A rational quest for selectivity through precise ligand-positioning in the tandem DNA-catalysed Friedel-Crafts alkylation/asymmetric protonation

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I. General Information

Pyridine, DIEA and diisopropylamine were distilled over calcium hydride. THF was distilled over sodium/benzophenone. All reactions were performed in anhydrous conditions under argon. 4,4’-Dimethyl-2,2’-bipyrine, 5-ethynyl-2’deoxyuridine, 2’-propargyl-deoxyuridine and 2,2’-anydrodeoxyuridine were purchased from Alfa and Carbosynth. Phosphoramidite precursors were purchased from Eurogenetech.

Thin-layer chromatographies (TLC) were performed on silica plate 60 F254 Merck and the different spots were revealed under λ illumination at 254 nm. Silica gel purifications were carried out with 0.040-0.063 mm silica from Merck.

NMR experiments were accomplished on a Bruker DRX 600 spectrometer, 400 spectrometer or 300 spectrometer at 20 °C in CDCl₃. The ¹H NMR spectra are described as follow: chemical shifts expressed in δ (ppm) values (part per million) and internal standard of residual CHCl₃ was fixed at 7.26 ppm. Multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet), coupling constant J (Hz) and integration.

The syntheses of the oligonucleotides were performed on solid support using an automated DNA synthesizer (Applied Biosystems 394). Crude oligonucleotides were analysed by RP-HPLC (Macherey-Nagel Nucleodur C-18, 100 Å, 8 x 125 mm, Buffer A: 50 mM TEAAc in 0.2% CH₃CN, Buffer B: 50 mM TEEAc in 80% CH₃CN, 2 mL/min flow rate, detection at 260 nm) and purified by flash chromatography (interchim column PF-15C18HQ-F0025, 15 mL/min flow rate, detection at 260 nm and λ scan 200-600 nm). Oligonucleotides were desalted using a dialysis membrane Float-A-Lyzer G2 Dialysis Device CE, Biotech CE, 0.5-1.0 kD MWCO, 1 mL, and transferred to a 2 mL Eppendorf-vial and lyophilized from water.

MALDI-TOF mass spectra were recorded on a Shimazu Alliance using 2,4,6-trihydroxyacetophenone as a saturated solution in a mixture of acetonitrile/0.1M ammonium citrate solution (1:1, v/v) for the matrix. Analytical samples were mixed with the matrix in a 1:5 (v/v) ratio, crystallized on a 100-well stainless steel plate and analysed.

Tm experiments were performed on a Varian Cary 300 Bio λ/Visible spectrometer by measuring absorbance at 260 nm. Oligonucleotides were diluted in 20 mM cacodylate buffer with 100 mM NaCl. All the ees were determined by HPLC using a chiral column (Chiralpak IA and IB). The sign before the ee values is arbitrarily attributed.
II. Synthesis of modified dmbipy and phosphoramidite

4-Methyl-4′-ethyltosylate-2,2′-bipyridine (3)

Under argon, a round-bottom flask was charged with 4-methyl-4′-hydroxyethyl-2,2′-bipyridine 2 synthetized as described in literature¹ (400 mg, 1.87 mmol), pyridine (1.30 mL, 14.9 mmol) in anhydrous dichloromethane (16.0 mL). The reaction was stirred overnight and after completion monitored by TLC, the mixture was diluted in 15.0 mL of ether. The organic phase was washed with 10.0 mL of water and neutralised with 10.0 mL of saturated NaHCO₃ solution. The aqueous phase was extracted with ether (3 x 20.0 mL) and the resulting organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuum. The crude product was purified by silica gel chromatography (0-100% EtOAc, cyclohexane, 4% of Et₃N) to afford product 3 as a yellow oil with 57% yield (255 mg, 1.07 mmol) Rf 0.40 (Cyclohexane EtOAc 3:7 with 4% Et₃N). ¹H NMR (300 MHz, CDCl₃) δ 8.53 (t, J = 5.7 Hz, 2H), 8.24 (s, 1H), 8.15 (s, 1H), 7.71-7.61 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 5.0, 0.9 Hz, 1H), 7.10 (dd, J = 5.0, 1.7 Hz, 1H), 4.31 (t, J = 6.6 Hz, 2H), 3.03 (t, J = 6.6 Hz, 2H), 2.45 (s, 3H), 2.32 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 154.8, 149.6, 149.3, 148.2, 147.0, 144.9, 132.6, 129.9, 128.9, 127.9, 126.1, 125.2, 124.7, 122.5, 121.8, 69.3, 34.9, 29.8, 21.6. HRMS-ESI m/z 369.1276 ([M+H]⁺ C₂₀H₂₁N₂O₃S calcd 369.1273).
4-Methyl-4’-azidoethyl-2,2’-bipyridine (4)

To a round-bottom flask filled with dry DMF (6.00 mL), was added 4-methyl-4’-ethyltosylate-2,2’-bipyridine 3 (230 mg, 0.63 mmol) and sodium azide (49.0 mg, 0.75 mmol). The reaction was stirred for 2 h at 0 °C. After total consumption of the starting material, the mixture was diluted in EtOAc (15.0 mL), washed with water (10.0 mL) and with a saturated NaCl solution. The aqueous phase was extracted with EtOAc (3 x 15.0 mL) and the organic layers were dried over anhydrous Na₂SO₄ before evaporation of solvent. The crude material was purified by silica gel chromatography (Cyclohexane/EtOAc 0-100%, 4% of Et₃N) to afford product 4 as a yellow oil with 85% yield (127 mg, 0.53 mmol) Rf 0.40 (Cyclohexane:EtOAc 8:2 with 4% Et₃N). ¹H NMR (300 MHz, CDCl₃) δ 8.57 (dd, J = 21.3, 4.5 Hz, 2H), 8.26 (d, J = 12.4 Hz, 2H), 7.16 (dd, J = 11.4, 4.6 Hz, 2H), 3.62 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H), 2.44 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 156.6, 155.7, 149.4, 149.0, 148.4, 148.2, 125.0, 124.2, 122.2, 121.5, 51.4, 35.0, 21.3. HRMS-ESI m/z 240.1253 ([M+H]+ C₁₃H₁₄N₅ calcld 240.1249).

4-Methyl-4’-(4”-(trimethylsilyl)-but-3”-inyl)-2,2’-bipyridine (5)

To a solution of diisopropylamine (1.40 mL, 8.00 mmol) in dry THF (6.70 mL) was added dropwise a solution of n-BuLi (1.80 M solution in hexane, 1.70 mL, 3.00 mmol) and the reaction mixture was stirred for 30 min at −78 °C. Commercially available 2,2’-dimethyl-4,4’-bipyridine 1 (1.00 g, 5.5 mmol) in dry THF (40.0 mL) was added dropwise and the black mixture was stirred for another 2 h. Trimethylsilylpropargyl bromide (2.00 mL, 12.2 mmol) in dry THF (33.0 mL) was added dropwise and stirred for 1 h at −78 °C, and then allowed to reach room temperature in 1 h. The colour of anion disappeared, and the mixture turned yellow. The excess LDA was quenched with water
(20.0 mL) and the aqueous phase was extracted with EtOAc (3 × 30.0 ml). The organics layers were washed with brine (10.0 mL) and dried over magnesium sulphate. Evaporation of the solvent gave an orange oil which was purified on reverse phase silica gel column chromatography with water/acetonitrile (0-100%) to afford 5 as a white powder with 46% yield (736 mg, 2.50 mmol). 

\( R_f 0.20 (\text{H}_2\text{O Acetonitrile 5:5}) \). ¹H NMR (300 MHz, CDCl₃) \( \delta 8.54 (\text{dd, } J = 15.1, 5.0 \text{ Hz, } 2\text{H}), 8.24 \) (d, \( J = 16.2 \text{ Hz, } 2\text{H} \)), 7.26-7.10 (m, 2H), 2.89 (t, \( J = 7.3 \text{ Hz, } 2\text{H} \)), 2.57 (t, \( J = 7.3 \text{ Hz, } 2\text{H} \)), 2.42 (s, 3H), 0.11 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) \( \delta 156.3, 156.0, 150.4, 149.0, 149.0, 148.2, 124.7, 124.1, 122.0, 121.5, 105.6, 86.2, 53.5, 34.4, 21.2, 21.1, 0.1 \). HRMS-ESI m/z 295.1630 ([M+H]+ C₁₈H₂₄N₂Si calcd 295.1631).

4-Methyl-4’-(but-3”-inyl)-2,2’-bipyridine (6)

To a stirred solution of trimethylsilyl-protected compound 5 (700 mg, 2.37 mmol) in CH₃OH/THF (1:1) was added KF (700 mg, 12.0 mmol) as a solid. After complete consumption of the starting material (ca. 20 h), the solution was concentrated in vacuum. Dichloromethane was added to the white crude product and the resulting solution was filtered through silica gel. The solvent was evaporated to afford compound 6 as a white solid powder with 98% yield (515 mg, 2.32 mmol) \( R_f 0.39 (\text{Cyclohexane/EtOAc = 9:1 with 4% Et₃N}) \). ¹H NMR (300 MHz, CDCl₃) \( \delta 8.57 (\text{dd, } J = 16.5, 5.0 \text{ Hz, } 2\text{H}), 8.27 \) (d, \( J = 12.8 \text{ Hz, } 2\text{H} \)), 7.23-7.14 (m, 2H), 2.93 (t, \( J = 7.4 \text{ Hz, } 2\text{H} \)), 2.58 (td, \( J = 7.4, 2.6 \text{ Hz, } 2\text{H} \)), 2.44 (s, 3H), 1.98 (t, \( J = 2.6 \text{ Hz, } 1\text{H} \)). ¹³C NMR (75 MHz, CDCl₃) \( \delta 156.3, 155.8, 150.3, 149.2, 148.9, 148.4, 124.8, 123.9, 122.2, 121.3, 82.9, 69.6, 34.3, 21.3, 19.5 \). HRMS-ESI m/z 223.1235 ([M+H]+ C₁₅H₁₈N₂ calcd 223.1235).
5′-O-(4,4′-Dimethoxytrityl)-2′-Deoxy-2′-(4′-ethyl-(4-méthyl-2,2′-bipyridine)-1,2,3-triazol-1-yl) uridine (14)

In a degassed solution of THF:H₂O:pyridine (6:3:2, 20.0 mL) under argon, 2′-Azido-5′-O-(4,4′-dimethoxytrityl)-2′-deoxyuridine 13 synthetized as described in the literature (990 mg, 1.73 mmol), and 4-methyl-4′-(4′′-(trimethylsilyl)-but-3′-inyl)-2,2′-bipyridine 6 (500 mg, 2.25 mmol) were dissolved. A degassed solution of sodium ascorbate (139 mg, 0.69 mmol) and CuSO₄·5H₂O (86 mg, 0.35 mmol) in water (3.00 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated to 2 mL and then diluted with CH₂Cl₂ (40.0 mL), and the mixture was washed with a saturated aqueous solution of NaHCO₃ (20.0 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20.0 mL) and the combined organic phases were dried under anhydrous Na₂SO₄. The resulting organic phase was concentrated to obtain a crude yellow oil which was purified by silica gel column chromatography: Cyclohexane-EtOAc (0-100%) and EtOAc-MeOH (0-50%) with 4% Et₃N to afford the product 14 as a yellow foam with 69% yield (882 mg, 1.19 mmol). Rᵣ 0.30 (EtOAc with 4% Et₃N). ¹H NMR (300 MHz, CDCl₃) δ 8.57 (d, J = 4.9 Hz, 1H), 8.25-8.09 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 7.47 (s, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.35-7.17 (m, 11H), 7.03 (d, J = 4.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 4H), 6.58 (d, J = 7.4 Hz, 1H), 5.45 (d, J = 8.2 Hz, 1H), 5.36-5.19 (m, 1H), 4.66-4.50 (m, 1H), 4.43 (d, J = 2.8 Hz, 1H), 3.78 (s, 6H), 3.56 (qd, J = 11.0, 2.8 Hz, 2H), 3.32-2.87 (m, 4H), 2.43 (s, 3H), 2.00 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 162.5, 158.9, 156.3, 155.1, 150.8, 150.3, 149.6, 149.4, 147.9, 145.8, 144.2, 139.3, 135.2, 135.1, 130.2, 128.2, 127.3, 124.9, 124.6, 123.5, 123.5, 113.5, 103.4, 87.5, 85.6, 71.0, 65.9, 63.0, 55.4, 35.6, 34.6, 29.8, 26.9, 21.3, 14.9. HRMS-ESI m/z 794.3303 ([M+H]+ C₄₅H₄₈N₅O₇ calcd 794.3302).
3′-O-(2-Cyanoethoxy(diisopropylamino)phosphinyl)-5′-O-(4,4′-dimethoxytrityl)-2′-Deoxy-2′-(4′-ethyl-(4'-méthyl-2,2′-bipyririne)-1,2,3-triazol-1-yl)uridine (15)

Under argon, diisopropylethylamine (0.70 mL, 3.21 mmol) was added to a solution of 14 (850 mg, 1.07 mmol) in dry CH$_2$Cl$_2$ (20.0 mL). Then 2-cyanoethyl-N,N-diisopropylchlorophosphoramidite (954 mg, 4.28 mmol) was added. After stirring for 2 h at room temperature, EtOAc previously washed with saturated aqueous NaHCO$_3$ solution was added (50.0 mL) and the reaction mixture was washed with 30.0 mL of solution NaCl/NaHCO$_3$ (1/1 v/v). The aqueous phase was extracted with EtOAc (3 x 20.0 mL) and the organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with cyclohexane-EtOAc (0-100%) and EtOAc-MeOH (0-50%) containing 10% Et$_3$N. The desired phosphoramidite 15 was obtained as white foam with 84% yield (883 mg, 0.89 mmol). $R_f$ = 0.45 (4% MeOH in EtOAc with adding of 10% Et$_3$N). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.64-8.45 (m, 2H), 8.31-8.15 (m, 2H), 7.89 (dd, $J$ = 42.0, 8.2 Hz, 1H), 7.60 (s, 1H), 7.42 (d, $J$ = 7.8 Hz, 2H), 7.37-7.20 (m, 9H), 7.16 (dd, $J$ = 17.4, 4.1 Hz, 2H), 6.85 (t, $J$ = 6.7 Hz, 4H), 6.47 (dd, $J$ = 41.6, 5.1 Hz, 1H), 5.64-5.25 (m, 2H), 5.03-4.50 (m, 2H), 3.79 (d, $J$ = 2.7 Hz, 6H), 3.75-3.14 (m, 7H), 3.14-3.00 (m, 6H), 2.59 (t, $J$ = 5.9 Hz, 1H), 2.43 (s, 3H), 2.06-1.93 (m, 7H), 1.39-1.21 (m, 6H), 1.17-0.97 (m, 7H), 0.90 (dd, $J$ = 13.3, 6.7 Hz, 6H). $^{31}$P NMR (121 MHz, CDCl$_3$) δ 151.57, 150.39. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.1, 163.2, 162.7, 158.9, 158.8, 158.9, 156.4, 156.0, 151.2, 151.0, 150.3, 149.9, 149.3, 149.0, 148.3, 146.4, 146.0, 144.2, 144.1, 139.7, 139.2, 135.2, 135.0, 130.3, 130.2, 128.3, 128.2, 128.1, 128.1, 127.4, 127.2, 124.8, 124.0, 123.9, 123.6, 122.6, 122.3, 122.2, 121.4, 121.4, 118.0, 117.4, 113.5, 113.5, 113.4, 103.3, 102.6, 88.1, 87.5, 87.2, 85.8, 84.8, 72.6, 72.5, 70.9, 70.7, 66.2, 62.4, 60.8, 58.1, 57.9, 57.9, 57.8, 55.4, 55.3, 46.8, 46.8, 45.5, 43.3, 43.3, 35.2, 35.0, 29.8, 26.6, 26.4, 26.4, 24.6, 24.5, 24.4, 23.0, 22.6, 21.6, 21.3, 20.6, 20.5, 20.4, 20.3, 19.3, 19.3, 14.9, 8.6, 2.0. HRMS-ESI $m/z$ 994.4381 ([M+H]+ C$_{54}$H$_{61}$N$_9$O$_8$P calcd 994.4381).
III. DNA sequences

a. Synthesis

1. Post-synthetic approach

Commercial phosphoramidites 7 and 10 were incorporated with 5 min time coupling (0.1 M) to synthesize ODN1 and ODN2. After synthesis of these modified oligonucleotide bearing an alkyne function, CPG beads were washed with a 0.2 M solution of sodium bisulfite (3 x 1 mL), water (3 x 2 mL), anhydrous acetonitrile (3 x 2 mL) and then dried by nitrogen flushing. To the solid-supported oligonucleotide (1 µmol) were added azido dmbipy 4 (2 equiv, 2 µmol, 20 µL of a 0.1 M solution in dioxane), freshly prepared CuSO4 (1 equiv, 1 µmol, 25 µL of a 0.04 M solution in degassed H2O), freshly prepared sodium ascorbate (5 equiv, 5 µmol, 50 µL of a 0.1 M solution in degassed H2O), THPTA (3 equiv, 3 µmol, 30 µL of a 0.1 M solution), and dioxane (20 µL). The resulting preparation was treated with microwave for 1h30 in a sealed vessel. The solution was removed by filtration, and the CPG beads were washed with dioxane, water, saturated EDTA acid solution, water, and acetonitrile (2 mL each).

2. Phosphoramidite approach

Commercial phosphoramidites 7 and 10 were incorporated with 5 min simple coupling (0.1 M) to synthetize ODN1 and ODN2.

Modified phosphoramidite 15 was incorporated with 2 x 20 min time coupling (0.2M) to synthesize ODN3.

b. HPLC and Mass Analysis

| Entry | Name   | Calcd | Found  |
|-------|--------|-------|--------|
| 1     | ODN1   | 3880.81 | 3880.26 |
| 2     | ODN2   | 3910.29 | 3910.45 |
| 3     | ODN3   | 3880.81 | 3881.22 |
| 4     | ODN4   | 3661.37 | 3661.93 |
| 5     | ODN5   | 3630.13 | 3630.42 |
1. **ODN1**

2. **ODN2**

3. **ODN3**

4. **ODN4**
5. **ODN5**

![Graph of ODN5](image)
c. Melting temperature

1. **ODN5/ODN4**

   ![Graph](image)

2. **ODN1/ODN4**

   ![Graph](image)

3. **ODN2/ODN3**

   ![Graph](image)

4. **ODN3/ODN4**

   ![Graph](image)
IV. Friedel-Crafts alkylation/protonation

a. Synthesis of starting materials

2-Methyl-1-(thiazol-2-yl)prop-2-en-1-ol

\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{Me} & \quad \text{OH} \\
\end{align*}
\]

2-(Trimethylsilyl)triazole (1.60 mL, 10.0 mmol, 1.00 equiv.) and methacrolein (0.82 mL, 10.0 mmol, 1.00 equiv.) were stirred at room temperature for 4 h. The mixture was then diluted in THF (200 mL) and tetrabutylammonium fluoride solution 1.0 M in THF (10.0 mL, 10.0 mmol, 1.00 equiv.) was added. After additional stirring for 1 h, the solvent was removed under vacuum and the crude residue was dissolved in EtOAc and washed with a saturated aqueous solution of NaHCO\textsubscript{3}. The crude reaction mixture was purified by flash column chromatography over silica gel (PE/EtOAc, from 100:0 to 80:20) to afford the desired alcohol as a yellow oil, with 50% yield (776 mg, 5.00 mmol). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra matched those reported in the literature.\textsuperscript{3}

2-Methyl-1-(thiazol-2-yl)prop-2-en-1-one (16)

\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

2-Methyl-1-(thiazol-2-yl)prop-2-en-1-ol (100 mg, 0.64 mmol, 1.00 equiv.) was dissolved in dichloromethane (3.50 mL) and MnO\textsubscript{2} (576 mg, 6.40 mmol, 10.0 equiv.) was added to the solution. The mixture was stirred at room temperature for 1.5 h. After completion of the reaction monitored by TLC (PE/EtOAc, 70:30), the crude was filtered over Celite\textsuperscript{©} and the solvent was removed under vacuum. The product was obtained as colourless oil with 87% yield (85.3 mg, 0.56 mmol) and was used on the same day without further purification. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra matched those reported in the literature.\textsuperscript{3}
5-(Piperidin-1-yl)-1H-indole (17m)

In an oven-dried tube, Pd\textsubscript{2}dba\textsubscript{3} (9.10 mg, 0.01 mmol, 1.00 mol%), 2-dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl (9.40 mg, 0.024 mmol, 2.40 mol%) and 5-bromoindole (196 mg, 1.00 mmol, 1.00 equiv.) were dissolved in THF (1.00 mL). LiHMDS solution 1.0 M in THF (2.20 mL, 2.20 mmol, 2.20 equiv.) and morpholine (105 μL, 1.20 mmol, 1.20 equiv.) were slowly added to the solution, which was stirred at 65 °C overnight. After cooling down at room temperature, HCl 1M (2.00 mL) was added and the mixture was stirred for additional 15 min. The crude was diluted with a saturated aqueous solution of NaHCO\textsubscript{3}, and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO\textsubscript{4} and concentrated under vacuum. The crude was purified by flash column chromatography over silica gel (PE/EtOAc, from 100:0 to 125:75) to afford the desired compound as a brown oil with 75% yield (150 mg, 0.75 mmol). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra matched those reported in the literature.\textsuperscript{3}

4-(1H-Indol-5-yl)morpholine (17n)

In an oven-dried tube, Pd\textsubscript{2}dba\textsubscript{3} (9.10 mg, 0.01 mmol, 1.00 mol%), 2-dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl (9.40 mg, 0.024 mmol, 2.40 mol%) and 5-bromoindole (196 mg, 1.00 mmol, 1.00 equiv.) were dissolved in THF (1.00 mL). LiHMDS solution 1.0 M in THF (2.20 mL, 2.20 mmol, 2.20 equiv.) and morpholine (105 μL, 1.20 mmol, 1.20 equiv.) were slowly added to the solution, which was stirred at 65 °C overnight. After cooling down at room temperature, HCl 1M (2.00 mL) was added and the mixture was stirred for additional 15 min. The crude was diluted with a saturated aqueous solution of NaHCO\textsubscript{3}, and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO\textsubscript{4} and concentrated under vacuum. The crude residue was purified by flash column chromatography over silica gel (PE/EtOAc, from 100:0 to 125:75) to afford the desired compound as a brown oil with 70% yield (142 mg, 0.70 mmol). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra matched those reported in the literature.\textsuperscript{4}
b. Preparation of racemic products

In an oven-dried tube, Cu(NO$_3$)$_2$•3H$_2$O (6.30 mg, 0.026 mmol, 10 mol%) and 4,4’-dimethyl-2,2’-bipyridyl (dmbipy, 5.70 mg, 0.03 mmol, 12 mol%) were dissolved in acetonitrile (2.00 mL). The mixture was stirred for 10 min and a solution of enone (16) (40.0 mg, 0.26 mmol, 1.00 equiv.) and the desired indole (0.39 mmol, 1.50 equiv.) in acetonitrile (2.00 mL) was added. The mixture was stirred at room temperature for 3 d. The solvent was removed under vacuum and the crude residue was purified by flash column chromatography over silica gel (n-Hexanes/EtOAc) to afford the desired compound.

c. Procedure of enantioselective Friedel-Crafts alkylation/protonation

1. Preparation of a 200 mM MES buffer (pH 5.0)
3-(N-Morpholino)ethanesulfonic acid (2.13 g, 10.0 mmol) was dissolved in Milli-Q H$_2$O (40.0 mL). The pH was adjusted to 5.0 using a pH meter with a NaOH solution 0.1 M. The volume was finally adjusted with MilliQ-H$_2$O to 50 mL.

2. Preparation of a 0.90 mM Cu(NO$_3$)$_2$·dmbipy stock solution
Cu(NO$_3$)$_2$·3H$_2$O (4.80 mg, 0.02 mmol, 1.00 equiv.) and 4,4’-dimethyl-2,2’-bipyridyl (dmbipy, 4.40 mg, 0.024 mmol, 1.20 equiv.) were dissolved in 22.2 mL of Milli-Q H$_2$O. The mixture was stirred at room temperature for 5 h and used in the next step without further purification.

3. Preparation of a 1.00 mM Cu(NO$_3$)$_2$ stock solution
Cu(NO$_3$)$_2$·3H$_2$O (4.80 mg, 0.02 mmol, 1.00 equiv.) was dissolved in 20.0 mL of Milli-Q H$_2$O. The mixture was stirred at room temperature for 1 h and used the next day.

4. General procedure A. Enantioselective Friedel-Crafts alkylation/protonation, supramolecular approach with st-DNA
St-DNA solution (29.0 µL, stock solution 4.5 mg/mL or 6.92 mM (bp) in Milli-Q H$_2$O, 2 mM final concentration) and Milli-Q H$_2$O (23.7 µL) were successively added to a 500 µL Eppendorf tube. The reaction mixture was briefly mixed. MES buffer solution (10.0 µL, stock solution 200 mM in Milli-Q
H₂O, pH 5.0, 1/10 Vtot) and Cu(NO₃)₂.dmbipy solution (33.3 μL, stock solution 0.90 mM in Milli-Q H₂O prepared 24 h in advance, 30.0 mol%) were then added. The resulting mixture was stirred at 19 °C for 20 min and frozen at −20 °C for 30 min. Freshly prepared enone (16) (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was added and the mixture was frozen again at −20 °C for 30 min. Desired indole (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was finally added in a cold room. The resulting solution was stirred at 4 °C for 3 d in a thermoshaker placed in a cold room. The mixture was then transferred into 1.5 mL Eppendorf tube. The initial Eppendorf tube was rinsed with H₂O (100 μL) and diethyl ether (100 μL). Additional diethyl ether (400 μL) was finally added. After stirring, the tube was placed in dry ice to freeze H₂O. The etheral phase was poured into a new 1.5 mL Eppendorf tube. The process was repeated twice (2 x 500 μL diethyl ether). After evaporation of diethyl ether, the sample was dissolved in i-PrOH (2 x 50 μL), transferred in an HPLC mini vial and injected to measure both the conversion and the ee.

5. General procedure B. Enantioselective Friedel-Crafts alkylation/protonation, supramolecular approach with ODN5/ODN4 duplex.

Strand solution ODN5 (21.8 μL, stock solution 1838 nmol/mL in Milli-Q H₂O, 40.0 mol%), counter strand solution ODN4 (15.4 μL stock solution 2599 nmol/mL in Milli-Q H₂O, 40.0 mol%) and Milli-Q H₂O (15.5 μL) were successively added to a 500 μL Eppendorf tube. The reaction mixture was briefly mixed, heated at 90 °C for 5 min and allowed to cool down at room temperature. MES buffer solution (10.0 μL, stock solution 200 mM in Milli-Q H₂O, pH 5.0, 1/10 Vtot) and Cu(NO₃)₂.dmbipy solution (33.3 μL, stock solution 0.90 mM in Milli-Q H₂O prepared 24 h in advance, 30.0 mol%) were then added. The resulting mixture was stirred at 19 °C for 20 min and frozen at −20 °C for 30 min. Freshly prepared enone (16) (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was added and the mixture was frozen again at −20 °C for 30 min. Desired indole (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was finally added in a cold room. The resulting solution was stirred at 4 °C for 3 d in a thermoshaker placed in a cold room. The mixture was then transferred into 1.5 mL Eppendorf tube. The initial Eppendorf tube was rinsed with H₂O (100 μL) and diethyl ether (100 μL). Additional diethyl ether (400 μL) was finally added. After stirring, the tube was placed in dry ice to freeze H₂O. The etheral phase was poured into a new 1.5 mL Eppendorf tube. The process was repeated twice (2 x 500 μL diethyl ether). After evaporation of diethyl ether, the sample was dissolved in i-PrOH (2 x 50 μL), transferred in a HPLC mini vial and injected to measure both the conversion and the ee.
6. General procedure C. Enantioselective Friedel-Crafts alkylation/protonation, covalent approach with ODN1/ODN4 duplex.

Strand solution ODN1 (18.7 µL, stock solution 2136 nmol/mL in Milli-Q H₂O, 40.0 mol%), counter strand solution ODN4 (15.4 µL stock solution 2599 nmol/mL in Milli-Q H₂O, 40.0 mol%) and Milli-Q H₂O (21.9 µL) were successively added to a 500 µL Eppendorf tube. The reaction mixture was briefly mixed, heated at 90 °C for 5 min and allowed to cool down at room temperature. MES buffer solution (10.0 µL, stock solution 200 mM in Milli-Q H₂O, pH 5.0, 1/10 Vₜot) and Cu(NO₃)₂ solution (30.0 µL, stock solution 1.00 mM in Milli-Q H₂O, 30.0 mol%) were then added. The resulting mixture was stirred at 19 °C for 20 min and frozen at −20 °C for 30 min. Freshly prepared enone (16) (2.00 µL, stock solution 0.05 M in DMSO, 0.10 µmol, 1.00 equiv.) was added and the mixture was frozen again at −20 °C for 30 min. Desired indole (2.00 µL, stock solution 0.05 M in DMSO, 0.10 µmol, 1.00 equiv.) was finally added in a cold room. The resulting solution was stirred at 4 °C for 3 d in a thermostaker placed in a cold room. The mixture was then transferred into 1.5 mL Eppendorf tube. The initial Eppendorf tube was rinsed with H₂O (100 µL) and diethyl ether (100 µL). Additional diethyl ether (400 µL) was finally added. After stirring, the tube was placed in dry ice to freeze H₂O. The etheral phase was poured into a new 1.5 mL Eppendorf tube. The process was repeated twice (2 x 500 µL diethyl ether). After evaporation of diethyl ether, the sample was dissolved in i-PrOH (2 x 50 µL), transferred in an HPLC mini vial and injected to measure both the conversion and the ee.

7. General procedure D. Enantioselective Friedel-Crafts alkylation/protonation, covalent approach with ODN2/ODN4 duplex.

Strand solution ODN2 (34.7 µL, stock solution 1153 nmol/mL in Milli-Q H₂O, 40.0 mol%), counter strand solution ODN4 (15.4 µL stock solution 2599 nmol/mL in Milli-Q H₂O, 40.0 mol%) and Milli-Q H₂O (5.90 µL) were successively added to a 500 µL Eppendorf tube. The reaction mixture was briefly mixed, heated at 90 °C for 5 min and allowed to cool down at room temperature. MES buffer solution (10.0 µL, stock solution 200 mM in Milli-Q H₂O, pH 5.0, 1/10 Vₜot) and Cu(NO₃)₂ solution (30.0 µL, stock solution 1.00 mM in Milli-Q H₂O, 30.0 mol%) were then added. The resulting mixture was stirred at 19 °C for 20 min and frozen at −20 °C for 30 min. Freshly prepared enone (16) (2.00 µL, stock solution 0.05 M in DMSO, 0.10 µmol, 1.00 equiv.) was added and the mixture was frozen again at −20 °C for 30 min. Desired indole (2.00 µL, stock solution 0.05 M in DMSO, 0.10 µmol, 1.00 equiv.) was finally added in a cold room. The resulting solution was stirred at 4 °C for 3 d in a thermostaker placed in a cold room. The mixture was then transferred into 1.5 mL Eppendorf tube. The initial Eppendorf tube was rinsed with H₂O (100 µL) and diethyl ether (100 µL). Additional diethyl ether (400 µL) was finally added. After stirring, the tube was placed in dry ice to freeze H₂O.
The ethereal phase was poured into a new 1.5 mL Eppendorf tube. The process was repeated twice (2 x 500 μL diethyl ether). After evaporation of diethyl ether, the sample was dissolved in \textit{i-PrOH} (2 x 50 μL), transferred in an HPLC mini vial and injected to measure both the conversion and the \textit{ee}.

8. \textit{General procedure E. Enantioselective Friedel-Crafts alkylation/protonation, covalent approach with ODN3/ODN4 duplex.}

Strand solution \textbf{ODN3} (50.2 μL, stock solution 797 nmol/mL in Milli-Q H₂O, 40.0 mol%) and counter strand solution \textbf{ODN4} (15.4 μL stock solution 2599 nmol/mL in Milli-Q H₂O, 40.0 mol%) successively added to a 500 μL Eppendorf tube. The reaction mixture was briefly mixed, heated at 90 °C for 5 min and allowed to cool down at room temperature. MES buffer solution (10.0 μL, stock solution 200 mM in Milli-Q H₂O, pH 5.0, 1/10 V\textsubscript{tot}) and Cu(NO\textsubscript{3})\textsubscript{2} solution (30.0 μL, stock solution 1.00 mM in Milli-Q H₂O, 30.0 mol%) were then added. The resulting mixture was stirred at 19 °C for 20 min and frozen at −20 °C for 30 min. Freshly prepared enone (\textbf{16}) (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was added and the mixture was frozen again at −20 °C for 30 min. Desired indole (2.00 μL, stock solution 0.05 M in DMSO, 0.10 μmol, 1.00 equiv.) was finally added in a cold room. The resulting solution was stirred at 4 °C for 3 d in a thermoshaker placed in a cold room. The mixture was then transferred into 1.5 mL Eppendorf tube. The initial Eppendorf tube was rinsed with H₂O (100 μL) and diethyl ether (100 μL). Additional diethyl ether (400 μL) was finally added. After stirring, the tube was placed in dry ice to freeze H₂O. The ethereal phase was poured into a new 1.5 mL Eppendorf tube. The process was repeated twice (2 x 500 μL diethyl ether). After evaporation of diethyl ether, the sample was dissolved in \textit{i-PrOH} (2 x 50 μL), transferred in an HPLC mini vial and injected to measure both the conversion and the \textit{ee}.
d. NMR description of racemate products, HPLC methods and results of enantioselective protonation reactions

3-(1H-Indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18a)

\[ \text{\begin{align*}
\text{HN} & \text{N} \\
\text{O} & \\
\text{Me}
\end{align*}} \]

\(^1\)H NMR and \(^{13}\)C NMR spectra matched those reported in the literature.\(^3\)

**HPLC:** Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, \( \lambda = 280 \) nm, t\(_R\) = 44.430 min and t\(_R\) = 53.322 min.

| Entry | General procedure | Sequences      | Indole/Product\(^a\) | ee (\%)\(^a\) |
|-------|------------------|----------------|-----------------------|----------------|
| 1     | A                | st-DNA         | 5 : 95                | (+) 21         |
| 2     | B                | ODNS/ODN4      | 13 : 87               | (+) 40         |
| 3     | C                | ODN1/ODN4      | 70 : 30               | (-) 20         |
| 4     | D                | ODN2/ODN4      | 24 : 76               | (-) 80         |
| 5     | E                | ODN3/ODN4      | 70 : 30               | (+) 7          |

\(^a\)Determined by HPLC.
3-(7-Methoxy-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18b)

![Chemical Structure](image)

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.³

**HPLC**: Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, $\lambda = 300$ nm, $t_R = 23.083$ min and $t_R = 27.820$ min.

| Entry | General procedure | Sequences        | Indole/Products$^a$ | ee (%)$^a$ |
|-------|------------------|------------------|---------------------|------------|
| 1     | A                | st-DNA           | 4 : 96              | (+) 17     |
| 2     | B                | ODN5/ODN4        | 20 : 80             | (+) 38     |
| 3     | C                | ODN1/ODN4        | 48 : 52             | (−) 12     |
| 4     | D                | ODN2/ODN4        | 22 : 78             | (−) 86     |
| 5     | E                | ODN3/ODN4        | 68 : 32             | (−) 29     |

$^a$Determined by HPLC.
3-(6-Methoxy-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18c)

\[
\text{\includegraphics[width=0.3\textwidth]{image.png}}
\]

\(^1\text{H NMR and } ^{13}\text{C NMR spectra matched those reported in the literature.}\)

**HPLC:** Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, \(t_R = 33.767\) min and \(t_R = 52.823\) min.

| Entry | General procedure | Sequences | Indole/Products\(^a\) | ee (%)\(^a\) |
|-------|------------------|-----------|---------------------|--------------|
| 1     | A                | st-DNA    | 12 : 88             | (+) 29       |
| 2     | B                | ODN5/ODN4 | 35 : 65             | (+) 5        |
| 3     | C                | ODN1/ODN4 | 56 : 44             | (−) 16       |
| 4     | D                | ODN2/ODN4 | 36 : 64             | (−) 86       |
| 5     | E                | ODN3/ODN4 | 79 : 21             | (−) 19       |

\(^a\)Determined by HPLC.
3-(5-Methoxy-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18d)

\[
\text{HN-} \begin{array}{c}
\text{N} \\
\end{array} \begin{array}{c}
\text{OMe} \\
\end{array}
\text{Me}
\]

\(^{1}\text{H NMR and }^{13}\text{C NMR spectra matched those reported in the literature.}\)

**HPLC:** Chiralpak IA column, 100 bar, \(T = 20^\circ\text{C}\), \(n\)-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, \(\lambda = 300\text{ nm}\), \(t_R = 24.167\text{ min}\) and \(t_R = 28.463\text{ min}\).

| Entry | General procedure | Sequences    | Indole/Products\(^a\) | ee (%)\(^a\) |
|-------|-------------------|--------------|------------------------|--------------|
| 1     | A                 | st-DNA       | 17 : 83                | (+) 43       |
| 2     | B                 | ODN5/ODN4    | 1 : 99                 | (+) 41       |
| 3     | C                 | ODN1/ODN4    | 22 : 78                | (−) 6        |
| 4     | D                 | ODN2/ODN4    | 15 : 85                | (−) 74       |
| 5     | E                 | ODN3/ODN4    | 35 : 65                | 0            |

\(^a\)Determined by HPLC.
2-Methyl-3-(7-methyl-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18e)

The racemic was isolated as a slightly yellow oil. $R_f = 0.59$ (PE/EtOAc 7:3). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 3.0$ Hz, 1H), 7.92 (br, -NH), 7.63 (d, $J = 3.0$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 7.02-6.97 (m, 2H), 4.30-4.21 (m, 1H), 3.40 (dd, $J = 14.4, 6.3$ Hz, 1H), 2.90 (dd, $J = 14.4, 7.9$ Hz, 1H), 2.46 (s, 3H), 1.31 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 197.5, 167.1, 144.8, 135.9, 127.3, 126.3, 122.6, 122.4, 120.3, 119.7, 117.0, 114.4, 42.6, 29.0, 17.0, 16.7. HRMS-ESI $m/z$: calculated for C$_{16}$H$_{17}$N$_2$OS [M+H]$^+$ 285. 1061. found 323.1063. IR (neat): 3411, 1676, 1388, 926, 733 cm$^{-1}$.

**HPLC:** Chiralpak IA column, 250 bar, $T = 30$ °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, $\lambda = 280$ nm, $t_R = 56.977$ min and $t_R = 66.383$ min.

| Entry | General procedure | Sequences | Indole/Products$^a$ | ee (%)$^a$ |
|-------|-------------------|-----------|---------------------|------------|
| 1     | A                  | st-DNA    | 8 : 92              | (+) 11     |
| 2     | B                  | ODN5/ODN4 | 8 : 92              | (+) 37     |
| 3     | C                  | ODN1/ODN4 | 75 : 25             | (-) 14     |
| 4     | D                  | ODN2/ODN4 | 12 : 88             | (-) 82     |
| 5     | E                  | ODN3/ODN4 | 74 : 26             | (+) 8      |

$^a$Determined by HPLC.
2-Methyl-3-(6-methyl-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18f)

The racemic was isolated as a slightly yellow oil. $R_f = 0.58$ (PE/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 3.0$ Hz, 1H), 7.85 (br, 1H), 7.63 (d, $J = 3.0$ Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.11 (br, 1H), 6.98 (dd, $J = 8.0$, 1.4 Hz, 1H), 6.93 (d, $J = 2.3$ Hz, 1H), 4.31-4.19 (m, 1H), 3.38 (dd, $J = 14.3$, 6.3 Hz, 1H), 2.88 (dd, $J = 14.3$, 7.9 Hz, 1H), 2.46 (s, 3H), 1.30 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 197.6, 167.1, 144.8, 136.8, 131.8, 126.3, 125.6, 122.0, 121.2, 118.9, 113.7, 111.1, 42.6, 28.9, 21.8, 16.9. HRMS-ESI $m/z$: calculated for C$_{16}$H$_{17}$N$_2$OS [M+H]$^+$ 285.1061. found 323.1063. IR (neat): 3406, 1677, 1453, 1388, 800, 734 cm$^{-1}$.

HPLC: Chiralpak IB column, 250 bar, $T = 30$ °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, $\lambda = 300$ nm, $t_R = 15.375$ min and $t_R = 19.436$ min.

| Entry | General procedure | Sequences     | Indole/Products$^a$ | ee (%)$^a$ |
|-------|------------------|---------------|---------------------|-----------|
| 1     | A                | st-DNA        | 5 : 95              | (+) 36    |
| 2     | B                | ODN5/ODN4     | 1 : 99              | (+) 36    |
| 3     | C                | ODN1/ODN4     | 56 : 44             | (−) 14    |
| 4     | D                | ODN2/ODN4     | 1 : 99              | (−) 73    |
| 5     | E                | ODN3/ODN4     | 58 : 42             | (+) 13    |

$^a$Determined by HPLC.
2-Methyl-3-(5-methyl-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18g)

1H NMR and 13C NMR spectra matched those reported in the literature.3

**HPLC:** Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, tR = 34.221 min and tR = 44.000 min.

| Entry | General procedure | Sequences | Indole/Productsa | ee (%)a |
|-------|-------------------|-----------|-----------------|---------|
| 1     | A                 | st-DNA    | 1 : 99          | (+) 43  |
| 2     | B                 | ODN5/ODN4 | 10 : 90         | (+) 43  |
| 3     | C                 | ODN1/ODN4 | 54 : 46         | (−) 4   |
| 4     | D                 | ODN2/ODN4 | 19 : 81         | (−) 67  |
| 5     | E                 | ODN3/ODN4 | 50 : 50         | (+) 20  |

*aDetermined by HPLC.
3-(5-Hydroxy-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18h)

![Chemical Structure](image)

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.$^3$

**HPLC:** Chiralpak IA column, 250 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, $\lambda = 300$ nm, $t_R = 29.340$ min and $t_R = 34.167$ min.

| Entry | General procedure | Sequences   | Indole/Products$^a$ | ee (%)$^a$ |
|-------|------------------|-------------|---------------------|------------|
| 1     | A                | st-DNA      | 17 : 83             | (+) 37     |
| 2     | B                | ODN5/ODN4   | > 1 : 99            | (+) 29     |
| 3     | C                | ODN1/ODN4   | 29 : 71             | (−) 20     |
| 4     | D                | ODN2/ODN4   | 12 : 88             | (−) 70     |
| 5     | E                | ODN3/ODN4   | 47 : 53             | (−) 15     |

$^a$Determined by HPLC.
3-(5-Fluoro-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18i)

The racemic was isolated as a slightly yellow oil. \( R_f = 0.34 \) (PE/EtOAc 7:3). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.03 (d, \( J = 3.1 \) Hz, 1H), 8.01 (s, 1H), 7.65 (d, \( J = 3.1 \) Hz, 1H), 7.39 (dd, \( J = 9.7, 2.5 \) Hz, 1H), 7.22 (dd, \( J = 9.7, 4.3 \) Hz, 1H), 7.04 (d, \( J = 2.4 \) Hz, 1H), 6.92 (td, \( J = 9.0, 2.5 \) Hz, 1H), 4.27-4.13 (m, 1H), 3.34 (dd, \( J = 14.4, 6.3 \) Hz, 1H), 2.84 (dd, \( J = 14.4, 7.9 \) Hz, 1H), 1.29 (d, \( J = 6.9 \) Hz, 3H).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 197.3, 167.0, 157.9 (d, \( J = 234.3 \) Hz), 144.9, 132.8, 128.1 (d, \( J = 9.8 \) Hz), 126.4, 124.4, 114.1 (d, \( J = 4.8 \) Hz), 111.7 (d, \( J = 9.7 \) Hz), 110.4 (d, \( J = 26.5 \) Hz), 104.2 (d, \( J = 23.5 \) Hz), 42.5, 28.9, 16.8. \(^1^9\)F NMR (377 MHz, CDCl\(_3\)) \( \delta \) -124.71. HRMS-ESI \( m/z \): calculated for C\(_{15}\)H\(_{13}\)FN\(_2\)OSNa [M+Na\(^+\)] 307.0630. found 307.0554. IR (neat): 3410, 1678, 1485, 1389, 936 cm\(^{-1}\).

HPLC: Chiralpak IA column, 250 bar, T = 30 °C, Hexane/-PrOH = 97:3, 1 mL/min, \( \lambda = 280 \) nm, \( t_R = 45.925 \) min and \( t_R = 53.440 \) min.

| Entry | General procedure | Sequences      | Indole/Products\(^a\) | ee (%)\(^a\) |
|-------|-------------------|----------------|------------------------|--------------|
| 1     | A                 | st-DNA         | 13 : 87                | (+) 27       |
| 2     | B                 | ODN5/ODN4      | 32 : 68                | (+) 42       |
| 3     | C                 | ODN1/ODN4      | 85 : 15                | (−) 2        |
| 4     | D                 | ODN2/ODN4      | 61 : 39                | (−) 80       |
| 5     | E                 | ODN3/ODN4      | 87 : 13                | (+) 8        |

\(^a\) Determined by HPLC.
3-(5-Chloro-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18j)

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.$^3$

**HPLC:** Chiralpak IA column, 250 bar, $T = 20 \, ^\circ\text{C}$, $n$-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, $\lambda = 300 \, \text{nm}$, $t_R = 26.413 \, \text{min}$ and $t_R = 32.027 \, \text{min}$.

| Entry | General procedure | Sequences | Indole/Products$^a$ | ee (%)$^a$ |
|-------|-------------------|-----------|---------------------|------------|
| 1     | A                 | st-DNA    | 31 : 69             | (+) 19     |
| 2     | B                 | ODN5/ODN4 | 53 : 47             | (+) 4      |
| 3     | C                 | ODN1/ODN4 | 89 : 11             | (+) 27     |
| 4     | D                 | ODN2/ODN4 | 68 : 32             | (−) 63     |
| 5     | E                 | ODN3/ODN4 | 95 : 5              | (+) 7      |

$^a$Determined by HPLC.
**3-(5-Bromo-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (18k)**

![Chemical Structure](image)

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.$^3$

**HPLC:** Chiralpak IA column, 250 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, $\lambda = 300$ nm, $t_R = 27.153$ min and $t_R = 33.570$ min.

| Entry | General procedure | Sequences   | Indole/Products$^a$ | ee (%)$^a$ |
|-------|-------------------|-------------|---------------------|------------|
| 1     | A                 | st-DNA      | 30 : 70             | (+) 16     |
| 2     | B                 | ODN5/ODN4   | 63 : 37             | (+) 20     |
| 3     | C                 | ODN1/ODN4   | 90 : 10             | (+) 11     |
| 4     | D                 | ODN2/ODN4   | 82 : 18             | (−) 54     |
| 5     | E                 | ODN3/ODN4   | 96 : 4              | (+) 19     |

$^a$Determined by HPLC.
Methyl 3-(2-methyl-3-oxo-3-(thiazol-2-yl)propyl)-1H-indole-5-carboxylate (18l)

The racemic was isolated as a slightly yellow oil. $R_t = 0.18$ (PE/EtOAc 7:3). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.56-8.51 (br, 1H), 8.36 (br, -NH), 8.02 (d, $J = 3.0$ Hz, 1H), 7.88 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.64 (d, $J = 3.0$ Hz, 1H), 7.31 (d, $J = 8.6$ Hz, 1H), 7.05 (d, $J = 2.2$ Hz, 1H), 4.29-4.15 (m, 1H), 3.95 (s, 3H), 3.41 (dd, $J = 14.5$, 6.5 Hz, 1H), 2.93 (dd, $J = 14.5$, 7.5 Hz, 1H), 1.31 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 197.3, 168.5, 166.8, 144.9, 138.9, 127.3, 126.4, 124.0, 123.4, 122.3, 121.4, 115.2, 110.9, 52.0, 42.7, 28.7, 16.9. HRMS-ESI m/z: calculated for C$_{17}$H$_{16}$N$_2$O$_3$SNa [M+Na]$^+$ 351.0779. found 351.0762. IR (neat): 3334, 1679, 1435, 1237, 747 cm$^{-1}$.

HPLC: Chiralpak IA column, 250 bar, $T = 30$ °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, $\lambda = 280$ nm, $t_R = 51.429$ min and $t_R = 57.744$ min.

| Entry | General procedure | Sequences | Indole/Products$^a$ | ee (%)$^a$ |
|-------|------------------|-----------|---------------------|-----------|
| 1     | A                | st-DNA    | 57 : 43             | (+) 23    |
| 2     | B                | ODN5/ODN4 | 76 : 24             | (+) 24    |
| 3     | C                | ODN1/ODN4 | traces              | nd        |
| 4     | D                | ODN2/ODN4 | 91 : 9              | (−) 49    |
| 5     | E                | ODN3/ODN4 | traces              | nd        |

$^a$Determined by HPLC.
2-Methyl-3-(5-(piperidin-1-yl)-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18m)

![Chemical Structure]

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.$^3$

**HPLC:** Chiralpak IB column, 250 bar, $T = 30 \degree C$, $n$-Hexane/$i$-PrOH = 92:8, 1 mL/min, $\lambda = 300$ nm, $t_R = 27.286$ min and $t_R = 34.958$ min.

| Entry | General procedure | ODN     | Indole/Products$^a$ | ee (%)$^a$ |
|-------|-------------------|---------|----------------------|------------|
| 1     | A                 | st-DNA  | 5 : 95               | (+) 72     |
| 2     | B                 | ODN5/ODN4 | 16 : 84         | (+) 72     |
| 3     | C                 | ODN1/ODN4 | traces           | nd         |
| 4     | D                 | ODN2/ODN4 | 53 : 47         | (−) 67     |
| 5     | E                 | ODN3/ODN4 | traces           | (+) 4      |

$^a$Determined by HPLC.
2-Methyl-3-(5-morpholino-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18n)

\[
\begin{align*}
\text{HN} & \text{Me} \\
\text{N} & \text{O} \\
\text{S} & \text{O}
\end{align*}
\]

\(^1\text{H} \text{NMR and } ^{13}\text{C} \text{NMR spectra matched those reported in the literature.}^3 \]

**HPLC:** Chiralpak IA column, 250 bar, \(T = 30 \, ^{\circ}\text{C}\), \(n\text{-Hexane/i-PrOH} = 90:10\), 1 mL/min, \(\lambda = 280 \, \text{nm}\), \(t_R = 29.559 \, \text{min}\) and \(t_R = 34.195 \, \text{min}\).

| Entry | General procedure | Sequences       | Indole/Products\(^a\) | ee (%)\(^a\) |
|-------|-------------------|-----------------|-----------------------|--------------|
| 1     | A                 | st-DNA          | 24 : 76               | (+) 79       |
| 2     | B                 | ODN5/ODN4       | 23 : 77               | (+) 71       |
| 3     | C                 | ODN1/ODN4       | 94 : 6                | (+) 8        |
| 4     | D                 | ODN2/ODN4       | 50 : 50               | (−) 65       |
| 5     | E                 | ODN3/ODN4       | 87 : 13               | (+) 8        |

\(^a\)Determined by HPLC.
2-Methyl-3-(1-methyl-1H-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (18o)

$^1$H NMR and $^{13}$C NMR spectra matched those reported in the literature.$^3$

**HPLC**: Chiralpak IB column, 250 bar, $T = 15$ °C, $n$-Hexane/$i$-PrOH = 98:2, 0.8 mL/min, $\lambda = 230$ nm, $t_R = 21.430$ min and $t_R = 25.843$ min.

| Entry | General procedure | Sequences       | Indole/Products$^a$ | ee (%)$^a$ |
|-------|------------------|-----------------|---------------------|------------|
| 1     | A                | st-DNA          | $> 1 : 99$          | (+) 3      |
| 2     | B                | ODN5/ODN4       | $> 1 : 99$          | (−) 36     |
| 3     | C                | ODN1/ODN4       | traces              | nd         |
| 4     | D                | ODN2/ODN4       | $> 1 : 99$          | (+) 61     |
| 5     | E                | ODN3/ODN4       | traces              | nd         |

$^a$Determined by HPLC.
V. NMR of compounds

a. $^1$H and $^{13}$C NMR spectra for compound (3)
b. $^1$H and $^{13}$NMR spectra of compound (4)
c. $^1$H and $^{13}$C NMR spectra for compound (5)
d. $^1$H and $^{13}$C NMR spectra for compound (6)
e. $^1$H and $^{13}$C NMR spectra of compound (14)
f. $^1$H, $^{13}$C and $^{31}$P NMR spectra of compound (15)
g. $^1$H and $^{13}$C spectra of compound (18e)
h. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compound (18f)
i. $^1$H, $^{13}$C and $^{19}$F NMR spectra of compound (18i)
j. $^1$H and $^{13}$C NMR spectra of compound (18)
VI. Results of catalysis: HPLC chromatograms

a. HPLC chromatograms of compound (18a)

Racemic [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, 
\( t_R = 44.430 \text{ min} \) and \( t_R = 53.322 \text{ min} \)].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 44.430         | 49.9295   |
| 2    | 53.322         | 50.0705   |

Indole [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, 
\( t_R = 13.494 \text{ min} \)].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18a of 5:95 and an enantiomeric excess of (+) 21 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 51.196 min and t_R = 58.355 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 51.196         | 39.3979   |
| 2    | 58.355         | 60.6021   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18a of 13:87 and an enantiomeric excess of (+) 40 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 44.668 min and t_R = 53.437 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 44.668         | 29.8503   |
| 2    | 53.437         | 70.1497   |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18a of 70:30 and an enantiomeric excess of (-) 20 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 45.948 min and t_R = 52.906 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18a of 24:76 and an enantiomeric excess of (-) 80 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 45.162 min and t_R = 54.145 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18a of 70:30 and an enantiomeric excess of (+) 7 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, tR = 45.641 min and tR = 51.833 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 45.641         | 46.5957   |
| 2    | 51.833         | 53.4043   |
b. HPLC chromatograms of compound (18b)

**Racemic** [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 23.083 min and t<sub>R</sub> = 27.820 min].

![HPLC Chromatogram of Racemic Compound](image)

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 23.083         | 50.04    |
| 2         | 27.82          | 49.96    |

**Indole** [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 9.053 min].

![HPLC Chromatogram of Indole](image)

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 9.053          | 100      |
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18b of 4:96 and an enantiomeric excess of (+) 17 [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, \( \lambda = 300 \) nm, \( t_R = 21.600 \) min and \( t_R = 26.183 \) min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18b of 20:80 and an enantiomeric excess of (+) 38 [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, \( \lambda = 300 \) nm, \( t_R = 23.207 \) min and \( t_R = 27.953 \) min].
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18b of 48:52 and an enantiomeric excess of (-) 12 [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tR = 23.213 min and tR = 28.000 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18b of 22:78 and an enantiomeric excess of (-) 86 [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tR = 23.200 min and tR = 27.993 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18b of 68:32 and an enantiomeric excess of (-) 29 [Chiralpak IB column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 23.270 min and t<sub>R</sub> = 28.037 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
|           | min            | %        |
| 1         | 23.27          | 64.64    |
| 2         | 28.037         | 35.36    |
c. HPLC chromatograms of compound (18c)

**Racemic** [Chiralpak IA column, 100 bar, T = 25°C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t_R = 33.767 min and t_R = 52.823 min].

![HPLC Chromatogram for Racemic](image)

| Peak Name | Retention Time | Rel. Area |
|-----------|----------------|-----------|
| 1         | 33.767         | 50.9      |
| 2         | 52.823         | 49.1      |

**Indole** [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t_R = 13.497 min].

![HPLC Chromatogram for Indole](image)

| Peak Name | Retention Time | Rel. Area |
|-----------|----------------|-----------|
| 1         | 13.497         | 100       |
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18c of 12:88 and an enantiomeric excess of (+) 29 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tᵣ = 33.633 min and tᵣ = 53.603 min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18c of 35:65 and an enantiomeric excess of (+) 5 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tᵣ = 33.163 min and tᵣ = 52.503 min].
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18c of 56:44 and an enantiomeric excess of (-) 16 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t_R = 33.193 min and t_R = 52.633 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18c of 36:64 and an enantiomeric excess of (-) 86 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t_R = 33.150 min and t_R = 52.657 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18c of 79:21 and an enantiomeric excess of (-) 19 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tR = 33.180 min and tR = 52.690 min].

| Peak Name | Retention Time | Rel. Area |
|-----------|----------------|-----------|
| 1         | 33.18 min      | 59.64 %   |
| 2         | 52.69 min      | 40.36 %   |
d. HPLC chromatograms of compound (18d)

**Racemic** [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t\(_R\) = 24.167 min and t\(_R\) = 28.463 min].

![HPLC chromatogram of racemic compound](image)

| Peak Name | Retention Time (min) | Rel.Area (%) |
|-----------|----------------------|--------------|
| 1         | 24.167               | 49.67        |
| 2         | 28.463               | 50.33        |

**Indole** [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t\(_R\) = 14.733 min].

![HPLC chromatogram of indole](image)

| Peak Name | Retention Time (min) | Rel.Area (%) |
|-----------|----------------------|--------------|
| 1         | 14.733               | 100          |
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18d of 17:83 and an enantiomeric excess of (+) 43 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, \( t_R = 24.100 \) min and \( t_R = 28.380 \) min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18d of 1:99 and an enantiomeric excess of (+) 41 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, \( t_R = 24.010 \) min and \( t_R = 28.230 \) min].
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18d of 22:78 and an enantiomeric excess of (-) 6 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tR = 24.010 min and tR = 28.257 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18d of 15:85 and an enantiomeric excess of (-) 74 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, tR = 23.990 min and tR = 28.273 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18d of 35:65 and an enantiomeric excess of 0 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 95:5, 1 mL/min, λ = 300 nm, t_R = 24.003 min and t_R = 28.263 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 24.003         | 50.27    |
| 2         | 28.263         | 49.73    |
e. HPLC chromatograms of compound (18e)

Racemic [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, 
\( t_R = 56.977 \) min and \( t_R = 66.383 \) min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 56.977         | 49.5647   |
| 2    | 66.383         | 50.4353   |

Indole [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, 
\( t_R = 12.066 \) min].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18e of 8:92 and an enantiomeric excess of (+) 11 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, t_R = 54.394 min and t_R = 61.506 min].

| Peak | Retention Time | Rel. Area |
|------|---------------|-----------|
|      | min           | %         |
| 1    | 54.394        | 44.5081   |
| 2    | 61.506        | 55.4919   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18e of 8:92 and an enantiomeric excess of (+) 37 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, t_R = 54.443 min and t_R = 61.179 min].

| Peak | Retention Time | Rel. Area |
|------|---------------|-----------|
|      | min           | %         |
| 1    | 54.443        | 31.3951   |
| 2    | 61.179        | 68.6049   |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18e of 75:25 and an enantiomeric excess of (-) 14 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, t_R = 58.679 min and t_R = 68.316 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18e of 12:88 and an enantiomeric excess of (-) 82 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, t_R = 54.533 min and t_R = 61.299 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18e of 74:26 and an enantiomeric excess of (+) 8 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 98:2, 1 mL/min, λ = 280 nm, t_R = 56.049 min and t_R = 68.013 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 56.049 min     | 45.9401   |
| 2    | 68.013 min     | 54.0599   |
f. HPLC chromatograms of compound (18f)

Racemic [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 15.375 min and t<sub>R</sub> = 19.436 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 15.375         | 50.1345   |
| 2    | 19.436         | 49.8655   |

Indole [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 8.736 min].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18f of 5:95 and an enantiomeric excess of (+) 36 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 15.744 min and t_R = 19.592 min].

| Peak | Retention Time | Rel. Area |
|------|---------------|-----------|
| 1    | 15.744        | 31.951    |
| 2    | 19.592        | 68.049    |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18f of 1:99 and an enantiomeric excess of (+) 36 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 15.582 min and t_R = 19.088 min].

| Peak | Retention Time | Rel. Area |
|------|---------------|-----------|
| 1    | 15.582        | 31.7679   |
| 2    | 19.088        | 68.2321   |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18f of 56:44 and an enantiomeric excess of (-) 14 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 15.703 min and t_R = 19.736 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 15.703         | 57.0111   |
| 2    | 19.736         | 42.9889   |

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18f of 1:99 and an enantiomeric excess of (-) 73 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 15.708 min and t_R = 19.308 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 15.708         | 86.5098   |
| 2    | 19.308         | 13.4902   |
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18f of 58:42 and an enantiomeric excess of (+) 13 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, tR = 15.879 min and tR = 19.941 min].
g. HPLC chromatograms of compound (18g)

Racemic [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, t_R = 34.221 min and t_R = 44.000 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 34.221 min     | 49.7761   |
| 2    | 44 min         | 50.2239   |

Indole [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, t_R = 12.395 min].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18g of 1:99 and an enantiomeric excess of (+) 43 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, t_R = 38.225 min and t_R = 43.982 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 38.225         | 28.6195   |
| 2    | 43.982         | 71.3805   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18g of 10:90 and an enantiomeric excess of (+) 43 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, t_R = 34.838 min and t_R = 46.129 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 34.838         | 28.3881   |
| 2    | 46.129         | 71.6119   |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18g of 54:46 and an enantiomeric excess of (-) 4 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, tR = 36.447 min and tR = 41.916 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 36.447         | 52.2224   |
| 2    | 41.916         | 47.7776   |

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18g of 19:81 and an enantiomeric excess of (-) 67 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3,1 mL/min, λ = 280 nm, tR = 34.297 min and tR = 46.508 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 34.297         | 83.7295   |
| 2    | 46.508         | 16.2705   |
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18g of 50:50 and an enantiomeric excess of (+) 20 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 37.651 min and t_R = 43.591 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 37.651         | 40.1075   |
| 2    | 43.591         | 59.8925   |
h. HPLC chromatograms of compound (18h)

**Racemic** [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, t_R = 29.340 min and t_R = 34.167 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 29.34          | 49.91    |
| 2         | 34.167         | 50.09    |

**Indole** [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, t_R = 19.767 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 19.767         | 100      |
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18h of 17:83 and an enantiomeric excess of (+) 37 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, t_R = 29.600 min and t_R = 34.463 min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18h of > 1:99 and an enantiomeric excess of (+) 29 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, t_R = 29.600 min and t_R = 34.460 min].
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18h of 29:71 and an enantiomeric excess of (-) 20 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, tR = 29.577 min and tR = 34.457 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 29.577         | 59.99    |
| 2         | 34.457         | 40.01    |

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18h of 12:88 and an enantiomeric excess of (-) 70 [Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, tR = 29.550 min and tR = 34.473 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 29.550         | 85.06    |
| 2         | 34.473         | 14.94    |
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18h of 47:53 and an enantiomeric excess of (-) 15

[Chiralpak IA column, 100 bar, T = 25 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 90:10, 1 mL/min, λ = 300 nm, t_R = 29.583 min and t_R = 34.480 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 29.6           | 57.58    |
| 2         | 34.487         | 42.42    |
i. HPLC chromatograms of compound (18i)

![HPLC chromatogram](image)

**Racemic** [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, \( t_R = 45.925 \) min and \( t_R = 53.440 \) min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 45.925         | 50.0692   |
| 2    | 53.440         | 49.9308   |

**Indole** [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, \( t_R = 16.861 \) min].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18i of 13:87 and an enantiomeric excess of (+) 27 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 47.126 min and t_R = 53.182 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 47.126         | 36.6143   |
| 2    | 53.182         | 63.3857   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18i of 32:68 and an enantiomeric excess of (+) 42 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 46.659 min and t_R = 52.234 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 46.659         | 29.0707   |
| 2    | 52.234         | 70.9293   |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18i of 85:15 and an enantiomeric excess of (-) 2 [Chiralpak IA column, 250 bar, $T = 30 \, ^\circ C$, $n$-Hexane/i-PrOH = 97:3, 1 mL/min, $\lambda = 280$ nm, $t_R = 45.585$ min and $t_R = 51.319$ min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 45.585         | 51.2158   |
| 2    | 51.319         | 48.7842   |

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18i of 61:39 and an enantiomeric excess of (-) 80 [Chiralpak IA column, 250 bar, $T = 30 \, ^\circ C$, $n$-Hexane/i-PrOH = 97:3, 1 mL/min, $\lambda = 280$ nm, $t_R = 46.312$ min and $t_R = 51.965$ min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 46.312         | 89.9368   |
| 2    | 51.965         | 10.0632   |
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18i of 87:13 and an enantiomeric excess of (+) 8 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 97:3, 1 mL/min, λ = 280 nm, t_R = 47.897 min and t_R = 54.957 min].
j. **HPLC chromatograms of compound (18j)**

**Racemic** [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, $t_R = 26.413$ min and $t_R = 32.027$ min].

```
| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 26.413         | 48.76    |
| 2         | 32.027         | 51.24    |
```

**Indole** [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, $t_R = 14.613$ min].

```
| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 14.613         | 100      |
```
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18j of 31:69 and an enantiomeric excess of (+) 19 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.137 min and t_R = 33.580 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 27,137         | 40,52    |
| 2         | 33,58          | 59,48    |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18j of 53:47 and an enantiomeric excess of (+) 4 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.190 min and t_R = 33.507 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 33,517         | 47,83    |
| 2         | 37,587         | 52,17    |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18j of 89:11 and an enantiomeric excess of (+) 27 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, tR = 27.287 min and tR = 33.593 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18j of 68:32 and an enantiomeric excess of (−) 63 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, tR = 27.233 min and tR = 33.563 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18j of 95:5 and an enantiomeric excess of (+) 7 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, tR = 27.243 min and tR = 33.500 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|---------|
| 1         | 27.243         | 46.31   |
| 2         | 33.5           | 53.69   |
k. HPLC chromatograms of compound (18k)

Racemic [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.153 min and t_R = 33.570 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 27.153         | 50.18    |
| 2         | 33.57          | 49.82    |

Indole [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 14.877 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
| 1         | 14.877         | 100      |
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18k of 30:70 and an enantiomeric excess of (+) 16 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.437 min and t_R = 33.980 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
|           | min            | %        |
| 1         | 27,437         | 41.86    |
| 2         | 33,98          | 58.14    |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18k of 63:37 and an enantiomeric excess of (+) 20 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.153 min and t_R = 33.583 min].

| Peak Name | Retention Time | Rel.Area |
|-----------|----------------|----------|
|           | min            | %        |
| 1         | 27,153         | 39.97    |
| 2         | 33,583         | 60.03    |
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18k of 90:10 and an enantiomeric excess of (+) 11 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.137 min and t_R = 33.657 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18k of 82:18 and an enantiomeric excess of (-) 54 [Chiralpak IA column, 100 bar, T = 20 °C, n-Heptane (+ 0.1% diethylamine)/EtOH (+ 0.1% diethylamine) = 97:3, 1 mL/min, λ = 300 nm, t_R = 27.147 min and t_R = 33.623 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18k of 96:4 and an enantiomeric excess of (+) 19 \([\text{Chiralpak IA column, } 100 \text{ bar, } T = 20 ^\circ \text{C, } n-\text{Heptane (}+ \ 0.1\% \ \text{diethylamine)/EtOH (}+ \ 0.1\% \ \text{diethylamine)} = 97:3, 1 \text{ mL/min, } \lambda = 300 \text{ nm, } t_R = 27.117 \text{ min and } t_R = 33.543 \text{ min}].\)
1. HPLC chromatograms of compound (18l)

**Racemic** [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm, 
$t_R = 51.429\text{ min}$ and $t_R = 57.744\text{ min}$].

![HPLC chromatograph of racemic compound](image)

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| min  | %              |           |
| 1    | 51.429         | 50.4008   |
| 2    | 57.744         | 49.5992   |

**Indole** [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm, 
$t_R = 24.381\text{ min}$].

![HPLC chromatograph of indole](image)
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18l of 57:43 and an enantiomeric excess of (+) 23 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm, t R = 51.608 min and t R = 57.735 min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18l of 76:24 and an enantiomeric excess of (+) 24 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm, t R = 51.501 min and t R = 57.730 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 51.608         | 38.7279   |
| 2    | 57.735         | 61.2721   |

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 51.501         | 38.1842   |
| 2    | 57.73          | 61.8158   |
Following the general procedure C. HPLC analysis of the crude residue did not detect any product [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18l of 91:9 and an enantiomeric excess of (-) 49 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm, t_R = 52.021 min and t_R = 58.393 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 52.021         | 74.4905   |
| 2    | 58.393         | 25.5095   |
Following the general procedure E. HPLC analysis of the crude residue did not detect any product [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 95:5, 1 mL/min, λ = 280 nm].
m. HPLC chromatograms of compound (18m)

**Racemic** [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 27.286 min and t_R = 34.958 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 27.286 min     | 50.2633%  |
| 2    | 34.958 min     | 49.7367%  |

**Indole** [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 300 nm, t_R = 16.386 min].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18m of 5:95 and an enantiomeric excess of (+) 72 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 28.374 min and t<sub>R</sub> = 37.377 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 28.374         | 85.8999   |
| 2    | 37.377         | 14.1001   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18m of 16:84 and an enantiomeric excess of (+) 72 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t<sub>R</sub> = 28.261 min and t<sub>R</sub> = 37.161 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 28.261         | 85.762    |
| 2    | 37.161         | 14.238    |
Following the general procedure C. HPLC analysis of the crude residue did not detect any product [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18m of 53:47 and an enantiomeric excess of (-) 67 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 28.587 min and t_R = 37.376 min].

| Peak | Retention Time (min) | Rel. Area |
|------|----------------------|-----------|
| 1    | 28.587               | 16.6409   |
| 2    | 37.376               | 83.3591   |
Following the general procedure E. HPLC analysis of the crude residue detected traces of 18m and an enantiomeric excess of (+) 4 [Chiralpak IB column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 92:8, 1 mL/min, λ = 300 nm, t_R = 28.552 min and t_R = 37.394 min].
n. **HPLC chromatograms of compound (18n)**

![HPLC Chromatogram](image)

**Racemic** [Chiralpak IA column, 250 bar, \( T = 30^\circ \text{C} \), \( n\)-Hexane/\( i\)-PrOH = 90:10, 1 mL/min, \( \lambda = 280 \text{ nm} \), \( t_R = 29.559 \text{ min} \) and \( t_R = 34.195 \text{ min} \)].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 29.559         | 50.329    |
| 2    | 34.195         | 49.671    |

**Indole** [Chiralpak IA column, 250 bar, \( T = 30^\circ \text{C} \), \( n\)-Hexane/\( i\)-PrOH = 90:10, 1 mL/min, \( \lambda = 280 \text{ nm} \), \( t_R = 14.237 \text{ min} \)].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/18n of 24:76 and an enantiomeric excess of (+) 79 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 280 nm, t_R = 30.642 min and t_R = 35.224 min].

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/18n of 23:77 and an enantiomeric excess of (+) 71 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 280 nm, t_R = 30.544 min and t_R = 35.111 min].
Following the general procedure C. HPLC analysis of the crude residue indicated a ratio indole/18n of 94:6 and an enantiomeric excess of (+) 8 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 280 nm, t_R = 29.938 min and t_R = 34.499 min].

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18n of 50:50 and an enantiomeric excess of (-) 65 [Chiralpak IA column, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 280 nm, t_R = 30.433 min and t_R = 35.358 min].
Following the general procedure E. HPLC analysis of the crude residue indicated a ratio indole/18n of 87:13 and an enantiomeric excess of (+) 8 [Chiralpak IA, 250 bar, T = 30 °C, n-Hexane/i-PrOH = 90:10, 1 mL/min, λ = 280 nm, t_R = 30.138 min and t_R = 34.758 min].

| Peak | Retention Time | Rel. Area  |
|------|----------------|------------|
| 1    | 30.138 min     | 45.8069 %  |
| 2    | 34.758 min     | 54.1931 %  |
o. HPLC chromatograms of compound (18o)

**Racemic** [Chiralpak IB column, 250 bar, T = 15 °C, n-Hexane/i-PrOH = 98:2, 0.8 mL/min, λ = 230 nm, t_R = 21.430 min and t_R = 25.843 min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 21.43          | 49.9162   |
| 2    | 25.843         | 50.0838   |

**Indole** [Chiralpak IB column, 250 bar, T = 15 °C, n-Hexane/i-PrOH = 98:2, 0.8 mL/min, λ = 230 nm, t_R = 14.091].
Following the general procedure A. HPLC analysis of the crude residue indicated a ratio indole/\(^{18}o\) of > 1:99 and an enantiomeric excess of (+) 3 [Chiralpak IB column, 250 bar, T = 15 °C, \(n\)-Hexane/i-PrOH = 98:2, 0.8 mL/min, \(\lambda = 230\) nm, \(t_R = 21.993\) min and \(t_R = 26.590\) min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 21.993         | 51.4863   |
| 2    | 26.59          | 48.5137   |

Following the general procedure B. HPLC analysis of the crude residue indicated a ratio indole/\(^{18}o\) of > 1:99 and an enantiomeric excess of (-) 36 [Chiralpak IB column, 250 bar, T = 15 °C, \(n\)-Hexane/i-PrOH = 98:2, 0.8 mL/min, \(\lambda = 230\) nm, \(t_R = 22.720\) min and \(t_R = 27.274\) min].

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
| 1    | 22.72          | 31.9129   |
| 2    | 27.274         | 68.0871   |
Following the general procedure C. HPLC analysis of the crude residue detected traces of 18o and an enantiomeric excess of 0 [Chiralpak IB column, 250 bar, T = 15 °C, n-Hexane/i-PrOH = 98:2, 0.8 mL/min, λ = 230 nm, t_R = 22.396 min and t_R = 27.132 min]. Presence of by-products.

Following the general procedure D. HPLC analysis of the crude residue indicated a ratio indole/18o of > 1:99 and an enantiomeric excess of (+) 61 [Chiralpak IB column, 250 bar, T = 15 °C, n-Hexane/i-PrOH = 98:2, 0.8 mL/min, λ = 230 nm, t_R = 21.786 min and t_R = 26.369 min].
Following the general procedure E. HPLC analysis of the crude residue detected traces of 18o and an enantiomeric excess of (−) 4 [Chiralpak IB column, 250 bar, T = 15 °C, n-Hexane/i-PrOH = 98:2, 0.8 mL/min, λ = 230 nm, tR = 23.152 min and tR = 27.804 min]. Presence of by-products.

| Peak | Retention Time | Rel. Area |
|------|----------------|-----------|
|      | min            | %         |
| 1    | 23.152         | 47.8492   |
| 2    | 27.804         | 52.1508   |
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