Electronic Supplementary Information

Phase-transfer-catalysed Asymmetric Synthesis of 2,2-Disubstituted 1,4-Benzoxazin-3-ones

Martin Pawliczek^a, Yuto Shimazaki^a, Hidenori Kimura^a, Kevin M. Oberg^a, Saman Zakpur^a, Takuya Hashimoto^{a†}, and Keiji Maruoka^{*a,b}

^a Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, (Japan).

^b School of Chemical Engineering and Light Industry, Guangdong University of Technology, Panyu District, Guangzhou, 510006 (China)

⁺ Present address: Department of Chemistry, Graduate School of Science, Chiba University, 1-33 Yayoi, Inage, Chiba, 263-8522 (Japan).

Table of Contents

General Information	2
Substrate Synthesis	3
Phase-transfer catalysis	17
Deprotection	33
Determination of the Absolute Configuration of 5ha	34
NMR Spectra	35
HPLC	87

General Information

Infrared (IR) spectra were recorded on a ThermoFischer Scientific NICOLET iS5 spectrometer. ¹H NMR spectra were measured on JEOL JNM-FX400 (400 MHz) and JNM-ECA500 (500 MHz) spectrometers. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard or from the residual solvent in in CDCl₃ or acetone-d₆, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and assignment. ¹³C NMR spectra were measured on JEOL JNM-FX400 (100 MHz) and JNM-ECA500 (125 MHz) spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 210 nm using 4.6 mm x 25 cm Daicel chiral columns. Highresolution mass spectra (HRMS) were performed on Thermo Scientific Exactive Plus Orbitrap LC-MS. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used. The products were purified by flash column chromatography silica gel 60 (Merck, 230-400 mesh) or preparative thin layer chromatography silica gel (PLC 60 F₂₅₄. 0.5 mm).

In experiments requiring dry solvent, CH₂Cl₂, toluene and THF were purchased from Kanto Chemical Co. Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. Commercially obtained reagents were used as received.

References

- ^a M. Hori, T. Kataoka, H. Shimizu, N. Ueda, *Tetrahedron Lett.*, **1981**, 22, 1701.
- ^b J. Perron, B. Joseph, J.-Y. Mérour, *Eur. J. Org. Chem.*, **2004**, 4606.

Substrate Synthesis

General Procedure 1 (GP1: benzoxazinone synthesis)



A mixture of ester (1.00 eq.) and Fe (4.00 eq.) in EtOH/AcOH (1:1, 0.4 M each) was stirred for 2 h at 70 °C under argon atmosphere. Afterwards, the reaction was allowed to cool down to room temperature, was diluted with EtOAc and aq. NaHCO₃-sol. was added. The phases were separated, the aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine. After drying over Na₂SO₄ the solvent was removed *in vacuo* and the resulting solid was used without further purification in next step.

The crude benzoxazinone and DMAP (10 mol%) were dissolved in MeCN and the resulting solution was cooled down to 0 °C. Boc₂O (0.80 - 1.20 eq.) was added and the reaction was stirred for 16 h at room temperature. Aq. NH₄Cl-sol. was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The resulting crude product was purified by column chromatography on silica gel.

Substrate Synthesis

Methyl 2-(4-methoxyphenyl)-2-(2-nitrophenoxy)acetate (7b)

OMe MeO₂C

To a mixture of 2-nitrophenol (189 mg, 1.36 mmol) and K_2CO_3 (563 mg, 4.08 mmol) in acetone (13 mL) was added methyl 2-bromo-2-(4-methoxyphenyl)acetate (389 mg, 1.50 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel

(hex:EtOAc = $3:1 \rightarrow 1:1$) to yield the title compound **7b** (352 mg, 1.11μ mol, 82%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.88 (dd, *J* = 8.1, 1.7, 1 H), 7.55 – 7.50 (m, 2 H), 7.47 (ddd, *J* = 8.4, 7.5, 1.7, 1 H), 7.11 – 7.05 (m, 1 H), 6.98 (dd, *J* = 8.4, 0.8, 1 H), 6.95 – 6.90 (m, 2 H), 5.71 (s, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.7, 160.7, 150.8, 141.0, 134.1, 128.7, 126.4, 126.1, 121.9, 116.2, 114.5, 79.7, 55.4, 52.9 ppm. IR (neat): 2955, 1751, 1605, 1512, 1350, 1244, 1030, 743 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₆H₁₅NNaO₆: *m/z* 340.0792 ([M + Na]⁺), found: *m/z* 340.0798 ([M + Na]⁺).

Methyl 2-(4-chlorophenyl)-2-(2-nitrophenoxy)acetate (7c)

MeO₂C

To a mixture of 2-nitrophenol (303 mg, 2.20 mmol) and K_2CO_3 (911 mg, 6.60 mmol) in acetone (15 mL) was added methyl 2-bromo-2-(4-chlorophenyl)acetate (631 mg, 2.40 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 4:1 \rightarrow 3:1) to yield the title compound **7c** (535 mg, 1.66 mmol, 76%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.93 – 7.87 (m, 1 H), 7.60 – 7.55 (m, 2 H), 7.54 – 7.46 (m, 1 H), 7.43 – 7.36 (m, 2 H), 7.15 – 7.08 (m, 1 H), 6.98 (d, *J* = 8.4, 1 H), 5.74 (s, 1 H), 3.73 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.1, 150.6, 140.9, 135.6, 134.2, 132.9, 129.3, 128.6, 126.3, 122.3, 116.0, 79.3, 53.1 ppm. IR (neat): 2955, 1754, 1605, 1524, 1350, 1212, 1172, 772 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂NNaO₅: *m/z* 344.0296 ([M + Na]⁺), found: *m/z* 344.0302 ([M + Na]⁺).

Methyl 2-(4-fluorophenyl)-2-(2-nitrophenoxy)acetate (7d)



To a mixture of 2-nitrophenol (189 mg, 1.36 mmol) and K₂CO₃ (563 mg, 4.08 mmol) in acetone (13 mL) was added methyl 2-bromo-2-(4-fluorophenyl)acetate (371 mg, 1.50 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 4:1→2:1) to yield the title compound **7d** (297 mg, 974 µmol, 72%) as pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ = 7.89 (dd, *J* = 8.1, 1.7, 1 H), 7.64 – 7.57 (m, 2 H), 7.49 (ddd, *J* = 8.4, 7.5, 1.7, 1 H), 7.13 – 7.06 (m, 3 H), 6.98 (dd, *J* = 8.4, 0.8, 1 H), 5.74 (s, 1 H), 3.72 (s, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ = 169.2 (d, *J* = 1.5), 163.3 (d, *J* = 248.6), 150.5, 140.8, 134.2, 130.1 (d, *J* = 3.4), 129.0 (d, *J* = 8.5), 126.2, 122.1, 116.0 (d, *J* = 21.9), 115.8, 79.2, 53.0 ppm. ¹⁹F NMR (466 MHz, CDCl₃) δ = -111.79 (tt, *J* = 8.5, 5.2) ppm. IR (neat): 2957, 1755, 1606, 1526, 1509, 1226, 841 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂FNNaO₅: *m/z* 328.0592 ([M + Na]⁺), found: *m/z* 328.0601 ([M + Na]⁺).

Methyl 2-(4-bromophenyl)-2-(2-nitrophenoxy)acetate (7e)

To a mixture of 2-nitrophenol (189 mg, 1.36 mmol) and K₂CO₃ (563 mg, 4.08 mmol) in acetone (13 mL) was added methyl 2-bromo-2-(4-bromophenyl)acetate (462 mg, 1.50 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 4:1→2:1) to yield the title compound **7e** (378 mg, 1.03 µmol, 76%) as yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.90 (dd, *J* = 8.1, 1.7, 1 H), 7.57 – 7.47 (m, 5 H), 7.15 – 7.07 (m, 1 H), 6.98 (dd, *J* = 8.4, 1.0, 1 H), 5.72 (s, 1 H), 3.72 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.1, 150.5, 140.9, 134.2, 133.4, 132.3, 128.8, 126.3, 123.8, 122.3, 116.0, 79.3, 53.1 ppm. IR (neat): 2954, 1753, 1523, 1348, 1071, 1011, 770 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂BrNNaO₅: *m/z* 387.9791 ([M + Na]⁺), found: *m/z* 387.9798 ([M + Na]⁺).

Methyl 2-(3-chlorophenyl)-2-(2-nitrophenoxy)acetate (7f)

To a mixture of 2-nitrophenol (303 mg, 2.20 mmol) and K_2CO_3 (911 mg, 6.60 mmol) in acetone (15 mL) was added methyl 2-bromo-2-(3-chlorophenyl)acetate (631 mg, 2.40 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 4:1→2:1) to yield the title compound **7f** (563 mg, 1.75 mmol, 80%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.91 (d, *J* = 8.1, 1 H), 7.62 (s, 1 H), 7.58 – 7.47 (m, 2 H), 7.40 – 7.34 (m, 2 H), 7.12 (t, *J* = 7.8, 1 H), 6.98 (d, *J* = 8.4, 1 H), 5.73 (s, 1 H), 3.74 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.0, 150.5, 140.9, 136.2, 135.0, 134.3, 130.4, 129.7, 127.3, 126.3, 125.3, 122.3, 116.0, 79.3, 53.2 ppm. IR (neat): 2955, 1754, 1605, 1586, 1523, 1350, 1168, 773 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂NNaO₅: *m/z* 344.0296 ([M + Na]⁺), found: *m/z* 344.0304 ([M + Na]⁺).

Methyl 2-(2-nitrophenoxy)-2-(p-tolyl)acetate (7g)

MeO₂C

To a solution of 2-nitrophenol (757 mg, 5.45 mmol), methyl 2-hydroxy-2-(p-tolyl)acetate (891 mg, 4.95 mmol) and PPh₃ (1.56 g, 5.94 mmol) in CH₂Cl₂ (25 mL) was added DIAD (1.19 g,

5.94 mmol) via syringe pump at 0 °C and stirred for additional 16 h at room temperature. The reaction was quenched with aq. sat. NH₄Cl and the phases were separated. The aqueous phase was extracted with CH₂Cl₂, the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = $6:1\rightarrow4:1$) to yield the title compound **7g** (1.43 mg, 4.75 mmol, 96%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.54 – 7.49 (m, 2 H), 7.42 – 7.35 (m, 3 H), 7.24 (t, *J* = 8.1, 1 H), 6.90 (d, *J* = 7.7, 1 H), 6.77 (d, *J* = 8.2, 1 H), 5.69 (s, 1 H), 3.72 (s, 3 H), 2.33 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.5, 148.8, 143.0, 134.4, 131.8, 130.7, 129.5, 129.1, 127.1, 124.2, 112.1, 79.6, 52.9, 17.2 ppm. IR (neat): 2955, 1756, 1583, 1530, 1267, 1097, 774 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₆H₁₅NNaO₅: *m/z* 324.0842 ([M + Na]⁺), found: *m/z* 324.0849 ([M + Na]⁺).

Methyl 2-(naphthalen-2-yl)-2-(2-nitrophenoxy)acetate (7h)



To a mixture of 2-nitrophenol (303 mg, 2.20 mmol) and K₂CO₃ (911 mg, 6.60 mmol) in acetone (15 mL) was added methyl 2-bromo-2-(naphthalen-2-yl)acetate (670 mg, 2.40 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 4:1 \rightarrow 3:1) to yield the title compound **7h** (587 mg, 1.74 mmol, 79%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 8.09 (s, 1 H), 7.93 – 7.82 (m, 4 H), 7.72 (dd, *J* = 8.6, 1.8, 1 H), 7.55 – 7.43 (m, 3 H), 7.12 – 7.06 (m, 1 H), 7.03 (dd, *J*=8.4, 1.0, 1 H), 5.92 (s, 1 H), 3.73 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.4, 150.8, 141.1, 134.2, 133.9, 133.3, 131.7, 129.1, 128.5, 128.0, 127.0, 127.0, 126.8, 126.2, 124.2, 122.1, 116.3, 80.3, 53.0 ppm. IR (neat): 2955, 1754, 1605, 1525, 1350, 1279, 1172, 1055, 744 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₅NNaO₅: *m/z* 360.0842 ([M + Na]⁺), found: *m/z* 360.0848 ([M + Na]⁺). Methyl 2-(4-methyl-2-nitrophenoxy)-2-phenylacetate (7j)

To a solution of 4-methyl-2-nitrophenol (151 mg, 1.00 mmol), methyl 2-hydroxy-2phenylacetate (183 mg, 1.10 mmol) and PPh₃ (315 mg, 1.20 mmol) in CH₂Cl₂ (10 mL) was added DIAD (242 mg, 1.2 mmol) *via* syringe pump at 0 °C and stirred for additional 16 h at room temperature. The reaction was quenched with aq. sat. NH₄Cl and the phases were separated. The aqueous phase was extracted with CH₂Cl₂, the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = $6:1\rightarrow4:1$) to yield the title compound **7**j (275 mg, 914 µmol, 91%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.70 (d, *J* = 2.1, 1 H), 7.65 – 7.58 (m, 2 H), 7.45 – 7.36 (m, 3 H), 7.30 – 7.24 (m, 1 H), 6.89 (d, *J* = 8.5, 1 H), 5.72 (s, 1 H), 3.71 (s, 3 H), 2.34 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.6, 148.6, 140.8, 134.7, 134.5, 132.2, 129.4, 129.0, 127.2, 126.2, 116.4, 80.3, 52.8, 20.3 ppm. IR (neat): 2955, 1755, 1530, 1354, 1282, 1213, 731 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₆H₁₅NNaO₅: *m/z* 324.0842 ([M + Na]⁺), found: *m/z* 324.0850 ([M + Na]⁺).

Methyl 2-(4-methoxy-2-nitrophenoxy)-2-phenylacetate (7j)

MeO₂C MeO

To a mixture of 4-fluoro-2-nitrophenol (33.8 mg, 200 μ mol) and K₂CO₃ (82.9 mg, 600 μ mol) in acetone (2 mL) was added methyl 2-bromo-2-phenylacetate (50.4 mg, 220 μ mol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 2:1) to yield the title compound **7**j (57.8 mg, 182 μ mol, 96%) as yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.59 (m, 2 H), 7.44 – 7.35 (m, 4 H), 7.02 (dd, *J* = 9.2, 3.1, 1 H), 6.95 (d, *J* = 9.1, 1 H), 5.66 (s, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.7, 154.5, 144.7, 141.5, 134.7, 129.4, 129.0, 127.4, 120.6, 119.1, 110.4, 81.3, 56.1, 52.8 ppm. IR (neat): 2923, 1751, 1529, 1496, 1353, 1353, 1213, 1033, 792 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₆H₁₅NNaO₆: *m/z* 340.0792 ([M + Na]⁺), found: *m/z* 340.0799 ([M + Na]⁺).

Methyl 2-(4-bromo-2-nitrophenoxy)-2-phenylacetate (7k)

To a solution of 4-bromo-2-nitrophenol (218 mg, 1.00 mmol), methyl 2-hydroxy-2phenylacetate (183 mg, 1.10 mmol) and PPh₃ (315 mg, 1.20 mmol) in CH₂Cl₂ (10 mL) was added DIAD (242 mg, 1.2 mmol) *via* syringe pump at 0 °C and stirred for additional 16 h at room temperature. The reaction was quenched with aq. sat. NH₄Cl and the phases were separated. The aqueous phase was extracted with CH₂Cl₂, the combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 6:1→4:1) to yield the title compound **7k** (344 mg, 942 µmol, 94%) as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.90 (dd, *J* = 8.1, 1.7, 1 H), 7.58 – 7.47 (m, 5 H), 7.15 – 7.08 (m, 1 H), 6.98 (dd, *J* = 8.4, 1.0, 1 H), 5.72 (s, 1 H), 3.72 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 169.1, 149.9, 141.4, 136.9, 134.0, 129.7, 129.2, 128.9, 127.2, 117.9, 113.8, 80.3, 53.1 ppm. IR (neat): 2953, 1754, 1603, 1530, 1481, 1351, 1278, 1104, 735 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂BrNNaO₆: *m/z* 387.9791 ([M + Na]⁺), found: *m/z* 387.9798 ([M + Na]⁺).

Methyl 2-(4-fluoro-2-nitrophenoxy)-2-phenylacetate (7I)

MeO₂C _

To a mixture of 4-fluoro-2-nitrophenol (157 mg, 1.00 mmol) and K₂CO₃ (415 mg, 3.00 mmol) in acetone (10 mL) was added methyl 2-bromo-2-phenylacetate (252 mg, 1.10 mmol) at room temperature and the resulting mixture was stirred for additional 16 h at 50 °C. After cooling back to room temperature aq. sat. NH₄Cl was added and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hex:EtOAc = 5:1) to yield the title compound **7l** (287 mg, 941 µmol, 94%) as yellow oil. ¹H NMR (495 MHz, CDCl₃) δ = 7.64 (dd, *J* = 7.7, 3.1, 1 H), 7.60 – 7.57 (m, 2 H), 7.44 – 7.38 (m, 3 H), 7.21 (ddd, *J* = 9.2, 7.2, 3.2, 1 H), 6.99 (dd, *J* = 9.2, 4.3, 1 H), 5.69 (s, 1 H), 3.72 (s, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ = 169.2, 156.4 (d, *J* = 246.1), 147.1 (d, *J* = 3.1), 140.9 (d, *J* = 9.9), 134.1, 129.6, 129.0, 127.2, 121.0 (d, *J* = 23.0), 118.3 (d, *J* = 7.9), 113.4 (d, *J* = 27.5), 80.8, 53.0 ppm. ¹⁹F NMR (466 MHz, CDCl₃) δ = -117.99 (td, *J* = 7.4, 4.3) ppm. IR (neat): 3078, 1751, 1531, 1495, 1356, 1270, 1200, 1047, 797 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₅H₁₂FNNaO₅: *m/z* 328.0592 ([M + Na]⁺), found: *m/z* 328.0597 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(4-methoxyphenyl)-1,4-benzoxazin-3-one 4b



Ester **7b** (296 mg, 932 µmol), Fe (208 mg, 3.73 mmol) in EtOH/AcOH (2.3 mL/2.3 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (244 mg, 1.12 mmol) and DMAP (11.4 mg, 93.2 µmol) in MeCN (9 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = $8:1 \rightarrow 6:1$) to obtain the title compound **4b** (207 mg, 582 µmol, 72%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.35 – 7.30 (m, 2 H), 7.10 – 7.06 (m, 1 H), 7.06 – 6.98 (m, 3 H), 6.89 – 6.84 (m, 2 H), 5.56 (s, 1 H), 3.78 (s, 3 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.4, 160.3, 150.2, 144.2, 128.9, 126.4, 126.2, 125.4, 122.9, 118.3, 117.6, 114.3, 86.0, 78.9, 55.3, 27.8 ppm. IR (neat): 2980, 1752, 1707, 1514, 1247, 1146, 1033 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₀H₂₁NNaO₅: *m/z* 378.1312 ([M + Na]⁺), found: *m/z* 378.1317 ([M + Na]⁺). *N-t*-Butoxycarbonyl-2-(4-chlorophenyl)-1,4-benzoxazin-3-one 4c



Ester **7c** (508 mg, 1.58 mmol), Fe (353 mg, 6.32 mmol) in EtOH/AcOH (4 mL/4 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (284 mg, 1.30 mmol) and DMAP (19.3 mg, 158 μ mol) in MeCN (15 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 8:1 \rightarrow 6:1) to obtain the title compound **4c** (431 mg, 1.19 mmol, 76%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.29 (m, 4 H), 7.11 – 6.98 (m, 4 H), 5.57 (s, 1 H), 1.61 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 163.8, 150.0, 144.0, 135.2, 132.7, 129.1, 128.8, 126.2, 125.6, 123.3, 118.2, 117.8, 86.3, 78.6, 27.8 ppm. IR (neat): 2982, 1750, 1706, 1497, 1247, 1145, 752 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈ClNNaO₄: *m/z* 382.0817 ([M + Na]⁺), found: *m/z* 382.0819 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(4-fluorophenyl)-1,4-benzoxazin-3-one 4d



Ester **7d** (264 mg, 866 μ mol), Fe (193 mg, 3.46 mmol) in EtOH/AcOH (2.2 mL/2.2 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (227 mg, 1.04 mmol) and DMAP (10.6 mg, 86.6 μ mol) in MeCN (9 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 10:1 \rightarrow 8:1) to obtain the title compound **4d** (214 mg, 623 μ mol, 72%) as a pale yellow solid.

¹H NMR (500 MHz, CDCl₃) δ = 7.42 – 7.37 (m, 2 H), 7.11 – 7.08 (m, 1 H), 7.08 – 6.99 (m, 5 H), 5.57 (s, 1 H), 1.63 (s, 9 H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ = 163.9, 163.1 (d, *J* = 248.1), 150.0, 144.0, 129.9 (d, *J* = 3.5), 129.3 (d, *J* = 8.6), 126.2, 125.5, 123.1, 118.2, 117.7, 115.8 (d, *J* = 21.9), 86.2, 78.5, 27.8 ppm. ¹⁹F NMR (466 MHz, CDCl₃) δ = -112.20 – -112.27 (m) ppm. IR (neat): 2982, 1750, 1708, 1510, 1248, 1146, 1042 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈FNNaO₄: *m/z* 366.1112 ([M + Na]⁺), found: *m/z* 366.1120 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(4-bromophenyl)-1,4-benzoxazin-3-one **4e**



Br

Ester **7e** (1.05 mg, 2.87 mmol), Fe (640 mg, 11.5 mmol) in EtOH/AcOH (7 mL/7 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (542 mg, 2.48 mmol) and DMAP (32.1 mg, 287 μ mol) in MeCN (30 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 10:1 \rightarrow 6:1) to obtain the title compound **4e** (951 mg, 2.35 mmol, 82%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.50 – 7.46 (m, 2 H), 7.30 (d, *J* = 8.5, 2 H), 7.10 – 7.00 (m, 4 H), 5.55 (s, 1 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 163.6, 150.0, 143.9, 133.1, 132.0, 129.0, 126.1, 125.6, 123.4, 123.2, 118.2, 117.7, 86.2, 78.5, 27.8 ppm. IR (neat): 2981, 1747, 1705, 1497, 1369, 1244, 1142, 750 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈BrNNaO₄: *m/z* 426.0311 ([M + Na]⁺), found: *m/z* 426.0313 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(3-chlorophenyl)-1,4-benzoxazin-3-one 4f



Ester **7f** (563 mg, 1.75 mmol), Fe (391 mg, 7.0 mmol) in EtOH/AcOH (4.5 mL/4.5 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (343 mg, 1.58 mmol) and DMAP (21.4 mg, 175 μ mol) in MeCN (20 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 8:1 \rightarrow 6:1) to obtain the title compound **4f** (472 mg, 1.31 mmol, 75%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.43 (s, 1 H), 7.32 – 7.23 (m, 3 H), 7.11 – 6.98 (m, 4 H), 5.55 (s, 1 H), 1.61 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 163.5, 149.9, 143.8, 136.1, 134.7,

130.0, 129.2, 127.4, 126.1, 125.6, 125.4, 123.2, 118.1, 117.7, 86.2, 78.3, 27.7 ppm. IR (neat): 2981, 1750, 1705, 1498, 1243, 1142, 750 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈CINNaO₄: *m/z* 382.0817 ([M + Na]⁺), found: *m/z* 382.0823 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(4-methylphenyl)-1,4-benzoxazin-3-one **4g**



Ester **7g** (1.369 g, 4.54 mmol), Fe (1.01 g, 18.2 mmol) in EtOH/AcOH (11 mL/11 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (858 mg, 4.09 mmol) and DMAP (55.4 mg, 454 µmol) in MeCN (40 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = $8:1 \rightarrow 6:1$) to obtain the title compound **4g** (1.10 g, 3.23 mmol, 71%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.28 (d, *J* = 8.1, 2 H), 7.13 (d, *J* = 8.0, 2 H), 7.10 – 6.94 (m, 4 H), 5.56 (s, 1 H), 2.28 (s, 3 H), 1.59 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.2, 150.2, 144.1, 139.0, 131.2, 129.5, 127.2, 126.3, 125.4, 122.9, 118.2, 117.5, 85.9, 79.1, 27.7, 21.1 ppm. IR (neat): 2981, 1749, 1704, 1498, 1243, 1142, 1040, 749 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₀H₂₁NNaO₄: *m/z* 362.1363 ([M + Na]⁺), found: *m/z* 362.1368 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-(2-naphthalenyl)-1,4-benzoxazin-3-one **4h**



Ester **7h** (582 mg, 1.80 mmol), Fe (400 mg, 7.18 mmol) in EtOH/AcOH (4.5 mL/4.5 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (353 mg, 1.62 mmol) and DMAP (22.0 mg, 180 μ mol) in MeCN (20 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 10:1 \rightarrow 8:1) to obtain the title compound **4h** (442 mg, 1.18 mmol, 65%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.88 – 7.78 (m, 4 H), 7.55 (d, *J* = 8.5, 1 H), 7.48 (dd, *J* = 5.8, 3.6, 2 H), 7.13 – 7.07 (m, 2 H), 7.07 – 6.96 (m, 2 H), 5.79 (s, 1 H), 1.64 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.2, 150.2, 144.2, 133.6, 133.1, 131.6, 128.8, 128.5, 127.9, 126.9, 126.8, 126.6, 126.4, 125.5, 124.6, 123.1, 118.3, 117.7, 86.2, 79.3, 27.8. IR (neat): 2981, 1749, 1704, 1498, 1244, 1142, 747 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₃H₂₁NNaO₄: *m/z* 398.1363 ([M + Na]⁺), found: *m/z* 398.1368 ([M + Na]⁺).

N-t-Butoxycarbonyl-6-methyl-2-phenyl-1,4-benzoxazin-3-one 4i



Ester **7I** (690 mg, 2.30 mmol), Fe (513 mg, 9.20 mmol) in EtOH/AcOH (6 mL/6 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (476 mg, 2.19 mmol) and DMAP (28.1 mg, 230 µmol) in MeCN (23 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = $10:1 \rightarrow 1:1$) to obtain the title compound **4i** (645 mg, 1.90 µmol, 93%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.44 – 7.38 (m, 2 H), 7.37 – 7.31 (m, 3 H), 6.94 (d, *J*=8.1, 1 H), 6.89 – 6.81 (m, 2 H), 5.58 (s, 1 H), 2.28 (s, 3 H), 1.63 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.4, 150.3, 142.0, 134.4, 132.7, 129.1, 128.8, 127.4, 126.0, 126.0, 118.1, 117.9, 86.0, 79.2, 27.9, 21.1 ppm. IR (neat): 2981, 1752, 1706, 1509, 1248, 1146, 844 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₀H₂₁NNaO₄: *m/z* 362.1363 ([M + Na]⁺), found: *m/z* 362.1369 ([M + Na]⁺).

N-t-Butoxycarbonyl-6-methoxy-2-phenyl-1,4-benzoxazin-3-one 4j



Ester **7j** (715 mg, 2.26 mmol), Fe (504 mg, 9.03 mmol) in EtOH/AcOH (6 mL/6 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc_2O (468 mg, 2.15 mmol) and (27.6 mg, 226 μ mol) in MeCN (13 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel

(Pentane:EtOAc = $8:1 \rightarrow 6:1$) to obtain the title compound **4j** (586 mg, 1.64 mmol, 73%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.43 – 7.39 (m, 2 H), 7.37 – 7.31 (m, 3 H), 6.97 (d, *J* = 8.8, 1 H), 6.67 (d, *J* = 2.8, 1 H), 6.58 (dd, *J* = 8.8, 2.8, 1 H), 5.56 (s, 1 H), 3.74 (s, 3 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.6, 155.4, 150.1, 138.1, 134.3, 129.1, 128.8, 127.4, 126.9, 118.6, 110.2, 104.0, 86.1, 79.3, 55.9, 27.8 ppm. IR (neat): 2982, 1754, 1708, 1615, 1508, 1250, 1145, 1044 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₀H₂₁NNaO₅: *m/z* 378.1312 ([M + Na]⁺), found: *m/z* 378.1281 ([M + Na]⁺).

N-t-Butoxycarbonyl-6-bromo-2-phenyl-1,4-benzoxazin-3-one 4k



Ester **7k** (509 mg, 1.39 mmol), Fe (310 mg, 5.56 mmol) in EtOH/AcOH (4 mL/4 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O (261 mg, 1.20 mmol) and DMAP (17.0 mg, 139 μ mol) in MeCN (15 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 8:1 \rightarrow 6:1) to obtain the title compound **4k** (438 mg, 1.08 mmol, 78%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.33 (m, 5 H), 7.27 (d, *J* = 2.2, 1 H), 7.15 (dd, *J* = 8.5, 2.2, 1 H), 6.94 (d, *J* = 8.6, 1 H), 5.62 (s, 1 H), 1.63 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 163.8, 149.7, 143.4, 133.7, 129.4, 129.0, 128.3, 127.5, 127.3, 120.9, 119.7, 115.1, 86.7, 79.2, 27.9 ppm. IR (neat): 2982, 1750, 1716, 1491, 1248, 1145, 1004, 699 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈BrNNaO₄: *m/z* 426.0311 ([M + Na]⁺), found: *m/z* 426.0316 ([M + Na]⁺).

N-t-Butoxycarbonyl-6-fluoro-2-phenyl-1,4-benzoxazin-3-one 4I



Ester **7I** (255 mg, 836 μ mol), Fe (187 mg, 3.34 mmol) in EtOH/AcOH (2 mL/2 mL) were reacted as described in the first part of **GP1**. The crude amide was reacted with Boc₂O

(200 mg, 920 μ mol) and DMAP (10.2 mg, 83.6 μ mol) in MeCN (8 mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 8:1 \rightarrow 6:1) to obtain the title compound **4I** (146 mg, 425 μ mol, 51%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.42 – 7.33 (m, 5 H), 7.00 (dd, *J* = 8.9, 5.1, 1 H), 6.91 (dd, *J* = 9.6, 2.8, 1 H), 6.80 – 6.71 (m, 1 H), 5.59 (s, 1 H), 1.63 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.16, 158.2 (d, *J* = 240.8), 149.9, 140.3 (d, *J* = 2.6), 133.9, 129.3, 128.9, 127.4, 127.1 (d, *J* = 10.8), 119.0 (d, *J* = 9.2), 111.8 (d, *J* = 23.5), 105.5 (d, *J* = 29.1), 86.6, 79.3, 27.8 ppm. ¹⁹F NMR (466 MHz, CDCl₃) δ = -118.36 (ddd, *J* = 9.7, 8.0, 5.2) ppm. IR (neat): 2981, 1750, 1711, 1624, 1505, 1250, 1145, 844 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₈FNNaO₄: *m/z* 366.1112 ([M + Na]⁺), found: *m/z* 366.1119 ([M + Na]⁺).

N-t-Butoxycarbonyl-2-phenyl-1,4-benzothiazin-3-one 4m



The corresponding benzothiazinone^{*a*} (768 mg, 3.19 mmol) was reacted with Boc₂O (764 mg, 3.50 μ mol) and DMAP (38.9 mg, 319 μ mol) in MeCN (20mL) as described in the second part of **GP1**. The crude product was purified by column chromatography on silica gel (Pentane:EtOAc = 8:1→6:1) to obtain the title compound **4m** (649 mg, 1.90 μ mol, 60%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.33 (m, 3 H), 7.32 – 7.24 (m, 3 H), 7.21 – 7.16 (m, 1 H), 7.04 (td, *J* = 7.6, 1.1, 1 H), 6.95 (dd, *J* = 8.2, 0.8, 1 H), 4.63 (s, 1 H), 1.61 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 164.9, 152.1, 136.5, 133.6, 128.9, 128.9, 128.5, 128.4, 127.4, 124.9, 122.4, 118.9, 85.9, 47.5, 27.7 ppm. IR (neat): 2981, 1760, 1683, 1477, 1238, 1133, 843 cm⁻¹. HRMS (ESI) exact mass calcd for C₁₉H₁₉NNaO₅S: *m/z* 364.0978 ([M + Na]⁺), found: *m/z* 364.0983 ([M + Na]⁺).

Phase-transfer catalysis





To a degassed test tube equipped with a magnetic stirring bar powdered KOH (11.2 mg, 200 μ mol) was added rapidly. After addition of lactam (100 μ mol) and catalyst **3** (1.9 mg, 2.0 mol%) the test tube was cooled to -25 °C and the components were dissolved in toluene (1 mL) to continue cooling at the same temperature for 1 h. The alkylation agent (250 μ mol) was added in one portion and the reaction mixture was stirred vigorously for the stated period. The reaction mixture was diluted by ethyl acetate and passed through a short pad of silica gel. After evaporation of the solvent, the residue was purified by PLC on silica gel (hexane/acetone or hexane/EtOAc) to yield the title compound.

GP3: General Procedure 3 (Catalysis with K₃PO₄ in mesitylene)

To a degassed test tube equipped with a magnetic stirring bar K_3PO_4 (212 mg, 1.00 mmol) was added. After addition of lactam (32.5 mg, 100 µmol) and catalyst **3** (1.9 mg, 2.0 mol%) the test tube was cooled to -25 °C, mesitylene (1 mL) was added and the cooling was continued for additional 30 min. Benzyl bromide (68.4 mg, 400 µmol) was added in one portion and the reaction mixture was stirred vigorously for the stated period. The reaction mixture was diluted by ethyl acetate and passed through a short pad of silica gel. After evaporation of the solvent, the residue was purified by PLC on silica gel (hexane/EtOAc) to yield the title compound.

Product 5aa

To a degassed test tube equipped with a magnetic stirring bar powdered KOH (11.2 mg, 200 μ mol) was added rapidly. After addition of 1,4-benzoxazin-3-one **4a**^b (32.5 mg, 100 μ mol) and catalyst **PTC** (1.9 mg, 2.0 mol%) the test tube was cooled to -25 °C and the components were dissolved in toluene (1 mL) to continue cooling at the same temperature for 1 h. Benzyl bromide (42.8 mg, 250 μ mol) was added in one portion and the reaction mixture was stirred vigorously for 72 h. The reaction mixture was diluted by ethyl acetate and passed through a short pad of silica gel. After evaporation of the solvent, the residue was purified by PLC on silica gel (hexane/acetone = 10:1.1) to give **5aa** as a colorless oil (32.6 mg, 78.5 μ mol, 79% yield, 96% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.27 – 7.18 (m, 2 H), 7.18 – 7.10 (m, 5 H), 7.09 – 7.00 (m, 4 H), 6.90 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1 H), 6.78 (m, 1 H), 6.73 (dd, *J* = 8.1, 1.6 Hz, 1 H), 3.53 (d, *J* = 14.2 Hz, 1 H), 3.25 (d, *J* = 14.2 Hz, 1 H), 1.48 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.3, 150.4, 143.5, 137.5, 135.3, 131.6, 128.5, 128.4, 127.8, 126.8, 126.1, 126.0, 125.0, 122.6, 118.5, 116.8, 85.8, 84.7, 45.7, 27.8 ppm. IR (neat): 2981, 1759, 1699, 1499, 1370, 1350, 1250, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₅NO₇: *m/z* 438.1676 ([M + Na]⁺), found: *m/z* 438.1680 ([M + Na]⁺). [α]_D²⁵ = +130.5 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 9.9 min (minor) and 11.7 min (major)).

2,2-disubstituted 1,4-benzoxazin-3-one 5ab



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 4-methylbenzyl bromide (46.3 mg, 250 μ mol) over the course of 62 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (34.5 mg, 80 μ mol, 80% yield, 97% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.34 – 7.27 (m, 2 H), 7.25 – 7.14 (m, 3 H), 7.12 – 7.03 (m, 3 H),

7.03 – 6.93 (m, 3 H), 6.88 – 6.83 (m, 2 H), 3.63 (d, J = 14.2 Hz, 1 H), 3.34 (d, J = 14.2 Hz, 1 H), 2.29 (s, 3 H), 1.61 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) $\delta = 165.4$, 150.4, 143.6, 137.6, 136.3, 132.2, 131.4, 128.5, 128.3, 128.3, 126.1, 126.1, 125.0, 122.5, 118.5, 116.8, 85.7, 84.7, 45.4, 27.8, 21.1 ppm. IR (neat): 2981, 1759, 1700, 1499, 1370, 1348, 1280, 1251, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₇H₂₇NO₇: m/z 452.1832 ([M + Na]⁺), found: m/z 452.1837 ([M + Na]⁺). [α]_D^{23.0} = +148.5 (c = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 10.8 min (minor) and 14.8 min (major)).

Product 5ac



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 3-methoxylbenzyl bromide (50.3 mg, 250 μ mol) over the course of 69 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (40.0 mg, 89.8 μ mol, 90% yield, 95% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.32 – 7.26 (m, 2 H), 7.23 – 7.16 (m, 3 H), 7.14 – 7.03 (m, 2 H), 6.97 (m, 1 H), 6.89 – 6.82 (m, 2 H), 6.80 – 6.72 (m, 2 H), 6.69 (m, 1 H), 3.71 (s, 3 H), 3.64 (d, J = 14.1 Hz, 1 H), 3.38 (d, J = 14.1 Hz, 1 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.0, 158.9, 150.1, 143.2, 137.1, 136.5, 128.3, 128.0, 125.8, 125.8, 124.7, 124.7, 123.8, 122.3, 118.2, 116.6, 116.5, 112.4, 85.5, 84.3, 54.9, 45.4, 27.5 ppm. IR (neat): 2981, 1760, 1699, 1600, 1585, 1499, 1449, 1370, 1351, 1250, 1146, 1056 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₇H₂₇NO₅: m/z 468.1781 ([M + Na]⁺), found: m/z 468.1787 ([M + Na]⁺). [α]^{22.0}_D = +139.0 (c = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 13.9 min (minor) and 16.2 min (major)).

Product 5ad



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 2-chlorobenzyl bromide (51.4 mg, 250 μ mol) over the course of 76 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (31.5 mg, 70.0 μ mol, 70% yield, 95% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.38 (m, 1 H), 7.30 – 7.22 (m, 3 H), 7.20 – 7.15 (m, 3 H), 7.15 – 7.09 (m, 2 H), 7.02 (m, 1 H), 6.94 (m, 1 H), 6.88 – 6.79 (m, 2 H), 3.82 (d, *J* = 14.5 Hz, 1 H), 3.75 (d, *J* = 14.5 Hz, 1 H), 1.63 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.2, 150.5, 143.4, 137.0, 136.5, 133.5, 132.9, 129.4, 128.5, 128.4, 128.3, 126.3, 126.2, 126.2, 125.1, 122.6, 118.6, 116.7, 85.9, 84.6, 41.4, 27.8 ppm. IR (neat): 2982, 1760, 1701, 1500, 1371, 1351, 1249, 1146 cm⁻¹; HRMS (ESI) exact mass calcd for C₂₆H₂₄NO₄Cl: *m/z* 472.1286 ([M + Na]⁺), found: *m/z* 472.1293 ([M + Na]⁺); [α]_D^{26.0} = +104.8 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 9.2 min (minor) and 11.0 min (major)).

Product 5ae



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 2,6-dichlorobenzyl bromide (60.0 mg, 250 μ mol) over the course of 68 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (11.9 mg, 24.6 μ mol, 25% yield, 96% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.24 – 7.18 (m, 2 H), 7.18 – 7.04 (m, 6 H), 6.99 – 6.87 (m, 2 H), 6.86 – 6.78 (m, 2 H), 4.08 (s, 2 H), 1.66 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.4, 150.6, 143.2, 138.4, 132.0, 128.6, 128.6, 128.2, 128.1, 128.0, 126.7, 126.2, 125.0, 122.6, 118.6, 116.7, 86.0, 84.0, 38.7, 27.8 ppm. IR (neat): 2982, 1760, 1700, 1500, 1436, 1370, 1350, 1250, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₃NO₄Cl₂: *m/z* 506.0896 ([M + Na]⁺), found: *m/z* 506.0879 ([M + Na]⁺). [α]_D^{23.0} = +142.9 (*c* = 1.0, CHCl₃). The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 9.9 min (minor) and 11.3 min (major)).

Product 5af



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 2-(bromomethyl)naphthalene (55.3 mg, 250 μ mol) over the course of 72 h. The residue was purified by PLC on silica gel (hexane/dichloromethane = 1:1). Colorless oil (28.1 mg, 60.4 μ mol, 60% yield, 95% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.81 – 7.69 (m, 2 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.61 (s, 1 H), 7.44 – 7.37 (m, 2 H), 7.34 – 7.26 (m, 3 H), 7.22 – 7.14 (m, 3 H), 7.04 (m, 1 H), 6.94 (m, 1 H), 6.89 – 6.78 (m, 2 H), 3.83 (d, *J* = 14.1 Hz, 1 H), 3.56 (d, *J* = 14.2 Hz, 1 H), 1.58 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.0, 150.0, 143.2, 137.1, 133.0, 132.6, 132.3, 130.1, 129.6, 128.1, 128.1, 127.7, 127.3, 126.7, 125.8, 125.8, 125.8, 125.4, 125.3, 124.7, 122.3, 118.2, 116.5, 85.5, 84.5, 45.6, 27.4 ppm. IR (neat): 2981, 1760, 1699, 1518, 1500, 1462, 1370, 1349, 1249, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₃₀H₂₇NO₄: *m/z* 488.1832 ([M + Na]⁺), found: *m/z* 488.1839 ([M + Na]⁺). [α]_D^{25.0} = +227.3 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 13.5 min (minor) and 17.0 min (major)).

Product 5ag

Вос

Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and allyl bromide (60.5 mg, 500 μ mol) over the course of 52 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (30.0 mg, 82.1 μ mol, 82% yield, 94% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.42 – 7.37 (m, 2 H), 7.29 – 7.18 (m, 3 H), 7.12 (m, 1 H), 7.03 – 6.97 (m, 1 H), 6.91 – 6.83 (m, 2 H), 5.91 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1 H), 5.18 – 5.07 (m, 2 H), 3.10 (dd, *J* = 14.6, 6.7 Hz, 1 H), 2.85 (dd, *J* = 14.6, 7.3 Hz, 1 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.1, 150.5, 143.7, 137.8, 132.1, 128.6, 128.4, 126.3, 125.9, 125.1, 122.6, 119.4, 118.5, 116.8, 85.9, 84.2, 44.3, 27.8 ppm. IR (neat): 3447, 2981, 1761, 1699, 1499, 1370, 1350, 1250, 1146, 1056 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₂H₂₃NO₄: *m/z* 388.1519 ([M + Na]⁺), found: *m/z* 388.1527 ([M + Na]⁺). [α]^{26.0} = +66.7 (*c* = 1.0, CHCl₃). The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 8.6 min (minor) and 9.7 min (major)).

Product 5ah



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and 3-bromo-2-methylpropene (67.5 mg, 500 μ mol) over the course of 54 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (23.6 mg, 62.2 μ mol, 62% yield, 97% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.37 (m, 2 H), 7.29 – 7.16 (m, 4 H), 7.11 (d, *J* = 7.6 Hz, 1 H), 7.04 – 6.97 (m, 1 H), 6.93 – 6.84 (m, 2 H), 4.90 – 4.76 (m, 2 H), 3.13 (d, *J* = 14.7 Hz, 2 H), 2.82 (d, *J* = 14.7 Hz, 2 H), 1.75 (s, 3 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.4, 150.5, 143.5, 140.2, 138.1, 128.5, 128.3, 126.2, 126.1, 125.1, 122.6, 118.5, 116.7, 116.1, 85.9, 84.8, 47.1, 27.8, 24.5 ppm. IR (neat): 2981, 1760, 1702, 1500, 1371, 1351, 1251, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₃H₂₅NO₄: *m/z* 402.1676 ([M + Na]⁺), found: *m/z* 402.1685 ([M + Na]⁺). [α]^{24.0} = +61.3 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 7.9 min (minor) and 9.4 min (major)).

Product 5ai



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4a** (32.5 mg, 100 μ mol) and propargyl bromide (59.5 mg, 500 μ mol) over the course of 96 h. The residue was purified by PLC on silica gel (hexane/acetone = 10:1.1). Colorless oil (18.3 mg, 50.4 μ mol, 50% yield, 88% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.37 – 7.29 (m, 2 H), 7.25 – 7.07 (m, 4 H), 6.95 (td, *J* = 7.7, 1.5 Hz, 1 H), 6.84 (td, *J* = 7.8, 1.4 Hz, 1 H), 6.76 (dd, *J* = 8.1, 1.5 Hz, 1 H), 3.09 (dd, *J* = 17.0, 2.6 Hz, 1 H), 2.89 (dd, *J* = 17.0, 2.7 Hz, 1 H), 2.32 (t, *J* = 2.6 Hz, 1 H), 1.50 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 164.5, 151.1, 144.0, 137.7, 129.9, 129.6, 127.2, 126.8, 126.2, 124.0, 119.5, 117.3, 86.9, 84.0, 79.7, 72.7, 31.1, 27.9 ppm. IR (neat): 3295, 2982, 1759, 1702, 1499, 1370, 1353, 1282, 1247, 1146 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₂H₂₁NO₄: *m/z* 386.1363 ([M + Na]⁺), found: *m/z* 386.1374 ([M + Na]⁺). [α]_D^{23.0} = +72.0 (*c* = 1.0, CHCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 12.0 min (minor) and 13.4 min (major)).

Product 5ba



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4b** (35.5 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 72 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (17.0 mg, 38.2 μ mol, 38% yield, 98% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.15 – 7.05 (m, 7 H), 7.01 (dd, *J* = 8.2, 1.3, 1 H), 6.90 (ddd, *J* = 8.0, 7.3, 1.6, 1 H), 6.82 – 6.76 (m, 1 H), 6.74 (dd, *J* = 8.0, 1.5, 1 H), 6.70 – 6.66 (m, 2 H), 3.60 (s, 3 H), 3.50 (d, *J* = 14.2, 1 H), 3.23 (d, *J* = 14.1, 1 H), 1.48 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.6, 160.8, 151.1, 144.0, 136.5, 132.3, 130.4, 128.6, 128.2, 127.6, 127.1, 125.9, 123.6, 119.3, 116.8, 114.7, 86.5, 85.2, 55.6, 46.3, 27.8 ppm. IR (neat): 2980, 1760, 1699, 1500, 1250, 1146, 841 cm⁻¹. HRMS (ESI) exact mass calcd for $C_{27}H_{27}NNaO_5$: *m/z* 468.1781 ([M + Na]⁺), found: *m/z* 468.1735 ([M + Na]⁺). $[\alpha]_D^{24.9} = 79.9$ (*c* = 0.90, MeCN). The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 15.7 min (minor) and 21.8 min (major)).

Product 5ca



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4c** (36.0 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 24 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (20.9 mg, 46.5 μ mol, 47% yield, 94% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.36 – 7.29 (m, 4 H), 7.27 – 7.15 (m, 6 H), 7.09 – 7.02 (m, 1 H), 6.95 (td, *J* = 7.7, 1.4, 1 H), 6.89 (dd, *J* = 8.1, 1.6, 1 H), 3.65 (d, *J* = 14.2, 1 H), 3.40 (d, *J* = 14.2, 1 H), 1.61 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.1, 150.8, 143.6, 137.3, 135.9, 134.8, 132.2, 129.3, 128.6, 128.6, 127.7, 126.8, 126.0, 123.9, 119.3, 116.9, 86.7, 84.9, 45.8, 27.7 ppm. IR (neat): 2980, 1760, 1699, 1499, 1249, 1146, 750 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₄ClNNaO₄: *m/z* 472.1286 ([M + Na]⁺), found: *m/z* 472.1239 ([M + Na]⁺). [α]_D^{25.1} = 75.3 (*c* = 1.29, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 16.0 min (minor) and 23.1 min (major)).

Product 5da



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4d** (34.3 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 16 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (39.0 mg, 90.0 μ mol, 90% yield, 95% ee).

¹H NMR (400 MHz, CD₃CN) δ = 7.24 (ddd, *J* = 6.8, 5.2, 2.2, 2 H), 7.17 – 7.12 (m, 5 H), 7.04 (dd, *J* = 8.1, 1.4, 1H), 6.99 – 6.83 (m, 4 H), 6.74 (dd, *J* = 8.2, 1.4, 1 H), 3.54 (d, *J* = 14.2, 1 H), 3.29 (d, *J* = 14.2, 1 H), 1.49 (s, 9 H) ppm. ¹³C NMR (100 MHz, CD₃CN) δ = 165.4, 163.6 (d, *J*=246.1), 150.9, 143.6, 136.2, 134.5 (d, *J*=3.1), 132.3, 129.1 (d, *J*=8.4), 128.7, 127.9, 126.7, 126.3, 124.1, 119.4, 117.0, 116.2 (d, *J*=21.8), 87.4, 85.1, 45.8, 27.7 ppm. ¹⁹F NMR (466 MHz, (CD₃)₂CO) δ = -109.72 (tt, *J*=8.9, 5.4) ppm. IR (neat): 2981, 1760, 1699, 1499, 1249, 1145, 842 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₄FNNaO₄: *m/z* 456.1582 ([M + Na]⁺), found: *m/z* 456.1536 ([M + Na]⁺). [α]_D^{24.5} = 173.1 (*c* = 1.50, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 10.1 min (minor) and 11.7 min (major)).

Product 5ea



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4e** (40.4 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 72 h at -35 °C. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (31.8 mg, 64.3 μ mol, 64% yield, 96% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.36 – 7.29 (m, 2 H), 7.18 – 7.03 (m, 8 H), 6.93 (td, *J* = 7.7, 1.5, 1 H), 6.82 (td, *J* = 7.7, 1.4, 1 H), 6.76 (dd, *J* = 8.1, 1.5, 1 H), 3.52 (d, *J* = 14.2, 1 H), 3.26 (d, *J* = 14.2, 1 H), 1.48 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.1, 150.9, 143.7, 138.0, 136.0, 132.5, 132.3, 129.1, 128.7, 127.8, 126.9, 126.1, 124.0, 123.1, 119.4, 117.0, 86.8, 85.1, 45.9, 27.8 ppm. IR (neat): 2980, 1760, 1703, 1370, 1250, 1146, 750 cm⁻¹. HRMS (ESI) exact

mass calcd for C₂₆H₂₄BrNNaO₄: m/z 516.0781 ([M + Na]⁺), found: m/z 516.0727 ([M + Na]⁺). [α]_D^{25.3} = 152.5 (c = 1.00, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 16.8 min (minor) and 25.0 min (major)).

Product 5fa



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4f** (35.9 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 16 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (28.5 mg, 63.3 μ mol, 63% yield, 86% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.22 – 7.03 (m, 10 H), 6.94 (ddd, *J* = 8.1, 7.3, 1.6, 1 H), 6.83 (td, *J* = 7.7, 1.4, 1H), 6.77 (dd, *J* = 8.1, 1.6, 1 H), 3.54 (d, *J* = 14.2, 1H), 3.28 (d, *J* = 14.2, 1 H), 1.49 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.0, 150.9, 143.6, 141.0, 136.0, 134.9, 132.3, 131.1, 129.6, 128.7, 127.9, 127.0, 126.8, 126.2, 125.5, 124.1, 119.4, 117.0, 86.9, 85.0, 45.9, 27.8 ppm. IR (neat): 2981, 1761, 1699, 1499, 1249, 1146, 751 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₄ClNNaO₄: *m/z* 472.1286 ([M + Na]⁺), found: *m/z* 472.1237 ([M + Na]⁺). [α]_D^{23.3} = 182.9 (*c* = 1.40, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 13.5 min (minor) and 17.0 min (major)).

Product 5ga



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4g** (33.9 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 48 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (34.2 mg, 79.6 μ mol, 80% yield, 91% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.17 – 7.04 (m, 7 H), 7.02 (dd, *J* = 8.1, 1.3, 1 H), 6.94 (dd, *J* = 8.5, 0.5, 2 H), 6.89 (ddd, *J* = 8.1, 7.3, 1.6, 1 H), 6.81 – 6.70 (m, 2 H), 3.51 (d, *J* = 14.2, 1 H), 3.22 (d, *J* = 14.2, 1 H), 2.09 (s, 3 H), 1.47 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.5, 151.1, 144.1, 139.2, 136.5, 135.7, 132.3, 130.0, 128.6, 127.6, 127.1, 126.8, 125.9, 123.6, 119.4, 116.8, 86.5, 85.4, 46.3, 27.8, 21.0 ppm. IR (neat): 2981, 1759, 1701, 1499, 1250, 1146, 752 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₇H₂₇NNaO₄: *m/z* 452.1832 ([M + Na]⁺), found: *m/z* 452.1841 ([M + Na]⁺). [α]_D^{23.6} = 187.9 (*c* = 1.24, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 10.1 min (minor) and 13.1 min (major)).

Product 5ha



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4h** (37.5 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 30 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (38.5 mg, 82.7 μ mol, 83% yield, 96% ee).

¹H NMR (400 MHz, CDCl₃) δ = 7.76 – 7.69 (m, 1 H), 7.66 (d, *J* = 8.7, 1 H), 7.45 – 7.35 (m, 3 H), 7.23 – 7.15 (m, 5 H), 7.11 (dd, *J* = 8.1, 0.7, 1 H), 6.98 – 6.91 (m, 1 H), 6.84 – 6.76 (m, 2 H), 3.75 (d, *J* = 14.2, 1 H), 3.49 (d, *J* = 14.2, 1 H), 1.62 (s, 8 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 165.4, 150.4, 143.6, 135.2, 135.1, 133.1, 133.0, 131.6, 128.5, 128.1, 127.8, 127.7, 126.9, 126.6, 126.4, 126.2, 125.7, 125.1, 123.7, 122.6, 118.5, 116.8, 85.8, 84.8, 45.6, 27.8 ppm. IR (neat): 2980, 1760, 1699, 1499, 1249, 1146, 747 cm⁻¹. HRMS (ESI) exact mass calcd for $C_{30}H_{27}NNaO_4$: m/z 488.1832 ([M + Na]⁺), found: m/z 488.1840 ([M + Na]⁺). $[\alpha]_D^{25.3}$ = 258.7 (c = 1.00, MeCN). The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 10.9 min (major) and

Product 5ia

11.8 min (minor)).



Prepared according to the general procedure **GP3** with 1,4-benzoxazin-3-one **4i** (33.9 mg, 0.10 mmol) and benzyl bromide (68.4 mg, 0.40 mmol) over the course of 72 h. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (23.1 mg, 53.8 μ mol, 54% yield, 81% ee).

¹H NMR (400 MHz, CD₃CN) δ = 7.34 – 7.16 (m, 10 H), 7.01 (d, *J* = 8.2, 1 H), 6.88 – 6.79 (m, 1 H), 6.59 (s, 1 H), 3.63 (d, *J* = 14.3, 1 H), 3.36 (d, *J* = 14.2, 1 H), 2.16 (s, 3 H), 1.59 (s, 9 H) ppm. ¹³C NMR (100 MHz, CD₃CN) δ = 165.8, 151.2, 141.7, 138.7, 136.7, 134.0, 132.4, 129.7, 129.6, 128.8, 127.9, 127.0, 126.8, 126.6, 119.3, 117.3, 87.4, 85.5, 46.0, 27.9, 20.9 ppm. IR (neat): 2980, 1759, 1700, 1509, 1250, 1145, 699 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₇H₂₇NNaO₄: *m/z* 452.1832 ([M + Na]⁺), found: *m/z* 452.1787 ([M + Na]⁺). [α]_D^{24.0} = 187.9 (*c* = 1.39, MeCN). The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 12.5 min (minor) and 21.3 min (major)).

Product 5ja



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4j** (35.5 mg, 0.10 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 68 h. The residue

was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (37.7 mg, 84.6 μmol, 85% yield, 92% ee).

¹H NMR (500 MHz, (CD₃)₂CO) δ = 7.35 – 7.30 (m, 2 H), 7.28 – 7.15 (m, 8 H), 7.09 – 7.04 (m, 1 H), 6.58 (dd, *J* = 8.9, 2.8, 1 H), 6.37 (d, *J* = 2.7, 1 H), 3.63 (s, 3 H), 3.60 (d, *J* = 14.2, 1 H), 3.33 (d, *J* = 14.2, 1 H), 1.59 (s, 9 H) ppm. ¹³C NMR (125 MHz, (CD₃)₂CO) δ = 165.6, 156.0, 150.9, 138.5, 137.6, 136.3, 132.2, 129.2, 129.2, 128.4, 127.5, 127.3, 126.7, 119.8, 110.5, 102.7, 86.6, 85.2, 55.9, 46.2, 27.7 ppm. IR (neat): 2981, 1761, 1703, 1508, 1251, 1146, 699 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₇H₂₇NNaO₅: *m/z* 468.1781 ([M + Na]⁺), found: *m/z* 468.1735 ([M + Na]⁺). [α]^{25.0} = 238.5 (*c* = 1.35, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 13.5 min (minor) and 20.1 min (major)).

Product 5ka



Prepared according to the general procedure **GP3** with 1,4-benzoxazin-3-one **4k** (20.2 mg, 0.05 mmol) and benzyl bromide (42.8 mg, 0.25 mmol) over the course of 48 h at 10 °C. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (22.9 mg, 46.3 μ mol, 76% yield, 88% ee).

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.37 – 7.18 (m, 11 H), 7.16 (d, *J* = 8.6, 1 H), 7.07 (d, *J* = 2.1, 1 H), 3.66 (d, *J* = 14.2, 1 H), 3.39 (d, *J* = 14.2, 1 H), 1.62 (s, 9 H) ppm. ¹³C NMR (100 MHz, (CD₃)₂CO) δ = 165.3, 150.6, 143.5, 138.0, 136.0, 132.2, 129.5, 129.4, 128.7, 128.5, 128.2, 127.7, 126.7, 121.2, 119.9, 115.0, 87.1, 85.7, 46.1, 27.7 ppm. IR (neat): 2980, 1756, 1709, 1491, 1252, 1145, 699 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₄BrNNaO₄: *m/z* 516.0781 ([M + Na]⁺), found: *m/z* 516.0790 ([M + Na]⁺). [α]_D^{24.3} = 208.8 (*c* = 1.00, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 13.3 min (minor) and 17.2 min (major)).

Product 5la



Prepared according to the general procedure **GP3** with 1,4-benzoxazin-3-one **4I** (34.3 mg, 0.10 mmol) and benzyl bromide (68.4 mg, 0.40 mmol) over the course of 144 h at 0 °C. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (27.3 mg, 63.0 μ mol, 63% yield, 89% ee).

¹H NMR (500 MHz, (CD₃)₂CO) δ = 7.34 – 7.30 (m, 2 H), 7.30 – 7.16 (m, 9 H), 6.80 (ddd, *J* = 8.9, 8.2, 2.9, 1 H), 6.69 (dd, *J* = 9.7, 2.8, 1 H), 3.63 (d, *J* = 14.2, 1 H), 3.35 (d, *J* = 14.2, 1 H), 1.60 (s, 9 H) ppm. ¹³C NMR (125 MHz, (CD₃)₂CO) δ = 164.5, 157.7 (d, *J* = 238.9), 149.8, 139.4 (d, *J* = 2.8), 137.2, 135.2, 131.3, 128.6, 128.5, 127.7, 126.8, 126.7 (d, *J* = 11.0), 125.8, 119.6 (d, *J* = 9.5), 111.2 (d, *J* = 23.5), 103.6 (d, *J* = 29.2), 86.1, 84.7, 45.4, 26.9 ppm. ¹⁹F NMR (466 MHz, ACETONE-D6) δ = -120.23 (ddd, *J*=9.7, 8.3, 5.2) ppm. IR (neat): 2981, 1756, 1704, 1505, 1248, 1143, 842, 698 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₄FNNaO₄: *m/z* 456.1582 ([M + Na]⁺), found: *m/z* 456.1587 ([M + Na]⁺). [α]_D^{25.2} = 155.6 (*c* = 1.32, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IC3, hexane/2-propanol = 200:1, flow rate = 0.5 mL/min, retention time; 19.1 min (major) and 23.5 min (minor)).

Product 5ma



Prepared according to the general procedure **GP2** with 1,4-benzoxazin-3-one **4m** (17.1 mg, 0.05 mmol), PTC (2.35 mg, 5 mol%) and benzyl bromide (21.3 mg, 125 μ mol) in mesitylene over the course of 48 h at -10 °C. The residue was purified by PLC on silica gel (hexane/EtOAc = 10:1). Colorless oil (18.7 mg, 43.3 μ mol, 87% yield, 91% ee).

¹H NMR (400 MHz, CD₃CN) δ = 7.35 (dd, *J* = 7.7, 1.4, 1 H), 7.08 (ddd, *J* = 8.2, 7.5, 1.5, 1 H), 7.01 - 6.95 (m, 1 H), 6.92 - 6.86 (m, 2 H), 6.68 (dd, *J* = 8.3, 1.1, 1 H), 3.55 (d, *J* = 14.1, 1 H),

3.49 (d, J = 14.1, 1 H), 1.61 (s, 3 H) ppm. ¹³C NMR (100 MHz, CD₃CN) $\delta = 167.9, 153.1, 137.4, 137.1, 136.4, 132.1, 130.0, 129.3, 129.2, 128.8, 128.6, 128.3, 128.2, 125.7, 121.8, 118.2, 87.0, 57.1, 44.8, 27.8 ppm. IR (neat): 2981, 1763, 1682, 1446, 1236, 1148, 699 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₆H₂₅NNaO₃S: <math>m/z$ 454.1447 ([M + Na]⁺), found: m/z 454.1453 ([M + Na]⁺). $[\alpha]_D^{25.3} = 315.1$ (c = 1.00, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 30:1, flow rate = 0.5 mL/min, retention time; 13.9 min (minor) and 17.0 min (major)).

Product 5jj



To a degassed test tube equipped with a magnetic stirring bar powdered KOH (11.2 mg, 200 μ mol) was added rapidly. After addition of 1,4-benzoxazin-3-one **4j** (17.8 mg, 50 μ mol) and catalyst **PTC** (2.4 mg, 5.0 mol%) the test tube was cooled to -25 °C and the components were dissolved in mesitylene (1 mL) to continue cooling at the same temperature for 1 h. Dimethyl sulfate (190 mg, 1.50 mmol) was added in one portion and the reaction mixture was stirred vigorously for 72 h. The reaction mixture was diluted by ethyl acetate and passed through a short pad of silica gel. After evaporation of the solvent, the residue was purified by PLC on silica gel (hexane/EtOAc = 10:1) to give **5jj** as a colorless oil (9.1 mg, 24.4 μ mol, 49% yield, 49% ee) along with 15% of the *O*-methylated side-product as inseparable mixture of region-isomers.

¹H NMR (400 MHz, (CD₃)₂CO) δ = 7.32 - 7.21 (m, 2 H), 7.22 - 7.15 (m, 2 H), 7.16 - 7.10 (m, 1 H), 6.95 (d, *J* = 8.8, 1 H), 6.47 (dd, *J* = 8.9, 2.8, 1 H), 6.26 (d, *J* = 2.8, 1 H), 3.54 (s, 3 H), 1.66 (s, 3 H), 1.51 (s, 9 H) ppm. ¹³C NMR (125 MHz, (CD₃)₂CO) δ = 165.4, 155.2, 150.2, 139.4, 137.1, 128.6, 128.4, 125.2, 118.9, 109.7, 102.1, 85.7, 81.8, 55.0, 26.9, 26.5 ppm. IR (neat): 1771, 1615, 1251, 1146, 1039 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₁H₂₃NNaO₅: *m/z* 392.1468 ([M + Na]⁺), found: *m/z* 392.1466 ([M + Na]⁺). [α]_D^{14.6} = 95.6 (*c* = 0.90, MeCN).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 20.1 min (minor)

and 31.4 min (minor)).

Deprotection

Product 6



To a solution of 1,4-benzoxazin-3-one **5ha** (22.8 mg, 49.0 μ mol) in CH₂Cl₂ (1.0 mL) was added trifluoro acetic acid (0.2 mL) at 0 °C and the resulting mixture was stirred at room temperature for addition 2 h. The reaction was neutralized with aq. sat. NaHSO₄, the phases were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by PTLC (hex:EtOAc = 4:1) to yield the title compound **6** (17.7 mg, 48.4 μ mol, 99%, 96% ee) as white solid.

H NMR (400 MHz, CDCl₃) δ = 8.36 (s, 1 H), 7.88 (s, 1 H), 7.78 – 7.65 (m, 3 H), 7.60 (dd, J = 8.7, 1.6, 1 H), 7.47 – 7.37 (m, 2 H), 7.30 (dd, J = 6.3, 2.8, 2 H), 7.24 – 7.12 (m, 4 H), 6.94 (t, J = 7.3, 1 H), 6.82 (t, J = 7.6, 1 H), 6.63 (d, J = 7.7, 1 H), 3.79 (d, J = 14.2, 1 H), 3.46 (d, J = 14.2, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 167.0, 160.7, 143.3, 136.2, 135.7, 133.1, 131.5, 128.5, 128.3, 127.9, 127.7, 126.9, 126.6, 126.4, 125.3, 124.3, 123.7, 122.6, 121.3, 117.8, 115.4, 102.0, 85.1, 48.9, 45.7, 15.1 ppm. IR (neat): 2341, 1681, 1501, 1082, 798, 745 cm⁻¹. HRMS (ESI) exact mass calcd for C₂₅H₁₉NO₂Na: m/z 388.1308 ([M + Na]⁺), found: m/z 388.1326 ([M + Na]⁺). [α]_D^{18.6} = 84.3 (c = 1.45, CDCl₃).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-H, hexane/2-propanol = 10:1, flow rate = 1.0 mL/min, retention time; 26.2 min (minor) and 37.9 min (major)).

Determination of the Absolute Configuration of 5ha

Crystals suitable for an x-ray analysis were obtained by layering a solution of the product in CH_2Cl_2 with hexane. The x-ray analysis revealed the absolute configuration of the product to be (*R*).

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1840492). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html.






0 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -1 19 F NMR (466 MHz, CDCl₃)



S39









S43



S44





S46



40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -1 ¹⁹F NMR (466 MHz, CDCl₃)



¹³C NMR (100 MHz, CDCl₃)

















S56







S59







S62





Product 5ac



S64









. (_____















S69









S71




140 130 120 110 100 90 80 70 60 50 40 30 20 10 $_{ppm}^{0}$ -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 19F NMR (466 MHz, (CD₃)₂CO)



S75



S76















140 130 120 110 100 90 80 70 60 50 40 30 20 10 $_{ppm}^{0}$ -10 -20 -30 40 -50 -60 -70 -80 -90 -100 -120 -140 19 F NMR (466 MHz, (CD₃)₂CO)





Product 6ha



HPLC

Product 5aa



^'-ŷ' 1/1

面積%レポート



Product 5ab







Product 5ad











Product 5ag



Product 5ah













Product 5ca



Product 5da



Product **5ea**



Product 5fa





S102

Product 5ha



Product 5ia



Product 5jj



Product 5ka





Product 5ja


Product 6ha



S109