at 37 °C. The number of viable cells remaining after treatment were measured at regular intervals in comparison to a control, in which the respective volume of DMSO solvent was used. In this assay, levofloxacin gave a significant (~10^5 fold) reduction in cell viability after 5 h of treatment (Figure 2), which was consistent with previous findings.[23e] In contrast, the analogs (*S*)-**11** and (±)-**11** had a similar profile to the solvent only control and did not show reduced cell viability after treatment. Very similar results were obtained on incubation at a higher concentration of these compounds (100 mg·mL^{-1}, see Supporting Information). These experiments suggest the presence of a phenyl group (rather than a methyl group) at C-3 of the benzoxazine was detrimental to antibiotic activity, likely the result of a poorer fit in the active site of the target enzyme (possibly DNA gyrase).[24]

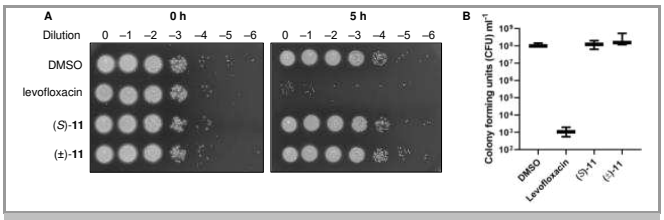


Figure 2 Antibacterial activity assays. **A**: Spot assay of *S. pneumoniae* strain D39 D*cps* incubated with: DMSO (as a control), levofloxacin, benzoxazines (*S*)-**11**, and (±)-**11** at 10 mg·mL^{-1} for up to 5 h; each column of spots represents a sequential 10-fold dilution (up to 10^{-6}) of the culture after treatment; plates are representative of at least three biological repeats. **B**: *S. pneumoniae* cell viability counts 5 h post-treatment; cell viability counts were determined by quantifying the colony forming units (CFU) after treatment using the following dilutions: 0 and 10^{-1} dilution for levofloxacin, 10^{-5} and 10^{-6} dilution for DMSO, (*S*)-**11**, and (±)-**11**; data show the mean (bar) ±standard deviation (whiskers) of three biological repeats

In conclusion, kinetic resolution of racemic *N*-Boc-3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines and *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinoxalines can be achieved by addition of the chiral ligand sparteine and the base *n*-butyllithium, followed by electrophilic quench with a chloroformate. This provides the recovered dihydro-1,4-benzoxazines and tetrahydroquinoxalines with very high levels of enantiopurity in yields approaching the optimum 50% (relative rate of reaction of the enantiomers, S ≈ 20). The side product from these reactions is the achiral *N*-Boc enamine formed by ring-opening of the organolithium intermediate. Removal of the Boc group from the enantioenriched *N*-Boc-3-aryl-3,4-dihydro-2*H*-1,4-benzoxazines results in little or no loss of enantiopurity. The chemistry provides access to highly enantioenriched substituted dihydrobenzoxazines and tetrahydroquinoxalines that could be exploited for the synthesis of chiral drug compounds, as illustrated by the preparation of an analog of levofloxacin.

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All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Solvents were purified using a Grubbs dry solvent system. Thin layer chromatography (TLC) analysis was performed on Merck silica gel 60 F_{254} plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was carried out on VWR silica gel (40-63 micron mesh). Petrol refers to petroleum ether, b.p. 40−60 °C. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum RX Fourier Transform IR System. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Melting points were recorded using a Gallenkamp hot stage. ^{1}H proton NMR spectra were recorded on a Bruker AC400 (400 MHz) instrument in deuterochloroform or hexadeuterodimethyl-sulfoxide. All chemical shifts are expressed in parts-

per-million (ppm) with respect to the residual solvent peaks. Coupling constants (*J*) are given in Hz to the nearest 0.5 Hz. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s = singlet, d = doublet, t = triplet, q=quartet, m = multiplet, br = broad. ^{13}C NMR were recorded on the same instrument above at 100 MHz. ^{19}F NMR were recorded on the same instrument above at 377 MHz. High resolution (accurate mass) mass spectra were recorded on a Walter LCT instrument for electrospray (ES).

(±)-*tert*-Butyl 3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1a[15b]

Potassium carbonate (38 g, 275 mmol) in water–CH_2Cl_2 (1:1) was added to 2-aminophenol (5.0 g, 45.8 mmol) and Bu_4NHSO_4 (0.4 g, 1.1 mmol) then bromoacetophenone (9.1 g, 45.8 mmol) was added. After 16 h the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the imine (7.0 g, 72%) as an amorphous solid; mp 106–108 °C (lit.[18e] 113 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.98–7.92 (m, 2H), 7.54–7.45 (m, 4H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 7.07 (td, *J* = 7.5, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.10 (s, 2H). Data consistent with the literature.[18e] Sodium borohydride (2.5 g, 65 mmol) was added to this imine (6.8 g, 32.4 mmol) in EtOH–water (4:1) and and mixture was heated at 90 °C. After 3 h the solvent was removed under reduced pressure. The crude mixture was partitioned between CH_2Cl_2 and water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the racemic dihydrobenzoxazine **3a** (5.9 g, 85%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.36 (m, 5H), 6.94–6.90 (m, 1H), 6.88 (td, *J* = 7.5, 1.5 Hz, 1H), 6.76 (td, *J* = 7.5, 1.5 Hz, 1H), 6.72 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.55 (ddd, *J* = 8.5, 3.0, 1.0 Hz, 1H), 4.37–4.30 (m, 1H), 4.08–4.00 (m, 2H). Data consistent with the literature.[18e] *n*-BuLi (1.51 mL, 3.78 mmol, 2.5 M in hexanes) was added to the racemic dihydrobenzoxazine **3a** (0.73 g, 3.44 mmol) in THF at –78 °C. After 30 min Boc_2O (0.75 g, 3.44 mmol) in THF was added and the mixture was allowed to warm to room temperature. The mixture was diluted with 10% sodium hydrogencarbonate solution and was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the racemic carbamate **1a** (0.56 g, 52%) as an amorphous solid; mp 81–83 °C (no lit. mp reported).[15b]

^1H NMR (400 MHz, $CDCl_3$) δ = 8.16–8.03 (m, 1H), 7.35–7.22 (m, 5H), 7.01–6.93 (m, 2H), 6.92–6.85 (m, 1H), 5.63 (t, *J* = 2.5 Hz, 1H), 4.57 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.39 (dd, *J* = 11.0, 3.0 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.7, 146.1, 139.0, 128.5, 127.4, 126.4, 126.2, 123.8, 123.0, 121.2, 117.1, 81.9, 68.5, 55.0, 28.2.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}NO_3Na$: 334.1414; found: 334.1413.

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.29; H, 6.85; N, 4.39.

Resolution between the enantiomers of the carbamate **1a** was achieved using a Beckman system fitted with a Lux Cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.5:0.5 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 8.9 min and 10.0 min. Alternatively, resolution was achieved using a Lux Cellulose-1, 5 µm column [*n*-hexane:isopropanol (95:5 v/v)] at 1 mL·min^{-1} with the components eluting at 5.2 min and 5.9 min. Alternatively, resolution was achieved using a Daicel ChiralCel OJ column [*n*-hexane:isopropanol (99:1 v/v)] at 1 mL·min^{-1} with the components eluting at 10.9 min and 14.5 min.

***(R)*-*tert*-Butyl 3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1a**[15b] and **2-[(*tert*-Butoxycarbonyl)(1-phenylethenyl)amino]phenyl ethyl carbonate 2a**

n-BuLi (0.17 mL, 0.34 mmol, 2 M in hexanes) was added to (+)-sparteine (80 mg, 0.34 mmol) and the racemic carbamate **1a** (105 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 30 min, ethyl chloroformate (0.11 mL, 1.15 mmol) was added, the mixture was allowed to warm to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave carbamate (*R*)-**1a** (41 mg, 39%); mp 97–98 °C (no lit.[15b] m.p. reported); data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (Cellulose 1 column, major component eluted at 5.2 min); $[\alpha]_D^{24}$ –87.4 (1.0, $CHCl_3$), lit.[15b] $[\alpha]_D^{20}$ –61.1 (0.4, $CHCl_3$).

The carbonate **2a** (79 mg, 61%) as an oil was also isolated:

IR (neat): 2979, 2933, 1763, 1713, 1624, 1496, 1454, 1368, 1348, 1298, 1239, 1202, 1162, 1140, 1086, 1059, 995, 899, 856, 768, 712, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.55 (m, 2H), 7.39–7.31 (m, 4H), 7.31–7.24 (m, 2H), 7.24–7.18 (m, 1H), 5.24 (s, 1H), 4.90 (s, 1H), 4.23 (q, *J* = 7 Hz, 2H), 1.26 (t, *J* = 7 Hz, 3H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 153.2, 153.0, 149.0, 146.3, 135.5, 128.4, 128.3, 128.2, 127.4, 126.6, 126.0, 123.5, 110.1, 81.5, 64.9, 27.8, 14.2.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{25}NO_5Na$: 406.1625; found: 406.1632.

***(S)*-*tert*-Butyl 3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1a**

n-BuLi (0.175 mL, 0.35 mmol, 2 M in hexanes) was added to (–)-sparteine (81 mg, 0.35 mmol) and the racemic carbamate **1a** (104 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 30 min, ethyl chloroformate (0.11 mL, 1.15 mmol) was added, the mixture was allowed to warm to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave carbamate (*S*)-**1a** (39 mg, 38%); mp 98–99 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (Cellulose 1 column, major component eluted at 5.9 min); $[\alpha]_D^{24}$ +91.3 (0.9, $CHCl_3$). The carbonate **2a** (79 mg, 62%) as an oil was also isolated, data as above.

(±)-*tert*-Butyl 3-(4-Fluorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1b

In the same way as **1a**, potassium carbonate (30 g, 220 mmol), 2-aminophenol (4.0 g, 36.7 mmol), 4-fluorophenacyl bromide (8.0 g, 36.7 mmol), and Bu_4NHSO_4 (0.3 g, 0.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the imine (6.7 g, 80%) as an amorphous solid; mp 130–131 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.92 (m, 2H), 7.45 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.22–7.14 (m, 3H), 7.06 (td, *J* = 7.5, 1.5 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.06 (s, 2H). Data consistent with the literature.[18e] This imine (6.6 g, 29.1 mmol) and sodium borohydride (2.2 g, 59 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic dihydrobenzoxazine **3b** (6.3 g, 94%) as an amorphous solid; mp 61–63 °C (lit.[18a] 70–72 °C for er 94:6); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.38 (m, 2H), 7.17–7.09 (m, 2H), 6.94–6.84 (m, 2H), 6.77 (td, *J* = 7.5, 1.5 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.52 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.33–4.26 (m, 1H), 4.06–3.96 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 113.8. Data consistent with the literature.[18a] The racemic dihydrobenzoxazine **3b** (1.07 g, 4.66 mmol), *n*-BuLi (2.05 mL, 5.12 mmol, 2.5 M in hexanes) and Boc_2O (1.02 g, 4.66 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **1b** (1.47 g, 95%) as an amorphous solid; mp 85–87 °C.

IR (neat): 3130, 3045, 2990, 2980, 2880, 1700, 1605, 1585, 1510, 1490, 1330, 1215, 1140, 1000, 830, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 7.0 Hz, 1H), 7.30–7.22 (m, 2H), 7.02–6.92 (m, 4H), 6.91–6.86 (m, 1H), 5.61 (t, *J* = 2.0 Hz, 1H), 4.54 (dd, *J* = 11.5, 2.0 Hz, 1H), 4.37 (dd, *J* = 11.5, 2.0 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0 (d, *J* = 245.5 Hz), 152.7, 145.8, 134.6 (d, *J* = 3.0 Hz), 128.2 (d, *J* = 8.0 Hz), 125.8, 124.0, 123.0, 121.2, 117.1, 115.4 (d, *J* = 21.5 Hz), 82.1, 68.3, 54.2, 28.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.1.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{20}FNO_3Na$: 352.1319; found: 352.1325.

Resolution between the enantiomers of the carbamate **1b** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 9.1 min and 12.4 min.

(*R*)-*tert*-Butyl 3-(4-Fluorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1b and **2-[(*tert*-Butoxycarbonyl)[1-(4-fluorophenyl)ethenyl]amino]phenyl ethyl carbonate 2b**

In the same way as (*R*)-**1a**, *n*-BuLi (0.17 mL, 0.34 mmol, 2 M in hexanes), (+)-sparteine (80 mg, 0.34 mmol), racemic carbamate **1b** (113 mg, 0.34 mmol), and ethyl chloroformate (0.10 mL, 1.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**1b** (45 mg, 40%) as an amorphous solid; mp 106–107 °C; data as above; the enantiomeric ratio was determined to be 97:3 by CSP-HPLC (major component eluted at 11.6 min); $[\alpha]_D^{24}$ –56.5 (0.9, $CHCl_3$).

The carbonate **2b** (82 mg, 60%) as an amorphous solid was also isolated; mp 73–75 °C:

IR (neat): 3010, 2995, 2985, 1755, 1720, 1705, 1630, 1600, 1500, 1350, 1245, 1160, 1075, 900, 845, 770, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.54 (m, 2H), 7.38–7.21 (m, 4H), 7.11–7.03 (m, 2H), 5.22–5.18 (m, 1H), 4.92–4.88 (m, 1H), 4.29–4.20 (m, 2H), 1.31–1.21 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 162.0 (d, *J* = 245.5 Hz), 153.0, 152.8, 147.8, 146.1, 135.1, 128.2, 128.2 (d, *J* = 8.0 Hz), 127.4, 126.5, 123.4, 115.4 (d, *J* = 21.5 Hz), 109.8, 81.5, 64.8, 27.7, 14.1.

^{19}F NMR (377 MHz, $CDCl_3$) δ = 114.0.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{24}FNO_5Na$: 424.1531; found: 424.1539.

(±)-*tert*-Butyl 3-(4-Methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1c

In the same way as **1a**, potassium carbonate (30 g, 220 mmol), 2-aminophenol (4.0 g, 36.7 mmol), 4- methoxyphenacyl bromide (8.4 g, 36.7 mmol), and Bu_4NHSO_4 (0.3 g, 0.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the imine (6.6 g, 75%) as an amorphous solid; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.89 (m, 2H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 (td, *J* = 8.0, 1.5 Hz, 1H), 7.08–6.98 (m, 3H), 6.94 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.06 (s, 2H), 3.89 (s, 3H). Data consistent with the literature.[18e] This imine (6.5 g, 27.3 mmol) and sodium borohydride (2.1 g, 55 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic dihydrobenzoxazine **3c** (5.7 g, 86%) as an amorphous solid; mp 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.32 (m, 2H), 6.99–6.93 (m, 2H), 6.89 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.84 (td, *J* = 7.5, 1.5 Hz, 1H), 6.74 (td, *J* = 7.5, 1.5 Hz, 1H), 6.70 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.32–4.25 (m, 1H), 4.04–3.96 (m, 2H), 3.85 (s, 3H). Data consistent with the literature.[18e,25] The racemic dihydrobenzoxazine **3c** (1.0 g, 4.2 mmol), *n*-BuLi (1.8 mL, 4.6 mmol, 2.5 M in hexanes) and Boc_2O (0.91 g, 4.2 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **1c** (1.16 g, 81%) as an amorphous solid; mp 95–96 °C.

IR (neat): 3125, 3015, 3000, 2985, 2975, 2840, 1705, 1610, 1585, 1510, 1490, 1330, 1245, 1140, 1030, 830, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 7.5 Hz, 1H), 7.25–7.19 (m, 2H), 7.01–6.91 (m, 2H), 6.91–6.86 (m, 1H), 6.86–6.80 (m, 2H), 5.60 (t, *J* = 2.5 Hz, 1H), 4.56 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.37 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.77 (s, 3H), 1.52 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8, 152.7, 146.0, 130.9, 127.7, 125.9, 123.9, 123.1, 121.1, 117.0, 113.9, 81.8, 68.5, 55.2, 54.1, 28.3.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{23}NO_4Na$: 364.1519; found: 364.1521.

Resolution between the enantiomers of the carbamate **1c** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 14.4 min and 20.5 min.

(*R*)-*tert*-Butyl 3-(4-Methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1c and **2-[(*tert*-Butoxycarbonyl)[1-(4-methoxyphenyl)ethenyl]amino]phenyl ethyl carbonate 2c**

In the same way as (*R*)-**1a**, *n*-BuLi (0.14 mL, 0.36 mmol, 2.5 M in hexanes), (+)-sparteine (84 mg, 0.36 mmol), racemic carbamate **1c** (102 mg, 0.30 mmol), and ethyl chloroformate (0.10 mL, 1.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), carbamate (*R*)-**1c** (42 mg, 41%) as an amorphous solid; mp 81–83 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (major component eluted at 20.0 min); $[\alpha]_D^{24}$ –90.7 (0.2, $CHCl_3$).

The carbonate **2c** (70 mg, 56%) as an amorphous solid was also isolated; mp 90–92 °C:

IR (neat): 3070, 3005, 2980, 2935, 2835, 1765, 1700, 1625, 1605, 1505, 1455, 1350, 1300, 1245, 1165, 1025, 975, 885, 770, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55–7.50 (m, 2H), 7.37–7.18 (m, 4H), 6.94–6.88 (m, 2H), 5.21 (s, 1H), 4.88 (s, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 1.33–1.25 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7, 153.1, 153.0, 148.4, 146.2, 135.4, 131.4, 128.0, 127.2 (2 × CH), 126.4, 123.3, 113.6, 108.8, 81.2, 64.7, 55.3, 27.8, 14.1.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_6Na$: 436.1731; found: 436.1735.

(±)-*tert*-Butyl 7-Chloro-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1d

In the same way as **1a**, potassium carbonate (40 g, 290 mmol), 2-amino-5-chlorophenol (7.0 g, 49 mmol), bromoacetophenone (9.7 g, 49 mmol), and Bu_4NHSO_4 (3.8 g, 11 mmol) gave, after extraction with CH_2Cl_2 (2 × 100 mL), drying ($MgSO_4$) and evaporation, the crude imine as an oil, which was used directly in the next step. This imine (4.5 g, 18 mmol) and sodium borohydride (1.4 g, 37 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the racemic dihydrobenzoxazine **3d** (3.3 g, 74%) as an amorphous solid; mp 61–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.30 (m, 5H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 4.48 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.28 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.08–3.81 (m, 2H). Data consistent with the literature.[18b] The racemic dihydrobenzoxazine **3d** (3.0 g, 8.8 mmol), *n*-BuLi (3.69 mL, 8.8 mmol, 2.4 M in hexanes) and Boc_2O (2.3 g, 10.6 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **1d** (2.8 g, 93%) as an amorphous solid; mp 118–120 °C.

IR (neat): 2973, 2970, 2930, 1708, 1577, 1492, 1368, 1257, 1140, 1061, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (d, *J* = 8.5 Hz, 1H), 7.36–7.20 (m, 5H), 6.97–6.83 (m, 2H), 5.62 (br s, 1H), 4.60 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.36 (dd, *J* = 11.0, 3.0 Hz, 1H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 146.5, 138.4, 128.6, 128.5, 127.5, 126.3, 124.8, 123.9, 121.2, 117.1, 82.3, 68.4, 54.5, 28.2.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{20}{}^{35}ClNO_3Na$: 368.1024; found: 368.1022.

Resolution between the enantiomers of the carbamate **1d** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 8.4 min and 9.5 min.

(*R*)-*tert*-Butyl 7-Chloro-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1d and **2-[(*tert*-Butoxycarbonyl)(1-phenylethenyl)amino]-5-chlorophenyl ethyl carbonate 2d**

In the same way as (*R*)-**1a**, *n*-BuLi (0.12 mL, 0.29 mmol, 2.5 M in hexanes), (+)-sparteine (88 mg, 0.38 mmol), racemic carbamate **1d** (100 mg, 0.29 mmol), and ethyl chloroformate (0.09 mL, 0.9 mmol, added after 90 min) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**1d** (40 mg, 40%) as an amorphous solid; mp 110–111 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (major component eluted at 9.9 min); $[\alpha]_D^{27}$ –15.3 (1.5, $CHCl_3$).

The carbonate **2d** (63 mg, 50%) as oil was also isolated:

IR (neat): 3083, 3060, 3026, 2980, 2933, 1780, 1700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.46 (m, 2H), 7.33–7.25 (m, 4H), 7.23–7.18 (m, 1H), 7.13 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.21 (br s, 1H), 4.83 (br s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 153.2, 153.0, 149.1, 146.8, 134.5, 132.5, 129.2, 128.8, 128.2, 127.2, 126.3, 124.3, 110.7, 82.1, 65.5, 28.1, 14.5.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{24}{}^{35}ClNO_5Na$: 440.1235; found: 440.1230.

(±)-*tert*-Butyl 3-(2-Naphthenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1e

In the same way as **1a**, potassium carbonate (38 g, 276 mmol), 2-amino-5-chlorophenol (5.0 g, 46 mmol), 2-bromo-2'-acetonaphthone (11.5 g, 46 mmol), and Bu_4NHSO_4 (2.2 g, 11 mmol) gave, after extraction with CH_2Cl_2 (2 × 100 mL), drying ($MgSO_4$) and evaporation, the crude imine as an amorphous solid, which was used directly in the next step; mp 140–142 °C, (lit.[18f] 140–145 °C). This imine (9.8 g, 38 mmol) and sodium borohydride (2.9 g, 76 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic dihydrobenzoxazine **3e** (8.0 g, 81%) as an amorphous solid; mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92–7.80 (m, 4H), 7.55–7.46 (m, 3H), 6.92–6.80 (m, 2H), 6.77–6.69 (m, 2H), 4.69 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.37 (ddd, *J* = 10.7, 3.0, 2.0 Hz, 1H), 4.13–4.05 (m, 2H). Data consistent with the literature.[18f] The racemic dihydrobenzoxazine **3e** (2.5 g, 9.6 mmol), *n*-BuLi (3.8 mL, 9.6 mmol, 2.5 M in hexanes) and Boc_2O (2.5 g, 11.5 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **1e** (1.4 g, 40%) as an amorphous solid; mp 100–102 °C.

IR (neat): 3000, 2979, 2930, 1710, 1586, 1493, 1368, 1252, 1140, 1065, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16–8.04 (m, 1H), 7.89–7.67 (m, 4H), 7.51–7.36 (m, 3H), 7.02–6.91 (s, 2H), 6.90–6.83 (m, 1H), 5.79 (m, 1H), 4.68 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.45 (dd, *J* = 11.0, 2.5 Hz, 1H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.9, 146.2, 136.3, 133.3, 132.8, 128.5, 128.1, 127.7, 126.2, 126.2, 126.0, 125.5, 124.7, 124.1, 123.2, 121.3, 117.2, 82.1, 68.4, 55.0, 28.4.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{23}NO_3Na$: 384.1576; found: 384.1575.

Resolution between the enantiomers of the carbamate **1e** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.6:0.4 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 19.4 min and 21.4 min.

(*R*)-*tert*-Butyl 3-(2-Naphthenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1e and **2-[(*tert*-Butoxycarbonyl)[1-(2-naphthenyl)ethenyl]amino]phenyl ethyl carbonate 2e**

In the same way as (*R*)-**1a**, *n*-BuLi (0.13 mL, 0.34 mmol, 2.5 M in hexanes), (+)-sparteine (88 mg, 0.38 mmol), racemic carbamate **1e** (100 mg, 0.29 mmol), and ethyl chloroformate (0.09 mL, 0.9 mmol, added after 60 min) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**1e** (40 mg, 40%) as an amorphous solid; mp 108–109 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major component eluted at 18.3 min); $[\alpha]_D^{27}$ –45.2 (0.6, $CHCl_3$).

The carbonate **2e** (52 mg, 43%) as oil was also isolated:

IR (neat): 3055, 3005, 2975, 2930, 2870, 1775, 1700, 1490, 1320, 1250, 1155, 1010, 815, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08–8.06 (m, 1H), 7.90–7.83 (m, 3H), 7.74 (dd, *J* = 8.5, 2 Hz, 1H), 7.54–7.46 (m, 2H), 7.44 (dd, *J* = 8, 1.5 Hz, 1H), 7.37–7.22 (m, 3H), 5.45 (br s, 1H), 5.07 (br s, 1H), 4.24 (q, *J* = 7 Hz, 2H), 1.25 (t, *J* = 7 Hz, 3H), 1.19 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1, 153.0, 148.8, 146.3, 136.2, 135.4, 133.3, 133.2, 128.3, 128.1, 127.9, 127.6, 127.3, 126.5, 126.3, 126.1, 124.8, 124.1, 123.4, 110.7, 81.4, 64.8, 27.7, 14.1.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{27}NO_5Na$: 456.1781; found: 456.1794.

(±)-*tert*-Butyl 3-(2-Chlorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1f

In the same way as **1a**, potassium carbonate (21.5 g, 156 mmol), 2-aminophenol (2.8 g, 26 mmol), 2-bromo-2'-chloroacetophenone (6.0 g, 26 mmol), and Bu_4NHSO_4 (1.2 g, 6.2 mmol) gave, after extraction with CH_2Cl_2 (2 × 100 mL), drying ($MgSO_4$) and evaporation, the crude imine as an oil, which was used directly in the next step. This imine (4.0 g, 16.5 mmol) and sodium borohydride (1.25 g, 33 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic dihydrobenzoxazine **3f** (3.0 g, 75%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.44 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.37–7.23 (m, 2H), 6.93–6.83 (m, 2H), 6.80–6.70 (m, 2H), 5.05 (dt, *J* = 7.0, 3.0 Hz, 1H), 4.43 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H), 4.09–3.95 (m, 2H). Data consistent with the literature.[18d] The racemic dihydrobenzoxazine **3f** (3.0 g, 12 mmol), *n*-BuLi (6.1 mL, 15 mmol, 2.4 M in hexanes) and Boc_2O (3.0 g, 13 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the racemic carbamate **1f** (3.6 g, 85%) as needles; mp 110–112 °C.

IR (neat): 3065, 3000, 2985, 2875, 1715, 1585, 1510, 1490, 1335, 1145 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, *J* = 7.5, 1H), 7.41 (dd, *J* = 7.5, 2.0, 1H), 7.23 (td, *J* = 7.5, 2.0, 1H), 7.18–7.08 (m, 2H), 7.07–6.98 (m, 2H), 6.95–6.91 (m, 1H), 5.91 (t, *J* = 3.0, 1H), 4.39 (dd, *J* = 11.0, 3.0, 1H), 4.30 (dd, *J* = 11.0, 3.0, 1H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.3, 146.4, 137.6, 131.7, 129.6, 128.7, 127.8, 127.4, 127.1, 123.4, 122.0, 121.4, 117.4, 82.0, 67.2, 55.0, 28.0.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{20}{}^{35}ClNO_3Na$: 368.1024; found: 368.1027.

Resolution between the enantiomers of the carbamate **1f** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 0.5 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 5.3 min and 7.3 min.

(*R*)-*tert*-Butyl 3-(2-Chlorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1f and **2-[(*tert*-Butoxycarbonyl)[1-(2-chlorophenyl)ethenyl)amino]phenyl ethyl carbonate 2f**

In the same way as (*R*)-**1a**, *n*-BuLi (0.07 mL, 0.17 mmol, 2.5 M in hexanes), (+)-sparteine (80 mg, 0.34 mmol), racemic carbamate **1f** (100 mg, 0.29 mmol), and ethyl chloroformate (0.09 mL, 0.9 mmol, added after 60 min) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), carbamate (*R*)-**1f** (41 mg, 41%) as an amorphous solid; mp 89–91 °C; data as above; the enantiomeric ratio was determined to be 75:25 by CSP-HPLC (major component eluted at 8.0 min); $[\alpha]_D^{23}$ +35.4 (1.9, $CHCl_3$).

The carbonate **2f** (63 mg, 53%) as oil was also isolated:

IR (neat): 3070, 3000, 2975, 2935, 1765, 1710, 1090, 800 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.53 (m, 2H), 7.41–7.36 (m, 1H), 7.33–7.20 (m, 5H), 5.00 (br s, 1H), 4.93 (br s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.23 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0, 152.0, 147.0, 145.2, 137.8, 134.5, 132.1, 130.3, 129.9, 128.9, 128.8, 127.8, 126.6, 126.5, 123.1, 110.8, 81.4, 64.8, 27.7, 14.2.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{24}NO_5Na$: 440.1235; found: 440.1233.

(±)-*tert*-Butyl 3-(2-Furenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1g

In the same way as **1a**, potassium carbonate (14 g, 101 mmol), 2-aminophenol (4.18 g, 16.8 mmol), 2-bromo-1-(furan-2-yl)ethanone (3.17 g, 16.8 mmol), and Bu_4NHSO_4 (0.8 g, 3.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the imine as an amorphous solid, mp 81–83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.62 (m, 1H) 7.45 (dd, *J* 7.5, 1.5 Hz, 1H), 7.14 (td, *J* 7.5, 1.5 Hz, 1H), 7.05–6.99 (m, 2H) 6.91 (dd, *J* 7.5, 1.5 Hz, 1H), 6.58 (dd, *J* 3.5, 1.5 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.9, 128.6, 127.8, 122.8, 115.9, 113.8, 112.4, 77.5, 77.2, 76.8, 62.0. Data consistent with the literature.[18d] This imine (2.4 g, 12 mmol) and sodium borohydride (1.0 g, 24 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic dihydrobenzoxazine **3g** (2.0 g, 82%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.37 (m, 1H), 6.88–6.79 (m, 2H), 6.76–6.63 (m, 2H), 6.38–6.37 (m, 2H), 4.64 (dt, *J* 7.0, 3.0 Hz, 1H), 4.43 (ddd, *J* 11.0, 3.0, 1.5 Hz, 1H), 4.25 (dd, *J* 11.0, 7.0 Hz, 1H), 4.08 (br s, 1H). Data consistent with the literature.[18d] The racemic dihydrobenzoxazine **3g** (1.68 g, 8.3 mmol), *n*-BuLi (3.5 mL, 8.3 mmol, 2.4 M in hexanes) and Boc_2O (1.8 g, 8.3 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **1g** (1.6 g, 64%) as needles; mp 69–71 °C.

IR (neat): 3149, 3119, 2959, 2918, 2856, 1680, 1584, 1491, 1364, 1255, 1152, 1013, 850 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 7.5 Hz, 1H), 7.32–7.30 (m, 1H), 7.00–6.93 (m, 1H), 6.92–6.82 (m, 2H), 6.23–6.21 (m, 1H), 6.09–6.07 (m, 1H), 5.75 (br s, 1H), 4.67 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.29 (dd, *J* = 11.0, 3.0 Hz, 1H), 1.55 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4, 151.1, 145.3, 142.0, 124.8, 124.4, 123.6, 120.8, 117.0, 110.5, 107.7, 82.3, 66.7, 48.9, 28.4.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{19}NO_4Na$: 324.1206; found: 324.1208.

Resolution between the enantiomers of the carbamate **1g** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.6:0.4 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 $g \cdot L^{-1}$ solution of the eluent. The components were eluted at 10.1 min and 13.0 min.

(*R*)-*tert*-Butyl 3-(2-Furenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1g and **2-[(*tert*-Butoxycarbonyl)[1-(2-furenyl)ethenyl)amino]phenyl ethyl carbonate 2g**

In the same way as (*R*)-**1a**, *n*-BuLi (0.09 mL, 0.23 mmol, 2.5 M in hexanes), (+)-sparteine (80 mg, 0.34 mmol), racemic carbamate **1g** (100 mg, 0.33 mmol), and ethyl chloroformate (0.10 mL, 1.0 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**1g** (43 mg, 43%) as an amorphous solid; mp 71–73 °C; data as above; the enantiomeric ratio was determined to be 80:20 by CSP-HPLC (major component eluted at 13.0 min); $[\alpha]_D^{21}$ –20.5 (2.0, $CHCl_3$).

The carbonate **2g** (64 mg, 52%) as oil was also isolated:

IR (neat): 3640, 2985, 2930, 1765, 1700, 1615, 1525, 1200, 1095, 895, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.39 (m, 1H), 7.37–7.33 (m, 1H), 7.30–7.26 (m, 2H), 7.23–7.18 (m, 1H), 6.51 (d, *J* = 3.5 Hz, 1H), 6.43 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.25 (s, 1H), 5.10 (s, 1H), 4.30 (q, *J* = 7 Hz, 2H), 1.41–1.32 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$, two C could not be observed) δ = 153.1, 152.9, 146.3, 142.2, 138.8, 127.7, 127.4, 126.4, 123.3, 111.4, 110.0, 107.5, 81.3, 64.8, 27.9, 14.2.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{23}NO_6Na$: 396.1418; found: 396.1430.

(±)-*tert*-Butyl 3-(2-Pyridinyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1h

In the same way as **1a**, potassium carbonate (18 g, 130 mmol), 2-aminophenol (1.89 g, 17.3 mmol), 2-(2-bromoacetyl)pyridinium bromide[12] (4.93 g, 17.6 mmol) and Bu_4NHSO_4 (0.1 g, 0.3 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (85:15), the imine as an amorphous solid, mp 85–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.63 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 8.37 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.81 (td, *J* = 8.0, 1.5 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.5 Hz, 1H), 6.93 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 153.7, 149.0, 147.2, 136.7, 133.7, 129.5, 128.1, 125.3, 122.3, 121.4, 116.0, 62.6. This imine (854 mg, 4.1 mmol) and sodium borohydride (333 mg, 8.8 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the racemic dihydrobenzoxazine **3h** (817 mg, 95%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.60 (d, *J* = 4.5 Hz, 1H), 7.69 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.26–7.21 (m, 1H), 6.88–6.81 (m, 2H), 6.76 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.71 (td, *J* = 7.5, 1.5 Hz, 1H), 4.67 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.51 (br s, 1H), 4.43 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.11 (dd, *J* = 10.5, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 149.6, 143.9, 137.1, 133.1, 123.0, 121.8, 121.5, 119.1, 116.9, 116.2, 69.1, 55.5. The racemic dihydrobenzoxazine **3h** (0.49 g, 2.3 mmol), *n*-BuLi (1.3 mL, 2.6 mmol, 2.5 M in hexanes) and Boc_2O (0.63 g, 2.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the racemic carbamate **1h** (719 mg, 99%) as an amorphous solid; mp 104–105 °C.

IR (neat): 2987, 2882, 1701, 1587, 1493, 1434, 1364, 1330, 1272, 1252, 1219, 1146, 1122, 1068, 1047, 1004, 933, 823, 751, 663, 606 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 8.58 (d, *J* = 4.5 Hz, 1H), 8.16 (br, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.15–7.07 (m, 2H), 6.98–6.89 (m, 2H), 6.83–6.77 (m, 1H), 5.68 (br s, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.30 (br d, *J* = 10.5 Hz, 1H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0, 152.8, 149.5, 146.0, 136.8, 125.8, 124.0, 122.8, 122.3, 121.2, 120.7, 117.3, 82.2, 67.4, 57.1, 28.3.

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}N_2O_3$: 313.1547; found: 313.1552.

Resolution between the enantiomers of the carbamate **1h** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (98:2 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm.

Injection volume was 20 μL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 11.5 min and 17.8 min.

***(R)*-*tert*-Butyl 3-(2-Pyridinyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate 1h** and **2-[(*tert*-Butoxycarbonyl)[1-(2-pyridinyl)ethenyl)amino]phenyl ethyl carbonate 2h**

In the same way as (*R*)-**1a**, *n*-BuLi (0.165 mL, 0.33 mmol, 2 M in hexanes), (+)-sparteine (80 mg, 0.34 mmol), racemic carbamate **1h** (103 mg, 0.33 mmol), and ethyl chloroformate (0.10 mL, 1.0 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (85:15), carbamate (*R*)-**1h** (33.5 mg, 32%) as an amorphous solid; mp 95–96 °C; data as above; the enantiomeric ratio was determined to be 72:28 by CSP-HPLC (major component eluted at 17.8 min); $[\alpha]_D^{21}$ –59.7 (1.7, $CHCl_3$).

The carbonate **2h** (85 mg, 67%) as oil was also isolated:

IR (neat): 3065, 2984, 2933, 1753, 1708, 1632, 1589, 1496, 1469, 1367, 1327, 1247, 1203, 1165, 1086, 1059, 1034, 992, 910, 866, 839, 797, 776, 767, 755, 713, 674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (ddd, *J* = 4.5, 1.5, 0.8 Hz, 1H), 7.70 (td, *J* = 7.5, 1.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.30–7.25 (m, 2H), 7.25–7.19 (m, 2H), 5.71 (s, 1H), 5.14 (s, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.22 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 153.2, 152.8, 149.2, 148.3, 146.4, 136.4, 135.5, 128.3, 127.5, 126.7, 123.3, 122.8, 120.5, 112.9, 81.4, 64.9, 27.8, 14.2.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}N_2O_5$: 385.1758; found: 385.1762.

***(R)*-3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine 3a**[26]

Trifluoroacetic acid (0.20 mL, 2.6 mmol) was added to the benzoxazine (*R*)-**1a** (32.5 mg, 0.105 mmol, er 98:2) in CH_2Cl_2 (1 mL) at room temperature. After 18 h, the solvent was evaporated and aqueous NaOH (1 M) was added. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the amine (*R*)-**3a** (21 mg, 95%) as an oil; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC using a Daicel Chiralpak IA column (250 mm × 4.6 mm i.d.) using a 15 μL injection volume, hexane–iPrOH (98:2), components eluting at 13.3 min (major) and 11.1 min (minor); $[\alpha]_D^{24}$ –101.6 (0.9, $CHCl_3$), lit.[26] $[\alpha]_D^{20}$ –118.1 (1.0, $CHCl_3$) for 98% ee.

***(R)*-3-(4-Fluorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine 3b**[18f]

In the same way as (*R*)-**3a**, trifluoroacetic acid (0.20 mL, 2.6 mmol) and the benzoxazine (*R*)-**1b** (37.5 mg, 0.11 mmol, er 99:1) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the amine (*R*)-**3b** (25 mg, 96%) as an amorphous solid, mp 69–70 °C, lit.[18a] mp 70–72 °C for er 94:6; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC using a Daicel Chiralpak IA column (250 mm × 4.6 mm i.d.) using a 10 μL injection volume, hexane–iPrOH (98:2), components eluting at 18.5 min (major) and 15.3 min (minor); $[\alpha]_D^{23}$ –104.3 (0.7, $CHCl_3$), lit.[18f] $[\alpha]_D^{25}$ –117.9 (1.0, $CHCl_3$) for 99% ee.

***(R)*-3-(4-Methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzoxazine 3c**[18e]

In the same way as (*R*)-**3a**, trifluoroacetic acid (0.07 mL, 0.9 mmol) and the benzoxazine (*R*)-**1c** (32 mg, 0.09 mmol, er 98:2) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the amine (*R*)-**3c** (16 mg, 71%) as an amorphous solid, mp 92–94 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC using a Daicel Chiralpak IA column (250 mm × 4.6 mm i.d.) using a 10 μL injection volume, hexane–iPrOH (9:1), components eluting at 15.1 min (major) and 9.5 min (minor); $[\alpha]_D^{22}$ –121.4 (0.7, $CHCl_3$), lit.[18e] $[\alpha]_D^{20}$ –126.5 (1.0, $CHCl_3$) for 98% ee.

***(R)*-7-Chloro-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine 3d**[18b]

In the same way as (*R*)-**3a**, trifluoroacetic acid (0.01 mL, 0.12 mmol) and the benzoxazine (*R*)-**1d** (41 mg, 0.12 mmol, er 98:2) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the amine (*R*)-**3d** (29 mg, 99%) as needles, mp 55–56 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC using a Daicel ChiralCel OJ column (250 mm × 4.6 mm i.d.) using a 20 μL injection volume, hexane–iPrOH (99:1), components eluting at 78.4 min (major) and 93.6 min (minor); $[\alpha]_D^{23}$ –73.2 (0.2, $CHCl_3$), lit.[18b] $[\alpha]_D^{20}$ –81.3 (1.2, $CHCl_3$) for 86% ee.

***(R)*-3-(2-Naphthenyl)-3,4-dihydro-2*H*-1,4-benzoxazine 3e**[18b]

In the same way as (*R*)-**3a**, trifluoroacetic acid (0.04 mL, 0.47 mmol) and the benzoxazine (*R*)-**1e** (17 mg, 0.05 mmol, er 98:2) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the amine (*R*)-**3e** (13 mg, 99%) as amorphous solid, mp 70–71 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC using a Daicel Chiralpak IA column (250 mm × 4.6 mm i.d.) using a 20 μL injection volume, hexane–iPrOH (99.3:0.7), components eluting at 13.7 min (major) and 17.6 min (minor); $[\alpha]_D^{27}$ –106 (1.5, $CHCl_3$), lit.[18b] $[\alpha]_D^{20}$ –119.6 (1.0, $CHCl_3$) for 85% ee.

(±)-1,4-di-*tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydroquinoxaline-1,4-dicarboxylate 4a

Sodium borohydride (1.8 g, 49 mmol) was added portionwise to 2-phenylquinoxaline (2.51 g, 12.2 mmol) in acetic acid (75 mL) at 0 °C. After 15 min, water (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (50 mL). Aqueous NaOH (50 mL, 5 M) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave 2-phenyl-1,2,3,4-tetrahydroquinoxaline (1.59 g, 62%) as an amorphous solid; mp 76–77 °C, lit.[27] mp 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.28 (m, 5H), 6.68–6.61 (m, 2H), 6.61–6.54 (m, 2H), 4.49 (dd, *J* 8.0, 3.0 Hz, 1H), 3.99–3.77 (m, 2H), 3.47 (dd, *J* 11.0, 3.0 Hz, 1H) 3.36 (dd, *J* 11.0, 8.0 Hz, 1H). Data consistent with the literature.[27] *n*-BuLi (7.86 mL, 18.8 mmol, 2.4 M in hexanes) was added to racemic 2-phenyl-1,2,3,4-tetrahydroquinoxaline (1.8 g, 8.6 mmol) in THF (35 mL) at –78 °C. After 20 min Boc_2O (4.0 g, 18.8 mmol) in THF (10 mL) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with 10% sodium hydrogencarbonate solution (20 mL) and was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the racemic carbamate **4a** (2.99 g, 85%) as needles; mp 166–167 °C.

IR (neat): 3010, 2925, 1715, 1600, 1500, 1250, 1140, 1065, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (d, *J* = 8.0 Hz, 1H), 7.52 (br s, 1H), 7.33–7.20 (m, 5H), 7.17–7.12 (m, 1H), 7.08–7.03 (m, 1H), 5.40 (t, *J* = 5.0 Hz, 1H), 4.04–3.75 (m, 2H), 1.35 (s, 9H), 1.26 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 153.1, 152.5, 141.8, 132.1, 128.5, 127.2, 125.7, 124.4, 124.1, 123.0, 122.7, 81.5, 81.0, 61.4, 49.4, 28.1, 27.9.

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{24}H_{30}N_2O_4Na$: 433.2098; found: 433.2103.

Resolution between the enantiomers of the carbamate **4a** was achieved using a Beckman system fitted with a Lux Cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.4:0.6 v/v) as the mobile phase at a flow rate of 0.8 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample in a 2 g·L^{-1} solution of the eluent. The components were eluted at 11.9 min and 15.5 min.

***(R)*-1,4-di-*tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydroquinoxaline-1,4-dicarboxylate 4a** and ***tert*-Butyl *N*-{2-[(*tert*-Butoxycarbonyl)(methoxycarbonyl)amino]phenyl}-*N*-(1-phenylethenyl)carbamate 5a**

In the same way as (*R*)-**1a**, *n*-BuLi (0.086 mL, 0.22 mmol, 2.5 M in hexanes), (+)-sparteine (68 mg, 0.29 mmol), racemic carbamate **4a** (100 mg, 0.24 mmol), and methyl chloroformate (0.06 mL, 0.7 mmol, added after 60 min) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**4a** (48 mg, 48%) as needles; mp 177–178 °C; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC (major component eluted at 11.8 min); $[\alpha]_D^{23}$ –8.2 (0.9, $CHCl_3$).

The carbonate **5a** (45 mg, 40%) as an oil was also isolated:

IR (neat): 3060, 2980, 2935, 1790, 1760, 1715, 1495, 1345, 1250, 1120, 1025, 855, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.47 (m, 2H), 7.39–7.25 (m, 7H), 5.16 (s, 1H), 4.92 (s, 1H), 3.68 (s, 3H), 1.42 (s, 9H), 1.17 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.3, 153.0, 151.2, 148.5, 140.5, 139.4, 134.9, 130.8, 129.1, 128.9, 128.2, 128.0, 127.0, 125.9, 109.9, 83.2, 81.4, 53.5, 27.8, 27.7.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{32}N_2O_6Na$: 491.2153; found: 491.2156.

(±)-1,4-di-*tert*-Butyl 2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoxaline-1,4-dicarboxylate 4b

In the same way as carbamate **4a**, sodium borohydride (1.1 g, 28 mmol), 2-(4-fluorophenyl)quinoxaline (1.6 g, 7.1 mmol) and acetic acid (40 mL) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), 2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoxaline (1.1 g, 70%) as an amorphous solid; mp 96–98 °C, lit.[28] mp 103–104 °C for *R* enantiomer; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.34 (m, 2H), 7.14–7.04 (m, 2H), 6.71–6.57 (m, 4H), 4.50 (dd, *J* 8.0, 3.0 Hz, 1H), 3.89 (br s, 2H), 3.46 (dd, *J* 11.0, 3.0 Hz, 1H) 3.32 (dd, *J* 11.0, 8.0 Hz, 1H). Data consistent with the literature.[28] In the same way as carbamate **4a**, *n*-BuLi (4.21 mL, 9.7 mmol, 2.3 M in hexanes), racemic 2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoxaline (1.0 g, 4.4 mmol) and Boc_2O (2.1 g, 9.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the racemic carbamate **4b** (1.1 g, 60%) as needles; mp 180–182 °C.

IR (neat): 2970, 1710, 1690, 1500, 1390, 1015, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.0 Hz, 1H), 7.51 (br s, 1H), 7.23–7.11 (m, 3H), 7.09–6.96 (m, 3H), 5.46 (t, *J* = 5.0 Hz, 1H), 3.99–3.57 (m, 2H), 1.38 (s, 9H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (d, *J* 259 Hz), 153.0, 152.5, 137.6, 131.8, 127.3 (d, *J* 8.3 Hz), 124.5, 124.1, 123.0, 122.8, 115.4 (d, *J* 21.4 Hz), 81.7, 81.2, 60.7, 49.3, 28.1, 27.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.4.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{29}FN_2O_4Na$: 451.2004; found: 451.2012.

Resolution between the enantiomers of the carbamate **4b** was achieved using a Beckman system fitted with a Lux Cellulose-4 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.2:0.8 v/v) as the mobile phase at a flow rate of 0.5 $mL{\cdot}min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 µL of the sample in a 2 $g{\cdot}L^{-1}$ solution of the eluent. The components were eluted at 18.7 min and 23.0 min.

***(R)*-1,4-di-*tert*-Butyl 2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoxaline-1,4-dicarboxylate 4b** and ***tert*-Butyl *N*-{2-[(*tert*-Butoxycarbonyl)(ethoxycarbonyl)amino]phenyl}-*N*-[1-(4-fluorophenyl)ethenyl]carbamate 5b**

In the same way as (*R*)-**1a**, *n*-BuLi (0.09 mL, 0.21 mmol, 2.3 M in hexanes), (+)-sparteine (70 mg, 0.3 mmol), racemic carbamate **4b** (100 mg, 0.23 mmol), and ethyl chloroformate (0.06 mL, 0.72 mmol, added after 60 min) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*R*)-**4b** (48 mg, 48%) as needles; mp 179–181 °C; data as above; the enantiomeric ratio was determined to be 96:4 by CSP-HPLC (major component eluted at 18.7 min); $[\alpha]_D^{21}$ –19.2 (1.3, $CHCl_3$).

The carbonate **5b** (50 mg, 43%) as an oil was also isolated:

IR (neat): 3073, 2992, 2916, 1793, 1750, 1695, 1540, 1218, 842 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.45 (m, 2H), 7.40–7.35 (m, 2H), 7.35–7.25 (m, 2H), 7.10–7.01 (m, 2H), 5.09 (s, 1H), 4.38 (s, 1H), 4.28–3.99 (m, 2H), 1.40 (s, 9H), 1.19 (s, 9H), 0.97–0.87 (m 3H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 163.0 (d, *J* = 259 Hz), 153.1, 152.6, 151.1, 147.2, 140.3, 134.8, 130.9, 129.3, 128.0, 127.5 (d, *J* = 8.1 Hz), 127.1, 115.0 (d, *J* = 21 Hz), 109.0, 83.1, 81.4, 62.9, 27.8, 27.7, 14.1.

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{33}FN_2O_6Na$: 523.2215; found: 523.2217.

(±)-*tert*-Butyl 7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine-4-carboxylate 6

n-BuLi (6.2 mL, 15 mmol, 2.4 M in hexane) was added to the benzoxazine (±)-**8** (3.32 g, 13.4 mmol) in dry THF (34 mL) at −78 °C. After 40 min, Boc_2O (4.28 g, 19.6 mmol) in dry THF (5 mL) was added and the mixture was allowed to warm to room temperature over 16 h. The mixture was diluted with aqueous 10% sodium hydrogencarbonate solution (20 mL) and was extracted with Et_2O (3 × 50 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2 to 95:5), gave the carbamate **6** (4.2 g, 90%) as an amorphous solid; mp 56–58 °C.

IR (neat): 3007, 2979, 2931, 2880, 1704, 1509, 1492, 1368, 1302, 1260, 1230, 1160, 1090, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.74 (m, 1H), 7.33–7.24 (m, 5H), 6.77–6.68 (m, 1H), 5.69 (t, *J* 3.0 Hz, 1H), 4.79 (dd, *J* 11.0, 3.0 Hz, 1H), 4.41 (dd, *J* 11.0, 3.0 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 146.9 (dd, *J* 244.0, 10.0 Hz), 140.1 (dd, *J* 245.5, 15.5 Hz), 137.7, 136.4 (dd, *J* 10.5, 3.0 Hz), 128.7, 127.7, 126.4, 123.2, 117.2 (dd, *J* 7.0, 4.0 Hz), 107.8 (d, *J* 18.0 Hz), 82.5, 68.6, 53.9, 28.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −142.9 (d, *J* 21.0 Hz, 1F), −159.6 (d, *J* 21.0 Hz, 1F).

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{19}F_2NO_3Na$: 370.1225; found: 370.1225.

Resolution between enantiomers of the carbamate **6** was achieved using a Beckman system fitted with a Lux Cellulose 1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 $mL{\cdot}min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 $g{\cdot}L^{-1}$ solution of the eluent. The components were eluted at 8.3 min and 9.2 min.

***(S)*-*tert*-Butyl 7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine-4-carboxylate 6** and **2-[(*tert*-Butoxycarbonyl)[1-phenylethenyl)amino]-5,6-difluorophenyl ethyl carbonate 7**

In the same way as (*R*)-**1a**, *n*-BuLi (0.24 mL, 0.58 mmol, 2.4 M in hexanes), (–)-sparteine (277 mg, 1.2 mmol), racemic carbamate **6** (335 mg, 0.97 mmol), and ethyl chloroformate (0.20 mL, 2 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), carbamate (*S*)-**6** (164 mg, 49%) as an amorphous solid; mp 50–52 °C; data as above; the enantiomeric ratio was determined to be 85:15 by CSP-HPLC (major component eluted at 8.5 min) and recrystallization (CH_2Cl_2–hexane) gave (*S*)-**6** (38%, er 98:2); $[\alpha]_D^{23}$ +90 (0.3, $CHCl_3$).

The carbonate **7** (202 mg, 50%) as an oil was also isolated:

IR (neat): 2981, 1779, 1714, 1508, 1298, 1249, 1215, 1161, 1008, 775, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, *J* 7.0 Hz, 2H), 7.42–7.30 (m, 3H), 7.16–7.03 (m, 2H), 5.30 (s, 1H), 4.93 (s, 1H), 4.40–4.15 (m, 2H), 1.36–1.17 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.7, 151.2, 149.3 (dd, *J* 249.5, 11.0 Hz), 148.5, 144.2 (dd, *J* 253.0, 15.0 Hz), 138.3, 136.3 (dd, *J* 11.0, 2.5 Hz), 133.0 (d, *J* 3.5 Hz), 128.4, 128.3, 125.8, 122.3 (dd, *J* 7.5, 3.5 Hz), 114.3 (d, *J* 18.0 Hz), 110.4, 81.9, 65.7, 27.6, 13.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −134.0 (d, *J* 21.0 Hz, 1F), −159.6 (d, *J* 21.0 Hz, 1F).

HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{23}F_2NO_5Na$: 442.1437; found: 442.1447.

(±)-7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine 8

2-Bromoacetophenone (4.84 g, 24.3 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of 6-amino-2,3-difluorophenol (3.49 g, 24.0 mmol), Bu_4NHSO_4 (277 mg, 0.814 mmol) and potassium carbonate (19.0 g, 138 mmol) in water (140 mL) and CH_2Cl_2 (140 mL). After 16 h, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The solvent was evaporated and the crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the imine (4.5 g, 76%) as an amorphous solid; mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–7.90 (m, 2H), 7.59–7.47 (m, 3H), 7.20 (ddd, *J* 8.5, 5.5, 2.0 Hz, 1H), 6.83 (ddd, *J* 10.0, 8.5, 7.5 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 158.2, 150.4 (dd, *J* 248.5, 10.5 Hz), 139.5 (dd, *J* 250.5, 16.0 Hz), 134.9, 131.6, 131.1 (dd, *J* 4.0, 2.0 Hz), 128.9, 126.4, 122.1 (dd, *J* 8.0, 3.5 Hz), 109.1 (d, *J* 18.5 Hz), 62.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −135.7 (d, *J* 20.0 Hz, 1F), −160.5 (d, *J* 20.0 Hz, 1F); HRMS (ES): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{23}F_2NO_5Na$: 442.1437; found: 442.1447. $NaBH_4$ (1.21 g, 31.9 mmol) was added to the imine (3.59 g, 14.4 mmol) in ethanol (50 mL) and water (13 mL) and the mixture was heated at 90 °C for 3 h. After cooling to room temperature, CH_2Cl_2 (100 mL) and H_2O (100 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the solvent was evaporated to give the benzoxazine **8** (3.4 g, 93%) as an amorphous solid; mp 54–56 °C.

IR (neat): 3369, 3064, 3029, 2956, 2921, 2851, 1612, 1500, 1324, 1255, 1223, 1055, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.35 (m, 5H), 6.63 (dt, *J* 9.0, 8.0 Hz, 1H), 6.37 (ddd, *J* 9.0, 5.0, 2.0 Hz, 1H), 4.50 (dd, *J* 9.0, 1.5 Hz, 1H), 4.44–4.37 (m, 1H), 4.11–3.94 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, one C could not be observed) δ = 144.5 (dd, *J* 237.5, 10.5 Hz), 140.7 (dd, *J* 244.5, 15.5 Hz), 138.2, 131.5 (dd, *J* 6.0, 3.5 Hz), 129.0, 128.7, 127.2, 108.4 (dd, *J* 7.5, 4.0 Hz), 108.0 (d, *J* 18.5 Hz), 71.2, 53.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −149.7 (d, *J* 21.0 Hz, 1F), −160.4 (d, *J* 21.0 Hz, 1F).

HRMS (ES): *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}F_2NO$: 248.0881; found: 248.0887.

Resolution between enantiomers of the amine **8** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. The components were eluted at 18.2 min and 20.8 min.

(*S*)-7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine 8

Trifluoroacetic acid (0.72 mL, 9.4 mmol) was added to the carbamate (*S*)-**6** (164 mg, 0.47 mmol, er 98:2) in CH_2Cl_2 (10 mL) at room temperature. After 24 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (96:4), gave the amine (*S*)-**8** (103 mg, 88%) as an amorphous solid; data as above; the enantiomeric ratio was determined to be 95:5 by CSP-HPLC (major component eluted at 18.7 min and minor at 21.2 min); $[\alpha]_D^{23}$ +110 (0.1, $CHCl_3$).

***(S)*-1,3-Diethyl 2-[(7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benoxazin-4-yl)methylidene]propanedioate 9**

Diethyl ethoxymethylenemalonate (268 mg, 1.24 mmol) was added to amine (*S*)-**8** (153 mg, 0.62 mmol, er 93:7) and the mixture was heated at 140 °C. After 26 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by recrystallization from hexane–CH_2Cl_2, gave the diester intermediate (255 mg, 98%) as an oil; (racemic compound was an amorphous solid, mp 108–110 °C); $[\alpha]_D^{23}$ +60 (0.2, $CHCl_3$);

IR (neat): 3037, 2986, 1723, 1594, 1564, 1480, 1304, 1250, 1170, 1084, 798, 699, 534 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.37–7.25 (m, 3H), 7.15–7.13 (m, 2H), 7.01–6.96 (m, 1H), 6.89–6.82 (m, 1H), 5.31 (br s, 1H), 4.71 (dd, *J* 11.0, 1.5 Hz, 1H), 4.39 (dd, *J* 11.0, 1.5 Hz, 1H), 4.33–4.16 (m, 2H), 3.98 (dq, *J* 11.0, 7.0 Hz, 1H), 3.37 (dq, *J* 11.0, 7.0 Hz, 1H), 1.28 (t, *J* 7.0 Hz, 3H), 0.93 (t, *J* 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.6, 166.2, 147.6 (dd, *J* 245.0, 10.5 Hz), 142.2, 140.4 (dd, *J* 248.5, 15.5 Hz), 136.1 (dd, *J* 11.5, 3.0 Hz), 135.7, 128.8, 128.1, 126.2, 126.1, 111.4 (dd, *J* 7.5 and 4.0 Hz), 109.1 (d, *J* 19.0 Hz), 103.1, 69.3, 61.4, 61.0, 57.3, 14.3, 13.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ = −141.4 (d, *J* 20.5 Hz, 1F), −157.5 (d, *J* 20.5 Hz, 1F).

HRMS (ES): *m/z* [M + H]$^+$ calcd for $C_{22}H_{22}F_2NO_5$: 418.1461; found: 418.1475.

(*S*)-Ethyl 6,7-Difluoro-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5(13),6,8,11-tetraene-11-carboxylate 10

Poly(phosphoric acid) (2.39 g, 24.5 mmol) was added to diester (*S*)-**9** (255 mg, 0.61 mmol) and the mixture was heated at 140 °C for 4 h. After cooling to room temperature, H_2O (10 mL) was added and the mixture was filtered to collect the crude product that was washed with H_2O to give ketone (*S*)-**10** (169 mg, 74%) as an amorphous solid; mp 190–192 °C, that was insufficiently soluble to obtain specific rotation, ^{1}H or ^{13}C NMR spectra.

IR (neat): 1725, 1595, 1565, 1483, 1305, 1252, 1172, 1086, 799, 751, 700 cm^{-1}.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −138.6 (d, *J* 22.8 Hz, 1F), −153.6 (d, *J* 22.8 Hz, 1F).

HRMS (ES): *m/z* [M + H]$^+$ calcd for $C_{20}H_{16}F_2NO_4$: 372.1042; found: 372.1053.

(*S*)-7-Fluoro-6-(4-methylpiperazinyl)-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5(13),6,8,11-tetraene-11-carboxylic acid 11

Aqueous HCl (1 mL, 12 M) and glacial acetic acid (2 mL) were added to the ketone (*S*)-**10** (169 mg, 0.46 mmol) in H_2O (1 mL) and the mixture was heated at 90 °C for 16 h. The mixture was cooled to 0 °C for 1 h and was filtered. The crude product was washed with H_2O to give the difluoro-carboxylic acid intermediate (140 mg, 89%) as an amorphous solid; mp 274–276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 14.7 (s, 1H), 8.94 (s, 1H), 8.01–7.79 (m, 1H), 7.45–7.36 (m, 3H), 7.23–7.14 (m, 2H), 6.17 (br s, 1H), 5.02 (br d, *J* 11.5 Hz, 1H), 4.81 (br d, *J* 11.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.1, 165.9, 149.4 (dd, *J* 249.0, 11.5 Hz), 148.0, 142.2 (dd, *J* 253.0, 17.0 Hz), 136.7 (dd, *J* 11.5, 3.0 Hz), 136.5, 129.6, 129.3, 127.1, 126.9, 121.7 (dd, *J* 8.0, 2.0 Hz), 108.6, 104.5 (d, *J* 19.5 Hz), 69.7, 61.7, ^{19}F NMR (376 MHz, DMSO-d_6) δ = −135.6 (d, *J* 22.5 Hz, 1F), −150.6 (d, *J* 22.5 Hz, 1F); HRMS (ES): *m/z* [M + H]$^+$ calcd for $C_{18}H_{12}F_2NO_4$: 344.0729; found: 344.0730. 1-Methylpiperazine (0.75 mL, 6.8 mmol) was added to the difluoro-carboxylic acid intermediate (140 mg, 0.41 mmol) in Et_3N (0.3 mL) and MeCN (0.3 mL) and the mixture was heated at 90 °C for 24 h. The mixture was cooled to room temperature and was filtered. The crude product was washed with MeOH to give the amine (*S*)-**11** (34 mg, 20%) as

an amorphous solid; mp (dec.) 252–254 °C, lit.[22] mp 252–253 °C; $[\alpha]_D^{23}$ –68 (0.2, DMSO).

IR (neat): 3064, 3032, 2924, 2852, 2793, 1724, 1619, 1520, 1448, 1374, 1291, 1238, 1089, 1005, 805, 744, 699, 449 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6) δ = 8.80 (s, 1H), 7.66 (d, *J* 12.5 Hz, 1H), 7.44–7.34 (m, 3H), 7.17–7.10 (m, 2H), 6.06 (br s, 1H), 4.88 (br d, *J* 11.5 Hz, 1H), 4.68 (br d, *J* 11.5 Hz, 1H), 3.26–3.21 (m, 4H), 2.43–2.33 (m, 4H), 2.20 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.1, 166.3, 155.9 (d, *J* 246.5 Hz), 147.2, 140.8, 137.3, 132.7, 129.6, 129.1, 127.0, 126.6, 119.8 (d, *J* 10.0 Hz), 107.5, 104.1 (d, *J* 24.0 Hz), 68.9, 61.6, 55.6, 50.5, 46.5.

^{19}F NMR (377 MHz, DMSO-d_6) δ = –120.0 (s, 1F).

HRMS (ES): *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}FN_3O_4$: 424.1667; found: 424.1674.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/XXXX

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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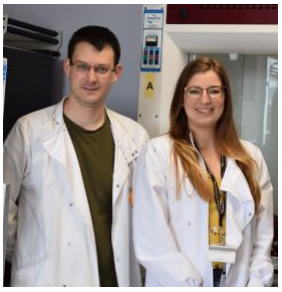
Biosketches

From left to right:
Joshua Priest obtained his Masters degree from the University of Loughborough (UK) in 2012 and his PhD from the University of Birmingham (UK) in 2017 under the supervision of Dr Paul Davies. He carried out postdoctoral research in the group of Prof. Coldham at the University of Sheffield (UK) from 2018–2019.
Soneni Ndlovu obtained her Masters degree from the University of Sheffield (UK) in 2020. She is now working towards her PhD under the supervision of Prof. Paul Wright at the University of St Andrews (UK).
Jennifer Yeo obtained her Masters degree from the University of Sheffield (UK) in 2018. She continued her research in the group of Prof. Coldham in Sheffield and is working towards her PhD.
Anthony Choi obtained his PhD in the group of Prof. Coldham at the University of Sheffield (UK) in 2019. He is currently a postdoctoral research associate in Sheffield that includes a collaboration with Liverpool ChiroChem.
Iain Coldham obtained his PhD from the University of Cambridge (UK) in 1989 working under the supervision of Dr Stuart Warren. After postdoctoral research in the USA with Prof. Phil Magnus, he returned to the UK to a Lectureship at the University of Exeter. He moved to the University of Sheffield (UK) in 2003 and was promoted to Professor in 2008.
Ashraf El-Tunsi obtained his Masters degree from the University of Benghazi (Libya) in 2008 and his PhD from the University of Sheffield (UK) in 2020.

Nick Carter obtained his PhD from the University of Sheffield (UK) in 2017 working under the supervision of Prof. Coldham. He moved to Manchester Metropolitan University (UK) for a postdoctoral position under the supervision of Dr Macia Ruiz, followed by work as a Technical Specialist at Nottingham Trent University (UK).



From left to right:
Andrew Fenton completed his PhD studies at the University of Nottingham (UK) under the supervision of Prof. Liz Sockett. After this, he worked at the Centre for Bacterial Cell Biology in Newcastle (UK) before working at Harvard Medical School (USA) under the supervision of Prof. Tom Bernhardt and Prof. David Rudner. Currently, he leads a research group studying cell wall biology, host-pathogen interactions and antimicrobial resistance in *Streptococcus pneumoniae* at the Florey Institute within the University of Sheffield (UK).
Carolin Kobras received her PhD in microbiology from the University of Bath (UK) in 2019. She then joined the group of Dr Andrew Fenton at the University of Sheffield (UK) as postdoctoral research associate to investigate antimicrobial resistance in the human pathogen *Streptococcus pneumoniae*.

Ilaria Proietti Silvestri is Head of R&D at Liverpool ChiroChem (LCC). She did doctoral work at Sapienza University of Rome and had postdoctoral research fellowships at the University of Copenhagen and at Politecnico of Milan. In 2015 Ilaria moved to the UK to join RedX Pharma and in 2017 she joined LCC, where she is currently leading the R&D team investigating the design and synthesis of novel 3D-rich *N*-heterocycles specifically designed for leading applications in drug discovery.