Flow chemistry and polymer-supported pseudoenantiomeric acylating agents enable parallel kinetic resolution of chiral saturated N-heterocycles

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1. General Information

All reactions were carried out in oven-dried glassware under an atmosphere of N₂ using standard manifold techniques.¹ Solid phase experiments were carried out in closed glass vessels under ambient air atmosphere. Chemicals were purchased from Acros, Novabiochem, TCI Deutschland GmbH, Aldrich or BioBlocks Inc. and used without further purification unless otherwise noted. Compounds that are not described in the experimental part were synthesized according to the literature procedures.

CH₃CN, THF, DMF and CH₂Cl₂ were dried by passage over two columns of anhydrous neutral A-2 alumina under an atmosphere of N₂.² Solution phase reactions unless indicated otherwise were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using potassium permanganate or ninhydrin stain.

Chromatographic purification of products (flash column chromatography) was performed on silica gel (Silicycle SiliaFlash F60, 230–400 mesh) using a forced flow of eluent at 0.2–0.4 bar. Concentration under reduced pressure was performed by rotatory evaporation at 35–40 ºC at the appropriate pressure.

The polymer was milled on a Retsch mixer mill MM 400 at 30 Hz frequency in 35 mL Teflon screw top jars using 20 mm (diameter) Teflon coated steel grinding balls. For parallel kinetic resolution experiments in flow Merck Hitachi L-6000A pump was used.

NMR spectra were recorded on BRUKER AVANCE 400 MHz, and VARIAN MERCURY 300 MHz spectrometers using CDCl₃ or d₆-DMSO as the solvent unless indicated otherwise. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26 ppm for ¹H and 77.0 ppm for ¹³C) and DMSO (2.54 ppm for ¹H and 40.5 ppm for ¹³C). All ¹³C and ¹⁹F spectra were measured with complete proton decoupling. Coupling constants are reported in Hz. IR (Infrared) data for small molecules were obtained on a JASCO FT-IR-4100 spectrometer with only major peaks being reported. The data for polymers were obtained on Varian 800 FT-IR Scimitar Series spectrometer. [α]₀ Optical rotations were measured on a JASCO P-1010 polarimeter operating at the sodium D line with a 100 mm path length cell. SFC (Supercritical Fluid Chromatography) and HPLC (High Performance Liquid Chromatography) on chiral stationary phase were performed on JASCO liquid chromatography units. Daicel Chiralcel or Chiralpak columns (0.46 × 25 cm) were used. Details of chromatographic conditions are indicated.

under each compound. **Mass spectra** were recorded by the MS service at ETH Zürich on a Waters/Micromass AutoSpec Ultime (EI); a Varian IonSpec FT-ICR (ESI); or a Bruker maXis (ESI) spectrometers.

2. Theoretical Background of Parallel Kinetic Resolution

The progress of the parallel kinetic resolution reaction (Figure 1) was simulated using *Tenua 2.1* reaction kinetic simulator available online at [http://www.bililite.com/tenua/](http://www.bililite.com/tenua/) (accessed 02 August 2016).

**Figure 1.** Parallel kinetic resolution of amines

Following approximations were adapted to generate the date set with *Tenua 2.1:

1) Reaction is first order in racemic amine and in hydroxamic acid:
   \[ r = k[\text{amine}][\text{acylhydroxamate}] \]

2) The hydroxamic acid produced in the process does not interact with other reactants and does not affect the rate of the reactions;

3) Rate constant in kinetic resolution of saturated N-heterocycles has been measured to be \(~3\cdot10^{-3} \text{(M\cdot h)}^{-1}\) (measured previously see *J.Am.Chem.Soc.* 2014, 136, 11783 – 11791)

4) Reaction of one enantiomer of the amine with acylating agents proceeds 20 times faster than the same reaction of the opposite enantiomer \((k_{\text{fast}}/k_{\text{slow}} = 20)\).
Reagent system with $s = 20$ at any given time yields the amide products in $\text{ee}_1 = 90\%$ and $\text{ee}_2 = 90\%$. The enantiopurity of the products remains constant throughout the course of the reaction.

Similar plots were generated for kinetic resolution (Figure 2)
Following approximations were adapted to generate the data set with Tenua 2.1:

1) Reaction is first order in racemic amine and in hydroxamic acid:
\[ r = k[\text{amine}][\text{acylhydroxamate}] \]

2) The hydroxamic acid produced in the process does not interact with other reactants and does not affect the rate of the reactions;

3) Rate constant in kinetic resolution of saturated N-heterocycles has been measured to be \(~3 \times 10^{-3} \text{(M}\cdot\text{h})^{-1}\) (measured previously see J. Am. Chem. Soc. 2014, 136, 11783 – 11791).

4) Reaction of one enantiomer of the amine with acylating agents proceeds 20 times faster than the same reaction of the opposite enantiomer (\(k_{\text{fast}}/k_{\text{slow}} = 20\)).

5) Acylhydroxamate is used in slight (0.6 equiv) excess.
Results:
The enantiopurity of the recovered starting material increases with time while that of the amide product decreases. For a reagent system with $s = 20$ at 51% conversion the amine can be recovered in $ee_1 = 83\%$ while the amide product in $ee_2 = 78\%$. 
Results:

**PKR** After 30 hours reagent system with \( s = 20 \) yields the amide products in ee\(_1\) = 90\% and ee\(_2\) = 90\%. The enantiopurity of the products remains constant throughout the course of the reaction.

**KR** After 30 hours reagent system with \( s = 20 \) yields the unreacted starting material in ee = 75\% and the amide product in ee = 80\%.

3. Preparation of Polymers.

3.1. Synthesis of acylating agents

**Benzyl** \((4aS,9aR)-6-bromo-3-oxo-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-4(4aH)-yl) carbonate (1a)

To a solution of \((4aS,9aR)-6-bromo-4-hydroxy-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2H)-one^3\) (125 mg, 0.44 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (4 mL) was added Et\(_3\)N (50.0 mg, 0.48 mmol, 1.10 equiv) and Cbz-Cl (75.0 mg, 0.44 mmol, 1.00 equiv) and the reaction was stirred at room temperature overnight. Upon completion the solvent was removed and the crude residue purified by column chromatography (hexanes EtOAc 2:1 \(\rightarrow\) 1:1) to afford the product as a colorless oil, 150 mg (82\% yield).

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[α]24\text{D} (c = 1.00, CHCl₃): +39.4; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (s, 1H), 7.50 – 7.38 (m, 6H), 7.18 (d, J = 8.1 Hz, 1H), 5.40 (d, J = 10.0 Hz, 1H), 5.35 (d, J = 10.0 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 4.77 (td, J = 4.6; 2.2 Hz, 1H), 4.36 (s, 2H), 3.17 (m, 1H), 3.09 (d, J = 16.9 Hz, 1H), 5.40 (d, J = 10.0 Hz, 1H), 5.35 (d, J = 10.0 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 4.77 (td, J = 4.6; 2.2 Hz, 1H), 4.36 (s, 2H), 3.17 (m, 1H), 3.09 (d, J = 16.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 162.8, 153.2, 140.4, 138.6, 133.8, 132.1, 129.2, 128.9, 128.7, 128.3, 126.8, 121.2, 78.8, 72.2, 67.6, 67.1, 37.1; HRMS (ESI) calculated for [C₁₉H₁₆NBrKO₅](K)⁺ m/z = 455.9843, found m/z = 455.9839; IR (υ/cm⁻¹, neat) 2913, 1792, 1703, 1413, 1325, 1219, 1045, 909, 734.

(4aS,9aR)-6-Bromo-3-oxo-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-4(4aH)-yl benzyl carbamate (1b)

To a solution of the (4aS,9aR)-6-bromo-4-hydroxy-4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2H)-one³ (170 mg, 0.60 mmol, 1.00 equiv) in CH₂Cl₂ (5 mL) was added benzyl isocyanate (80.0 mg, 0.60 mmol, 1.00 equiv) and the reaction was stirred at room temperature overnight. Upon completion the solvent was removed and the crude residue purified by column chromatography (hexanes EtOAc 2:1 → 1:1) to afford the product as a colorless oil, 200 mg (80% yield).

[α]24\text{D} (c = 0.75, CHCl₃): +60.0; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.45 – 7.28 (m, 6H), 7.15 (d, J = 8.0 Hz, 1H), 5.95 (s, 1H), 5.19 (d, J = 4.2 Hz, 1H), 4.80 (m, 1H), 4.47 (d, J = 5.9 Hz, 2H), 4.39 (d, J = 16.4 Hz, 1H), 4.33 (d, J = 16.4 Hz, 1H), 3.17 (dd, J = 17.3; 4.5 Hz, 1H), 3.07 (d, J = 16.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 163.5, 153.5, 141.1, 138.6, 137.1, 131.9, 128.9, 128.2, 127.9, 127.8, 126.8, 121.0, 78.6, 67.5, 67.4, 45.7, 37.2; HRMS (ESI) calculated for [C₁₉H₁₈N₂BrO₄]⁺ m/z = 417.0444, found m/z = 417.0449 IR (υ/cm⁻¹, neat) 3308, 3058, 3033, 2914, 1773, 1684, 1325, 1237, 1044, 1027.

3-(2-Nitrophenyl)propanoic acid

To a solution of diethyl malonate (17.2 g, 0.11 mol, 1.40 equiv) in DMF (100 mL) was added solid K₂CO₃ (16.0 g, 0.11 mol, 1.50 equiv) followed by dropwise addition of 1-(bromomethyl)-2-nitrobenzene (16.5 g, 0.08 mol, 1.00 equiv) solution in DMF (20 mL). The reaction mixture was allowed to stir for 2 h. Upon completion the mixture was filtered, solvent removed under reduced pressure and the residue taken up in EtOAc (300 mL). The organic layer was washed with brine (5 × 40 mL), dried over anhydrous
Na₂SO₄, filtered and evaporated to dryness. The crude product was dissolved in a mixture of acetic acid (80 mL) and (6 M) aqueous HCl and heated to reflux overnight. Upon completion the solvent was partially removed under reduced pressure and EtOAc (200 mL) was added. The layers were separated and aqueous phase extracted with EtOAc (5 × 50 mL). The combined organics were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was recrystallized from hexane/EtOAc mixture to yield the title compound as a brown crystalline solid (9.5 g, 63% yield). Analytical data match the literature.⁴

¹H NMR (400 MHz, d₆-DMSO) δ 12.3 (br.s, 1H), 7.94 (dd, J = 8.16, 1.4 Hz, 1H), 7.67 (td, J = 7.5, 1.4 Hz, 1H), 7.56 (m, 1H), 7.50 (m, 1H), 3.05 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H).

Synthesis of the requisite monomers have been described in detail in our previous work.⁵

### 3.2. Polymerization

Norbornene derived monomer (30.0 g, 0.07 mol, 1.00 equiv) was dissolved in CH₂Cl₂ (340 mL) under ambient conditions. To this solution was rapidly added [(H₂Mes)(3-Br-Py)₂(Cl)₂Ru=CHPh]⁶ (121 mg, 0.14 mmol, 0.002 equiv) solution in CH₂Cl₂ (5 mL). Within a minute after the addition the homogenous mixture gelled and formed a solid mass. The reaction was quenched with ethyl vinyl ether (120 mL) and the gel mechanically sliced into pieces with a metal spatula. The mixture was decanted and washed multiple times with Et₂O. The resulting white amorphous solid was dried overnight under high vacuum and grinded with a ball mill (5 min at 30Hz) to yield a free flowing polymer powder (25 g). The polymer was suspended in THF (300 mL) and treated with PrNH₂ (50 mL) for 10 h. The solution was decanted and the polymer support washed with THF (3 × 3 volume beds) and Et₂O (2 × 3 volume beds) and dried.

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3.3. Preparation of the Polymer for the PKR

To generate the active acylating agents the polymers were treated with excess of the corresponding anhydrides - α-PEARL was acylated by treatment with excess of pent-4-enoic anhydride while β-PEARL with 3-(2-nitrophenyl)propanoic anhydride solution in THF at 45 °C for 10 h. After the reaction the polymers were once more washed with THF (3 × 3 volume beds) and Et₂O (2 × 3 volume beds) to yield the acylating agents. All polymers were analyzed by infrared spectroscopy.

The requisite anhydrides were prepared by treating the corresponding carboxylic acid (1.0 equiv.) with DIC (0.5 equiv) in CH₂Cl₂ for 4 h. After the reaction the precipitated urea derivative was filtered and washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure to yield the anhydride, which was directly used for the resin acylation.
3.4. Regeneration of the Polymer-Bound Reagent

After the parallel kinetic resolution, polymer was washed with THF (3 × 3 volume beds) and Et$_2$O (2 × 3 volume beds). The α-PEARL was reacylated by treatment with excess of pent-4-enoic anhydride while β−PEARL with 3-(2-nitrophenyl)propanoic anhydride solution in THF at 45 °C for 10 h. Washing of the resin was performed as described above.

3.5. Quantification of the Resin Loading

A 8 mL vial was charged with the resin beads containing active acylating agent (100 mg) and n-PrNH$_2$ (1.40 g, 24.0 mmol, 2.00 mL) solution in THF (4 mL) and shaken for 8 h at 23 °C. The reaction mixture was filtered, washed with THF (5 × 5 mL), concentrated under reduced pressure and dried under high vacuum (0.2 mm Hg), to afford the corresponding amide product. Resin loading in mmol was calculated according to the amount of the amide in mmol (equation 1):

$$ n_{resin} (mmol) = \frac{n_{amide} (mmol) \times m_{resin} (mg)}{100 (mg)} $$

(1)

The average resin loading of the polymer used for PKR was 1.50 mmol/g.

3.6. Synthesis of the Racemic Amides

To a solution of the corresponding amine (1.0 equiv) and Et$_3$N (2.0 equiv) in dry CH$_2$Cl$_2$, was added either 3-(2-nitrophenyl)propanoic acid (1.0 equiv) or pent-4-enoic acid (1.0 equiv) and T$_3$P (1.0 equiv). The reaction mixture was stirred for 3 h at 23 °C, after completion solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (silica gel). For most of the amide products NMR analysis showed presence of rotamers.
4. Synthesis of Racemic Amines

2-amino-3-(4-fluorophenyl)propan-1-ol

To a suspension of 2-amino-3-(4-fluorophenyl)propanoic acid (3.00 g, 16.4 mmol, 1.0 equiv) in THF (50 mL) was added solid NaBH₄ (1.50 g, 39.0 mmol, 2.4 equiv) over two portions. Iodine (4.20 g, 11.0 mmol, 1.0 equiv) solution in THF (25 mL) was added dropwise over 15 minutes. As the reaction exhibited slight exotherm the flask was cooled in a water bath. After the addition flask was equipped with a condenser and reaction refluxed overnight. Upon completion the reaction was cooled in an ice bath and quenched by slow addition of MeOH. The solvent was removed under reduced pressure and the residue taken up in 60 mL aqueous (20%) KOH and stirred for 4 h. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL) and combined organics washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude product (2.80 g, quant) which was directly used for the next step.

5-(4-Fluorobenzyl)morpholin-3-one

To the solution of 2-amino-3-(4-fluorophenyl)propan-1-ol (2.80 g, 16.4 mmol, 1.0 equiv) in THF (180 mL) was added NaH (60% suspension in mineral oil) (730 mg, 18.0 mmol, 1.1 equiv). The mixture was left stirring for 45 minutes and neat ethyl 2-chloroacetate (2.00 g, 16.4 mmol, 1.0 equiv) was added dropwise over 10 minutes. The flask was equipped with a condenser and reaction refluxed for 5 h. Upon completion the reaction was quenched with saturated aqueous NH₄Cl, the organic solvent was removed under reduced pressure and the remaining aqueous layer extracted with EtOAc (3 × 60 mL) and combined organics washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex:EtOAc 1:1 to EtOAc 100%) to yield the title compound as a white solid (950 mg, 28%).

3-(4-Fluorobenzyl)morpholine

To a cooled suspension of LiAlH₄ (600 mg, 15.0 mmol, 3.0 equiv) in THF (10 mL) was added 5-(4-fluorobenzyl)morpholin-3-one (1.10 g, 5.20 mmol, 1.0
equiv) solution in THF (10 mL) dropwise over 10 min. Afterwards the flask was equipped with a condenser and the reaction mixture refluxed for 48 h. Upon completion, the reaction was cooled in an ice bath and quenched by slow addition of water (0.6 mL) followed by 10% aqueous NaOH (1.2 mL) and once more water (1.8 mL). The resulting white precipitate was filtered and filter cake washed with THF. The filtrate was removed under reduced pressure to yield the product as a yellow oil (800 mg, 79%).

1H NMR (400 MHz, CDCl₃) δ 7.20 - 7.15 (m, 2H), 7.00 (m, 2H), 3.82 (m, 2H), 3.55 (m, 1H), 3.25 (m, 1H), 3.00 (m, 1H), 2.88 (m, 2H), 2.66 (dd, J = 13.6, 4.9 Hz, 1H), 2.48 (m, 1H), 1.60 (br. 1H); 13C NMR (101 MHz, CDCl₃) δ 161.7 (d, J = 245 Hz), 133.4 (d, J = 3 Hz), 130.5 (d, J = 8 Hz), 115.4 (d, J = 21 Hz), 72.4, 67.5, 56.1, 46.2, 38.0; 19F NMR (377 MHz, CDCl₃) –116.6; HRMS (ESI) calculated for [C₁₁H₁₅NFO]⁺ m/z = 196.1132, found m/z = 196.1133; IR (υ/cm⁻¹, neat) 3311, 2953, 2915, 2851, 1509, 1447, 1322, 1221, 1158, 1165.

7-(2-Fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane

The title compound was prepared according to the previously described method.¹

1H NMR (400 MHz, CDCl₃) δ 7.20 (m, 2H), 7.05 (m, 2H), 3.93 (m, 4H), 3.10 (m, 2H), 2.78 (m, 3H), 1.66 (m, 3H), 1.48 (m, 1H); 13C NMR (101 MHz, CDCl₃) δ 161.3 (d, J = 246 Hz), 131.7 (d, J = 5 Hz), 128.3 (d, J = 8 Hz), 125.2 (d, J = 16 Hz), 124.0 (d, J = 4 Hz), 115.5 (d, J = 22 Hz), 107.5, 64.3, 64.2, 54.7, 43.7, 41.5, 36.0, 35.1; 19F NMR (377 MHz, CDCl₃) –117.0; HRMS (ESI) calculated for [C₁₄H₁₉NFO₂]⁺ m/z = 252.1394, found m/z = 252.1394; IR (υ/cm⁻¹, neat) 3313, 2953, 2926, 2882, 1584, 1492, 1454, 1229, 1180, 1147.

Ethyl piperidine-2-carboxylate

Piperidine-2-carboxylic acid (10.0 g, 0.08 mol, 1.00 equiv) was suspended in EtOH (150 mL) and the suspension was cooled to 0 °C. Neat SOCl₂ (27.6 g, 0.23 mol, 3.00 equiv) was added dropwise over 10 min. The reaction mixture was heated to reflux for 4 hours upon which the precipitate dissolved. Upon completion the reaction was cooled to 0 °C and neutralized by slow addition of saturated aq. NaHCO₃. The solvent was removed under reduced pressure and remaining slurry dissolved in CH₂Cl₂ (200 mL). The organic layer was washed with sat. aq. NaHCO₃ (2 × 40 mL), once with brine (30 mL) dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to afford the product as a brown oil (7.0 g, 58%). Additional Kugelrohr distillation yielded the product as a colourless oil.
$^1$H NMR (300 MHz, CDCl$_3$) δ 4.18 (q, $J = 7.1$ Hz, 2H), 3.35 (m, 1H), 3.10 (m, 1H), 2.65 (m, 1H), 1.98 (m, 2H), 1.78 (m, 1H), 1.60 – 1.40 (m, 4H), 1.27 (t, $J = 7.1$Hz, 3H). (These spectral data match literature reports$^7$)

5. General Method for Parallel Kinetic Resolution

In an 8 mL screw cap vial mixture of α- and β- PEARL reagents (1.0 equiv) were swollen in THF. The solvent was removed with a syringe and a THF solution of the corresponding amine (0.2 – 0.3 m, 1.0 equiv.) was added. The vial was closed and left shaking for 12 – 18 h at 45 °C. After the reaction the liquid was removed via syringe and polymer washed with THF (3 × volume beds) and Et$_2$O (2 × volume beds). The solution phases were combined and the solvent removed under reduced pressure to yield a mixture of enantiomerically enriched amides, which were separated by column chromatography.

5.1. Ethyl piperidine-2-carboxylate (2)

Racemic ethyl piperidine-2-carboxylate (63 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (260 mg, 1.50 mmol/g, 1.00 equiv.) in THF (3 mL) for 14 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 1:1), to yield 1) (S)-Ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate as a yellow oil (40 mg, 42%) in e.r. = 92:8 and 2) (R)-Ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate as a yellow oil (35 mg, 26 %) e.r. = 94:6

(S)-Ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate (2a)

$[\alpha]_{D}^{27}$ (c = 0.25, CHCl$_3$): –55.9 (e.r. = 92:8); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.90 (m, 1H), 5.40 (m, 0.8 H), 5.05 (m, 1H), 4.60 (m, 0.4H), 4.20 (m, 2H), 3.80 (m, 0.8H), 3.29 (td, $J = 13.0$, 3.0 Hz, 0.8 H), 2.65 (m, 0.2H), 2.50 – 2.20 (m, 5H), 1.80 – 1.50 (m, 4H), 1.50 – 1.30 (m, 2H), 1.29 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.4, 172.0, 171.4, 170.9, 137.5, 115.2, 61.6, 61.1, 56.1, 51.9, 43.4, 39.4, 32.7, 32.4, 29.2, 29.1, 27.4, 26.7, 25.4, 24.6, 21.0, 20.9, 14.3; HRMS (ESI) calculated for [C$_{13}$H$_{22}$NO$_3$]$^+$ m/z = 240.1594, found m/z = 240.1595; IR (υ/cm$^{-1}$, neat) 2977, 2939, 2861, 1737, 1650, 1424, 1198, 1160, 1145, 1025. SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R$ = 4.0 min (minor), 4.6 (major).

(R)-Ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate (2b)

[α]$_D^{28}$ (c = 0.15, CHCl$_3$): +55.9 (e.r. = 94:6); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.95 (m, 1H), 7.56 (m, 1H), 7.50 (m,1H), 7.36 (m, 1H), 5.39 (m, 0.8H), 4.60 (m, 0.4H), 4.20 (m, 2H), 3.80 (m, 0.8H), 3.25 (m, 3H), 2.85 – 2.65 (m, 2H), 2.28 (m, 3H), 1.40 (m, 2H), 1.30 (m, 3H);
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.7, 171.4, 171.3, 170.7, 149.3, 136.5, 133.2, 132.7, 127.4, 127.4, 124.8, 61.6, 61.1, 56.1, 52.1, 43.3, 39.6, 34.3, 34.0, 29.0, 28.9, 27.2, 26.6, 25.3, 24.6, 20.9, 20.8, 14.3, 14.2; HRMS (ESI) calculated for [C$_{17}$H$_{23}$N$_2$O$_5$]+ m/z = 335.1601, found m/z = 335.1600; IR (υ/cm$^{-1}$, neat) 2941, 2861, 1735, 1649, 1525, 1426, 1349, 1200, 1160, 1144. SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R$ = 6.2 min (major), 6.5 (minor).

5.2. Dimethyl piperidine-2,3-dicarboxylate (3)

Racemic dimethyl piperidine-2,3-dicarboxylate (80.0 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (260 mg, ~1.50 mmol/g, 1.00 equiv.) in THF (4 mL) for 45 h. The amide products were separated via column chromatography (hexanes:EtOAc 6:1 → 1:1), to yield 1) (2S,3R)-dimethyl 1-(pent-4-enoyl)piperidine-2,3-dicarboxylate as a yellow oil (40 mg, 35%) in e.r. = 93:7 and 2) ((2R,3S)-dimethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2,3-dicarboxylate as a yellow oil (40 mg, 26 %) e.r. = 96:4.
(25,3R)-dimethyl 1-(pent-4-enoyl)piperidine-2,3-dicarboxylate (3a)

\[ \text{[\alpha]}^{27\text{D}} (c = 0.35, \text{CHCl}_3): -94.4 \quad (\text{e.r.} = 93:7); \quad \text{\textsuperscript{1}H NMR} \quad (400 \text{ MHz, CDCl}_3) \delta 6.04 \quad (d, J = 4.9 \text{ Hz, 0.7 H}), 5.90 \quad (m, 1H), 5.15 - 4.95 \quad (m, 2.3 H), 4.58 \quad (m, 0.3H), 3.81 \quad (m, 0.7H), 3.73 \quad (m, 6H), 3.03 \quad (td, J = 13.4, 3.0 \text{ Hz, 0.7H}), 2.50 \quad (m, 5.3H), 2.15 \quad (m, 1H), 1.85 - 1.55 \quad (m, 2H), 1.45 \quad (m, 1H); \quad \text{\textsuperscript{13}C NMR} \quad (101 \text{ MHz, CDCl}_3) \delta 171.8, 171.7, 171.0, 169.5, 137.4, 137.3, 115.4, 57.3, 53.2, 52.7, 52.4, 52.1, 51.9, 43.5, 42.9, 42.8, 38.8, 32.7, 32.3, 29.1, 29.1, 24.9, 24.0, 22.5, 22.5; \quad \text{HRMS (ESI) calculated for \([C_{14}H_{22}NO_3]^+\) m/z = 284.1492, found m/z = 284.1493}; \quad \text{IR (v/cm\(^{-1}\), neat)} \quad 2953, 2873, 1740, 1650, 1434, 1234, 1211, 1153, 1000. \quad \text{SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO\(_2\) to 50 % iPrOH in CO\(_2\) over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t\text{R} = 4.4 \text{ min (minor), 4.8 (major).} \]

(2R,3S)-dimethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2,3-dicarboxylate (3b)

\[ \text{[\alpha]}^{27\text{D}} (c = 0.20, \text{CHCl}_3): +89.0 \quad (\text{e.r.} = 96:4); \quad \text{\textsuperscript{1}H NMR} \quad (400 \text{ MHz, CDCl}_3) \delta 7.97 \quad (m, 1H), 7.57 \quad (m, 1H), 7.50 \quad (m, 1H), 6.03 \quad (d, J = 4.9 \text{ Hz, 0.7H}), 5.07 \quad (d, J = 4.6\text{Hz, 0.3H}), 4.60 \quad (m, 0.3H), 3.80 \quad (m, 0.7H), 3.75 \quad (m, 6H), 3.27 \quad (m, 2H), 3.05 \quad (td, J = 13.4, 3.0 \text{ Hz, 0.7H}), 2.85 \quad (m, 2H), 2.55 \quad (m, 0.7H), 2.43 \quad (m, 0.6H), 2.10 \quad (m, 1H), 1.80 - 1.55 \quad (m, 2H), 1.40 \quad (m, 1H); \quad \text{\textsuperscript{13}C NMR} \quad (101 \text{ MHz, CDCl}_3) \delta 171.7, 171.5, 171.2, 171.1, 169.9, 169.3, 136.3, 133.3, 133.3, 132.8, 132.8, 127.6, 124.9, 124.8, 57.2, 53.3, 52.8, 52.5, 52.1, 51.9, 43.3, 42.9, 42.8, 39.0, 34.2, 33.9, 29.1, 28.9, 24.8, 23.9, 22.5, 22.4; \quad \text{HRMS (ESI) calculated for \([C_{18}H_{23}N_2O_7]^+\) m/z = 379.1500, found m/z = 379.1500}; \quad \text{IR (v/cm\(^{-1}\), neat)} \quad 2953, 2875, 1742, 1651, 1524, 1434, 1348, 1235, 1210, 1153, 1026. \quad \text{SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO\(_2\) to 50 % iPrOH in CO\(_2\) over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t\text{R} = 6.7 \text{ min (major), 7.4 (minor).} \]
5.3. 1-Phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (4)

Racemic dimethyl 1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (80.0 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (260 mg, 1.50 mmol/g 1.00 equiv.) in THF (4 mL) for 45 h. The amide products were separated via column chromatography (hexanes:EtOAc 6:1 → 1:1), to yield 1) (R)-1-(1-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pent-4-en-1-one as a yellow oil (35 mg, 31%) in e.r. = 94:6 and 2) (S)-3-(2-nitrophenyl)-1-(1-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)propan-1-one as a yellow oil (30 mg, 20%) e.r. = 96:4.

(R)-1-(1-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pent-4-en-1-one (4a)

\[\alpha\]D\textsuperscript{27} (c = 0.25, CHCl\textsubscript{3}): −111.9 (e.r. = 94:6); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.40 – 7.25 (br.m, 5H), 7.06 (br, 0.5H), 6.68 (m, 1H), 6.25 (br, 1H), 6.23 (br, 0.5H), 6.07 (br, 1H), 5.87 (br.m, 1H), 5.05 (m, 2H), 4.75 (br, 0.5H), 4.05 (br, 1.5H), 3.93 (m, 1H), 3.62 (br, 0.5H), 3.30 (br.m, 0.5H), 2.70 (m, 0.5H), 2.60 – 2.35 (m, 3.5H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 171.8, 141.6, 137.2, 128.8, 128.3, 127.7, 127.5, 126.5, 119.7, 119.0, 115.5, 108.6, 108.3, 106.4, 106.1, 56.0, 51.9, 44.6, 44.0, 40.1, 37.5, 32.8, 29.2; HRMS (ESI) calculated for [C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}O]\textsuperscript{+} m/z = 281.1648, found m/z = 281.1641; IR (υ/cm\textsuperscript{-1}, neat) 3063, 2921, 1643, 1492, 1447, 1421, 1283, 1211, 1190, 916, 700. SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO\textsubscript{2} to 50 % iPrOH in CO\textsubscript{2} over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t\textsubscript{R} = 7.0 min (major), 7.6 (minor).
(S)-3-(2-nitrophenyl)-1-(1-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)propan-1-one

(4b)

\[ [\alpha]_{D}^{27} \text{ (c = 0.30, CHCl}_3): + 96.7 \text{ (e.r. = 96:4); } ^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.95 \text{ (m, 1H), 7.50 \text{ (m, 1H), 7.45 - 7.18 \text{ (m, 7H), 7.06 \text{ (br, 0.5H), 6.65 \text{ (s, 1H), 6.25 \text{ (m, 1.5H), 6.03 \text{ (br.m, 1H), 4.70 \text{ (br.m, 0.5H), 3.95 \text{ (m, 2.5H), 3.60 \text{ (br.m, 0.5H), 3.30 \text{ (m, 2.5H), 3.05 - 2.75 \text{ (m, 2H); } ^13\text{C NMR (101 MHz, CDCl}_3) \delta 136.1, 133.4, 133.2, 132.9, 132.7, 129.0, 128.8, 128.4, 128.3, 127.8, 127.6, 126.4, 124.9, 119.6, 119.0, 108.6, 108.4, 106.3, 55.9, 52.1, 44.6, 43.9, 40.0, 37.6, 34.3, 29.3, 29.1; HRMS (ESI) calculated for [C}_{22}H_{22}N_{3}O_{3}]^+ m/z = 376.1656, found m/z = 376.1654; IR (υ/cm⁻¹, neat) 2950, 2924, 1644, 1610, 1523, 1492, 1447, 1421, 1346, 701. SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \text{t}_R = 7.0 \text{ min (major), 7.6 (minor).}]

5.4. Cis-decahydroquinoline (5)

Racemic cis-decahydroquinoline (56 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (300 mg, 1.50 mmol/g, ~1.10 equiv) in THF (4 mL) for 18 h. The amide products were separated via column chromatography (hexanes:EtOAc 9:1 → 3:1), to yield 1) (1-((4aR,8aR)-Octahydroquinolin-1(2H)-yl)pent-4-en-1-one as a colorless oil (38 mg, 40%) in e.r. = 91:9 and 2) 3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (40 mg, 32 %) e.r. = 93:7.

1-((4aR,8aR)-Octahydroquinolin-1(2H)-yl)pent-4-en-1-one (5a)

\[ [\alpha]_{D}^{28} \text{ (c = 0.25, CHCl}_3): - 42.6 \text{ (e.r. = 91:9); } ^1\text{H NMR (400 MHz, CDCl}_3) \delta 5.85 \text{ (m, 1H), 5.05 \text{ (m, 2H), 4.68 \text{ (m, 0.5H), 4.55 \text{ (m, 0.5H), 3.78 \text{ (m, 0.5H), 3.65 \text{ (m, 0.5H), 3.07 \text{ (td, } J = 13.3, 3.0Hz, 0.5H), 2.60 \text{ (td, } J = 13.3, 3.0Hz, 0.5H), 2.55 - 2.30}\]
(m, 4H), 1.95 – 1.50 (m, 7H), 1.50 – 1.20 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.8, 170.6, 137.9, 137.8, 115.0, 115.0, 55.5, 50.5, 40.9, 36.4, 35.9, 34.8, 33.2, 32.6, 31.5, 29.6, 29.6, 26.6, 25.9, 25.7, 25.6, 25.1, 24.1, 23.9, 23.7, 20.3, 20.1; HRMS (ESI) calculated for [C$_{14}$H$_{23}$NONa]$^+$ m/z = 244.1672, found m/z = 244.1669; IR (υ/cm$^{-1}$, neat) 3076, 2926, 2861, 1639, 1467, 1429, 1374, 1316, 1266, 1251. SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 3.2$ min (major), 3.7 (minor).

3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one (5b)

$[\alpha]^{28}_D$ (c = 0.20, CHCl$_3$): +24.9 (e.r. = 93:7); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (m, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.38 (m, 1H), 4.65 (m, 0.5H), 4.55 (m, 0.5H), 3.78 (m, 0.5H), 3.60 (m, 0.5H), 3.25 (m, 2H), 3.00 (m, 0.5H), 2.85 (m, 0.5H), 2.75 – 2.55 (m, 2H), 1.95 – 1.50 (m, 6.5H), 1.45 – 1.25 (m, 6.5H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.1, 169.8, 149.4, 149.3, 136.7, 136.7, 133.2, 133.2, 132.8, 127.4, 127.4, 124.7, 124.7, 55.5, 50.7, 40.8, 36.6, 35.8, 34.8, 34.6, 34.2, 31.3, 31.3, 29.5, 29.3, 26.5, 25.7, 25.7, 25.6, 25.1, 24.0, 23.9, 23.7, 20.3, 20.0; HRMS (ESI) calculated for [C$_{18}$H$_{25}$NO$_3$]$^+$ m/z = 317.1860, found m/z = 317.1864; IR (υ/cm$^{-1}$, neat) 2926, 2862, 1633, 1521, 1433, 1348, 1311, 1265, 1244. SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 5.3$ min (minor), 5.7 (major).
5.5. *Trans*-decahydroquinoline (6)

Racemic *trans*-decahydroquinoline (42.0 mg, 0.30 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (200 mg, 1.50 mmol/g 1.00 equiv) in THF (4 mL) for 45 h. The amide products were separated via column chromatography (hexanes:EtOAc 6:1 → 1:1), to yield 1) 1-((4aR,8aS)-octahydroquinolin-1(2H)-yl)pent-4-en-1-one as a colorless oil (20 mg, 30%) in e.r. = 91:9 and 2) (3-(2-nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (20 mg, 21 %) e.r. = 92:8.

1-((4aR,8aS)-octahydroquinolin-1(2H)-yl)pent-4-en-1-one (6a)

\[ \alpha \] \text{D}^{25} (c = 0.35, CHCl\textsubscript{3}): + 105.8 (e.r. = 91:9); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 5.90 (m, 1H), 5.05 (m, 2H), 3.75 (br, 1H), 3.35 (br.t, \( J \approx 11.1\) Hz, 1H), 3.17 (br, 1H), 2.45 (m, 4H), 2.08 (br, 1H), 1.90 – 1.40 (m, 8H), 1.20 – 1.00, 2H; \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 171.6, 137.8, 115.0, 61.4, 38.4, 38.2, 33.1, 33.0, 31.0, 29.6, 26.3, 25.9, 25.4, 23.0; HRMS (ESI) calculated for \([\text{C}_{14}\text{H}_{24}\text{N}O]^+\) \( m/z = 222.1852 \), found \( m/z = 222.1859 \); IR (\( \nu/cm^-1 \), neat) 2926, 2855, 1637, 1458, 1429, 1362, 1173, 1138, 1009, 913; SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO\textsubscript{2} to 50 % iPrOH in CO\textsubscript{2} over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 2.5 \) min (minor), 3.1 (major).

3-(2-nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one (6b)

\[ \alpha \] \text{D}^{27} (c = 0.10, CHCl\textsubscript{3}): - 147.5 (e.r. = 92:8); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.94 (dd, \( J = 8.1, 1.3\) Hz, 1H), 7.55 (m, 2H), 7.38 (m, 1H), 3.75 (br, 1H), 3.30 (br, 1H), 3.25 (t, \( J = 7.6\) Hz, 2H), 3.10 (br, 1H), 2.76 (m, 1H), 2.66 (m, 1H), 2.04 (br, 1H), 1.80 – 1.40 (m, 8H), 1.25 (m, 2H), 1.10 – 0.90 (m, 2H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 170.9, 149.4, 136.6, 133.1, 132.8, 127.4, 124.7, 61.6, 38.4, 38.2, 34.5, 32.9, 30.8, 29.3, 26.2, 25.8, 25.4, 22.9; HRMS (ESI) calculated for \([\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3]^+\) \( m/z = 317.1860 \), found \( m/z = 317.1860 \); IR (\( \nu/cm^-1 \), neat) 2927, 2856, 1635, 1525, 1434, 1347, 743, 662. SFC column: Daicel
Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 4.8 \) min (minor), 5.1 (major).

5.6. 3-(4-Fluorobenzyl)morpholine (7)

Racemic dimethyl 3-(4-fluorobenzyl)morpholine (100 mg, 0.60 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (400 mg, 1.50 mmol/g, 1.00 equiv) in THF (4 mL) for 25 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 1:1), to yield 1) (R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one as a colorless oil (35 mg, 21%) in e.r. = 95:5 and 2) (S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one as a pale yellow oil (60 mg, 27%) e.r. = 95:5.

(R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one (7a)

\[ \alpha \] \( ^{28} \)b (c = 0.20, CHCl₃): + 21.3 (e.r. = 95:5); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.25 (m, 1H), 7.15 (m, 1H), 7.00 (m, 2H), 5.75 (m, 2H), 4.70 (m, 0.55H), 4.45 (m, 0.45H), 3.95 (m, 1H), 3.75 (m, 1.45H), 3.50 (m, 3H), 3.10 (m, 2H), 2.80 (m, 0.55H), 2.45 – 2.10 (m, 3.45H), 1.75 (m, 0.55H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 171.3, 171.1, 161.9, (d, \( J = 245 \) Hz), 161.7 (d, \( J = 245 \) Hz), 137.3, 137.3, 133.8 (d, \( J = 3 \) Hz), 133.4 (d, \( J = 3 \) Hz), 130.9 (d, \( J = 8 \) Hz), 115.8, 115.6, 115.4 (d, \( J = 6 \) Hz), 115.2 (d, \( J = 6 \) Hz), 68.6, 67.3, 67.3, 66.7, 55.5, 50.3, 41.7, 37.1, 35.0, 33.9, 32.5, 31.8, 29.1, 29.0; \(^{19}\)F NMR (377 MHz, CDCl₃) –115.7, –116.7; HRMS (ESI) calculated for \([C_{16}H_{21}NO\text{F}]^{+}\) m/z = 278.1551, found m/z = 278.1548; IR (v/cm\(^{-1}\), neat) 2971, 2924, 2858, 1640, 1509, 1425, 1221, 1119, 1070, 1015. SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 2.9 \) min (minor), 3.4 (major).
(S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitropheryl)propan-1-one (7b)

\[ \alpha \] \text{H NMR} (400 MHz, CDCl\textsubscript{3}) \delta 7.95 (m, 1H), 7.55 (m, 1H), 7.45 – 7.30 (m, 2H), 7.25 (m, 1H), 7.10 (m, 1H), 7.00 – 6.90 (m, 2H), 4.65 (m, 0.5H), 4.42 (m, 0.5H), 4.00 (m, 1H), 3.78 (m, 1H), 3.60 – 3.25 (m, 3H), 3.20 – 2.90 (m, 4H), 2.83 – 2.70 (m, 1H), 2.60 (m, 1H), 2.00 (m, 0.5H); \text{IR} (\nu/cm\textsuperscript{-1}, neat) 2965, 2925, 2859, 1642, 1523, 1509, 1425, 1348, 1220, 1118.

5.7. 7-(2-Fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane (8)

Racemic dimethyl 7-(2-fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane (100 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (260 mg, 1.50 mmol/g, 1.00 equiv) in THF (4 mL) for 25 h. The amide products were separated via column chromatography (hexanes:EtOAc
4:1 \rightarrow 1:1), to yield 1) \((R)-1-(7-(2-fluorobenzyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pent-4-en-1-one\) as a colorless oil (35 mg, 26\%) in e.r. = \textbf{92:8} and 2) \((S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one\) as a pale yellow oil (60 mg, 35\%) e.r. = \textbf{92:8}.

\[(\text{R})-1-(7-(2-fluorobenzyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pent-4-en-1-one\) (8a)

\[
[a]_{D}^{27} \text{ (c = 0.20, CHCl}_3\text{)} = +32.1 (\text{e.r. = 92:8}); \quad ^{1}H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 7.26 - 7.18 (m, 2H), 7.10 (m, 2H), 5.80 (m, 1H), 5.30 (br, 0.4H), 5.00 (m, 2H), 4.75 (m, 0.6H), 4.35 (m, 0.6H), 4.10 (m, 2H), 3.95 (m, 2H), 3.80 (m, 0.4H), 3.55 (m, 0.4H), 3.20 - 3.00 (m, 3H), 2.45 - 2.10 (m, 4H), 2.00 (m, 0.6H), 1.85 - 1.50 (m, 3H); \quad ^{13}C \text{ NMR (101 MHz, CDCl}_3\text{)} \delta 171.2, 161.5 (d, \text{J} = 245 \text{ Hz}), 137.5, 132.1 (d, \text{J} = 5 \text{ Hz}), 131.7, 128.6 (d, \text{J} = 8 \text{ Hz}), 125.7, 124.2, 124.2, 123.8, 123.8, 115.4 (d, \text{J} = 22 \text{ Hz}), 114.9, 107.2, 64.8, 64.0, 53.0, 48.5, 39.1, 39.1, 37.0, 35.7, 35.5, 34.6, 34.6, 32.9, 31.8, 31.7, 30.1, 29.3; \quad ^{19}F \text{ NMR (377 MHz, CDCl}_3\text{)} = -117.9, -118.4; \quad \text{HRMS (ESI) calculated for [C}_{19}H_{25}NO_3F^+] m/z = 334.1813, found m/z = 334.1810; \quad \text{IR (v/cm}^{-1}\text{, neat) 2959, 2928, 2885, 1642, 1492, 1454, 1228, 1183, 1104, 759. SFC column: Daicel Chiralpak OJH (4.6 \times 250 \text{ mm}); gradient: 5 \% \text{iPrOH in CO}_2 \text{ to 50 \% \text{iPrOH in CO}_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t}_R = 2.9 \text{ min (minor), 3.3 (major).}

\[(\text{S})-1-(7-(2-fluorobenzyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pent-4-en-1-one\) (8b)

\[
[a]_{D}^{27} \text{ (c = 0.15, CHCl}_3\text{)} = -58.5 (\text{e.r. = 92.8}); \quad ^{1}H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 7.95 (m, 1H), 7.55 (m, 1H), 7.40 - 7.22 (m, 3H), 7.20 - 6.90 (m, 3H), 5.25 (m, 0.4H), 4.75 (m, 0.6H), 4.30 (m, 0.6H), 4.05 (m, 2H), 3.95 (m, 2H), 3.80 (m, 0.4H), 3.50 (m, 0.4H), 3.20 - 3.10 (m, 4H), 2.80 - 2.60 (m, 2H), 2.20 (m, 0.6H), 1.80 - 1.50 (m, 4H); \quad ^{13}C \text{ NMR (101 MHz, CDCl}_3\text{)} \delta 170.4, 170.0, 161.6 (d, \text{J} = 245 \text{ Hz}), 161.4 (d, \text{J} = 245 \text{ Hz}), 149.3, 136.5, 133.2, 133.2, 132.8, 131.9 (d, \text{J} = 5 \text{ Hz}), 131.7 (d, \text{J} = 5 \text{ Hz}), 128.5 (d, \text{J} = 8 \text{ Hz}), 128.0 (d, \text{J} = 8 \text{ Hz}), 127.6, 127.4, 127.3, 125.6, 125.4, 124.9, 124.7, 124.2, 123.9, 115.3 (d, \text{J} = 22 \text{ Hz}), 115.2 (d, \text{J} = 22 \text{ Hz}), 107.0, 106.9, 64.8, 64.0, 64.0.
53.2, 48.7, 39.1, 37.2, 35.8, 34.7, 34.5, 34.4, 33.2, 31.6, 30.2, 29.1, 28.8, 28.3; $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ –117.9, –118.3; HRMS (ESI) calculated for [C$_{23}$H$_{26}$N$_2$FO$_3$]$^+$ m/z = 429.1820, found m/z = 429.1818; IR (µ/cm$^{-1}$, neat) 2959, 2887, 1643, 1524, 1492, 1453, 1428, 1348, 1185, 1130. HPLC column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: hexane : isopropanol 9:1 flow: 1.0 mL/min; detection: 254 nm. Retention time: $t_R$ = 31.0 min (major), 33.0 min (minor).

5.8. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (9)

Racemic dimethyl 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (108 mg, 0.40 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (400 mg, 1.50 mmol/g, 1.10 equiv) in THF (4 mL) for 18 h. The amide products were separated via column chromatography (hexanes:EtOAc 5:1 → 2:1), to yield 1) (R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one as a colorless oil (65 mg, 46%) in e.r. = 93:7 and 2) (S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one as a pale yellow oil (90 mg, 50%) e.r. = 97:3.

(R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one (9a)

[$\alpha$]$^\text{D}$(c = 0.45, CHCl$_3$) = –111.9 (e.r. = 93:7); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.20 (m, 5H), 6.90 (s, 0.8H), 6.67 (m, 1 H), 6.60 (s, 0.2H), 6.52 (s, 0.8H), 5.95 (s, 0.2H), 5.85 (m, 1H), 5.02 (m, 2H), 4.39 (m, 0.2H), 3.89 (s, 2.8H), 3.83 (m, 0.4H), 3.76 (m, 3H), 3.38 (m, 0.8H), 3.13 (m, 0.2H), 2.93 (m, 1H), 2.75 (m, 1.6H), 2.60 – 2.40 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.7, 148.1, 147.7, 142.6, 137.5, 128.8, 128.6, 128.2, 127.5, 127.4, 127.0, 126.3, 115.3, 111.4, 111.1, 56.0, 55.9, 54.6, 39.4, 32.8, 29.3, 28.7, 27.4; HRMS (ESI) calculated for [C$_{22}$H$_{26}$NO$_3$]$^+$ m/z = 352.1907, found m/z = 352.1899; IR (µ/cm$^{-1}$, neat) 3001, 2932, 2833, 1637, 1516, 1493, 1438, 1360, 1250, 1233.
SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵢ = 5.6 min (minor), 5.9 (major).

(S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one (9b)

\[ [\alpha]^{28}_{D} \text{ (c = 0.50, CHCl}_3) = + 72.0 \text{ (97:3)} \]

\(^1H\) NMR (400 MHz, CDCl₃) δ 7.92 (d, J = 8.0 Hz, 0.75H), 7.85 (d, J = 8.0 Hz, 0.25H), 7.50 – 7.40 (m, 2H) 7.38 – 7.20 (m, 5H), 7.10 (m, 0.5H), 6.90 (s, 0.75H), 6.65 (s, 1H), 6.55 (s, 0.25H), 6.52 (s, 0.75H), 5.95 (s, 0.25H), 4.30 (m, 0.5H), 3.88 (s, 3H), 3.80 (s, 0.5H), 3.75 (s, 2.5H), 3.70 (m, 0.5H), 3.35 – 3.25 (m, 3H), 3.20 – 3.00 (m, 0.5H), 2.95 – 2.55 (m, 4H); \(^{13}C\) NMR (101 MHz, CDCl₃) δ 170.0, 149.3, 148.1, 147.7, 142.5, 136.4, 133.2, 132.8, 128.8, 128.6, 128.3, 127.7, 127.5, 127.4, 126.9, 126.4, 124.8, 111.3, 110.9, 59.2, 56.0, 55.9, 54.8, 39.3, 37.0, 34.6, 29.6, 29.2, 28.6, 27.4; HRMS (ESI) calculated for \([C_{26}H_{27}N_2O_5]^+ m/z = 447.1914\), found m/z = 447.1909; IR (υ/cm\(^{-1}\), neat) 2935, 1638, 1520, 1492, 1440, 1347, 1251, 1117. SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵢ = 7.4 min (major), 8.8 (minor).
5.9. 2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (10)

Racemic 2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (113 mg, 0.30 mmol, 1.50 mmol/g, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (180 mg, ~1.10 equiv.) in THF (4 mL) for 36 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 2:1), to yield 1) 1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one as a colorless oil (35 mg, 25%) in e.r. = 93:7 and 2) 1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one as a pale yellow oil (35 mg, 21%) e.r. = 95:5. After column chromatography 35 mg of compound was obtained as a mixture of both amides.

1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one (10a)

\[ \alpha \] \text{D}^20 \text{ (c = 0.10, CHCl}_3\text{): } -6.0 \text{ (e.r. = 93:7); } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 8.79 \text{ (d, } J = 8.5 \text{ Hz, 1H), 8.12 \text{ (s, 1H), 8.10 \text{ (d, } J = 7.3 \text{Hz, 1H), 7.67 \text{ (t, } J = 7.9 \text{Hz, 1H), 5.98 \text{ (m, 2H), 5.05 \text{ (m, 2H), 4.55 \text{ (m, 1H), 3.60 \text{ (m, 2H), 3.35 \text{ (s, 1H), 2.50 \text{ (m, 4H), 1.90 -- 1.50 \text{ (m, 4H), 1.35 \text{ (m, 1H), 1.20 \text{ (m, 1H); } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{): } \delta 173.2, 151.1, 148.1 \text{ (q, } J = 35\text{Hz), 143.5, 137.1, 129.1, 128.9 \text{ (q, } J = 5\text{Hz), 128.3, 127.3, 126.6, 124.9, 122.4 \text{ (d, } J = 53\text{Hz), 119.7, 119.5, 115.6, 115.0, 71.7, 55.9, 43.2, 33.5, 29.4, 23.9, 20.8, 19.1; } ^{19}\text{F NMR (377 MHz, CDCl}_3\text{): } \delta -60.3, -67.9; \text{ HRMS (ESI) calculated for } [\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2\text{F}_6]^+ \text{ m/z } = 461.1658, \text{ found m/z } = 461.1651; \text{ IR (u/cm}^{-1}, \text{ neat) 3347, 2921, 2845, 1659, 1632, 1600, 1433, 1371, 1310, 1214, 1143, 1110, 916. SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5% iPrOH in CO}_2\text{ to 50% iPrOH in CO}_2\text{ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: } t_R = 5.2 \text{ min (major), 5.5 (minor).} \]
1-((R)-2-((S)-2,8-bis(trifluoromethyl)quinolin-3-y1)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one (10b)

\[
\text{NO}_2\quad \text{CF}_3\quad \text{N}^+\quad \text{OH}^-\quad \text{F}\quad \text{C}
\]

\[\text{[a]}^{28}_{D} (c = 0.35, \text{CHCl}_3): + 0.5 \text{ (e.r.} = 95:5); \text{^1H NMR} (400 MHz, CDCl}_3\) \(\delta\) 8.92 (d, \(J = 8.6\)Hz, 1H), 8.19 (d, \(J = 7.2\)Hz, 1H), 8.09 (s, 1H), 7.99 (d, \(J = 8.2\)Hz, 1H), 7.82 (d, \(J = 7.9\)Hz, 1H), 7.60 (m, 1H), 7.45 (m, 2H), 6.05 (s, 1H), 4.55 (m, 1H), 3.80 – 3.55 (m, 2H), 3.30 (t, \(J = 7.7\)Hz, 1H), 3.00 (br, 1H), 2.85 (m, 2H), 1.90 – 1.45 (m, 4H), 1.35 (br, 1H), 1.15 (br, 1H); \text{^13C NMR} (101 MHz, CDCl}_3\) \(\delta\) 172.3, 150.9, 149.4, 147.9, 143.6, 138.0, 136.2, 133.4, 132.5, 128.9, 128.5, 127.7, 127.5, 126.7, 126.6, 125.0, 122.2, 115.0, 71.9, 56.2, 43.2, 35.2, 29.3, 23.9, 20.8, 19.2; \text{^19F NMR} (282 MHz, CDCl}_3\) –60.3, –67.9; \text{HRMS} (ESI) calculated for [C\(_{26}\)H\(_{24}\)N\(_3\)O\(_4\)F\(_6\)]\(^+\) m/z = 556.1666, found m/z = 556.1660; \text{IR} (\upsilon/cm\(^{-1}\), neat) 3377, 2950, 2870, 1603, 1557, 1525, 1472, 1310, 1277, 1141, 1109. \text{SFC} column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient: 5 % iPrOH in CO\(_2\) to 50 % iPrOH in CO\(_2\) over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \(t_R = 6.9\) min (major), 7.4 (minor).

6. General Procedure for PKR in Membrane Reactor and Amide Hydrolysis.

The chambers of the reactor were separately charged with polymer reagents – chamber A with \(\alpha\)-PEARL and chamber B with \(\beta\)-PEARL reagents. The reactor chambers were separated with multiple layers of membrane mesh (140 micron pore size) and the amine was added as solution in sufficient amount of THF to fully cover the resins. The reactor was placed on a shaker in a preheated (45 °C) oven and allowed to react for 18 – 24 hours. The solvent was removed with a syringe and polymer washed multiple times as described above. The resulting amides were purified by column chromatography and subjected to the amide cleavage conditions, while the polymer reagents were regenerated by treatment with the corresponding anhydride as described before. The membrane reactor in detail can be seen on Figures 1 to 3. The quantities of the polymer, racemic amine and amount of solvent is separately indicated under each substrate.
6.1. Pent-4-enoyl derivatives.

To the amide (1.0 equiv.) solution in a 1:1 mixture of THF:H$_2$O was added I$_2$ (3.0 equiv) and the mixture was stirred at room temperature for 2 - 8 h. After completion as monitored by TLC, the mixture was quenched with saturated aqueous solution of Na$_2$S$_2$O$_3$ and neutralized by addition of neat K$_2$CO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 times) and combined organics were washed with brine, dried over anhydrous Na$_2$SO$_4$ filtered. The solvent was removed under reduced pressure and the crude product purified by column chromatography.

6.2. 3-(2-Nitrophenyl)propanoyl derivatives.

Method A.

To the amide solution in acetic acid (0.05 M) was added Zn (6.0 – 8.0 equiv.) and the mixture heated to 90 °C for 2 – 5 h. After completion as monitored by TLC the reaction was allowed to cooled to rt, filtered and precipitate washed with toluene. The filtrate was then concentrated under reduced pressure and the crude product purified by column chromatography.

Method B:

To the amide solution in THF (0.1 – 0.2 M) was added catalytic amount of (10 wt%) Pd/C. H$_2$ gas was bubbled through the mixture for 5 min and the flask was placed under 1 atm of H$_2$ (balloon). Upon completion N$_2$ gas was bubbled through the mixture for 15 min. The reaction mixture was filtered through a short pad of celite and the precipitate washed with THF. The filtrate was concentrated under reduced pressure. The resulting product was dissolved in AcOH and the mixture
heated to 90 °C to induce the intramolecular cyclization. Upon completion the solvent was removed under reduced pressure and the product purified by column chromatography.

7. Obtained Products

7.1. Ethyl piperidine-2-carboxylate (2)

Racemic ethyl piperidine-2-carboxylate (314 mg, 2.00 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (2.00 g, 1.50 mmol/g, ~ 1.70 equiv) for 24 hours. The amide products were separated via column chromatography hexanes:EtOAc (4:1 → 2:1) to yield 1) (S)-ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate as a colorless oil (220 mg, 46% yield) in e.r. = 89:11 and 2) (R)-ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate as a pale yellow oil (320 mg, 48% yield) in e.r. = 89:11.

(S)-ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate (2a)

e.r. = 89:11

SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm.

Retention time: tᵣ = 4.0 min (minor), 4.6 (major).

(S)-1-benzyl 2-ethyl piperidine-1,2-dicarboxylate (13a)

(S)-ethyl 1-(pent-4-enoyl) piperidine-2-carboxylate (200 mg, 0.83 mmol, 1.00 equiv) was hydrolyzed according to the general procedure using I₂ (667 mg, 2.63 mmol, 3.00 equiv) in 6 mL (1:1) H₂O:THF mixture for 4 h. After aqueous workup the amine
product was in situ converted to the corresponding carbamate by treatment with Cbz-Cl (143 mg, 0.83 mmol, 1.00 equiv) and Et$_3$N (86 mg, 0.85 mmol, 1.10 equiv). After purification by column chromatography (hexanes:EtOA 9:1) the product was obtained as a colorless oil (200 mg, 83%).

$[\alpha]^{28}_{D}$ (c = 0.25, CHCl$_3$): $-50.6$ (e.r. = 89:11); lit: $[\alpha]^{29}_{D}$ (c = 0.6, CHCl$_3$) = $-31.3$ (83:17)$^8$;

SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 4.2$ min (major), 4.7 (minor).

(R)-ethyl 1-(3-(2-nitropheryl)propanoyl)piperidine-2-carboxylate (2b)

e.r. = 89:11

SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 4.0$ min (minor), 4.6 (major).

(R)-1-benzyl 2-ethyl piperidine-1,2-dicarboxylate (16a)

(R)-ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate (300 mg, 0.89 mmol, 1.00 equiv) was hydrolyzed according to Method B using Pd/C (40.0 mg). The obtained amine was converted to the corresponding carbamate by treatment with CbzCl (150 mg, 0.89 mmol, 1.00 equiv) and Et3N (95 mg, 0.94 mmol, 1.05 equiv) in CH2Cl2 for 3 hours. The product was purified by column chromatography hexanes:EtOAc (9:1) to afford the product as a colorless oil (200 mg, 77%) in e.r. = 89:11.

[α]D28 (c = 0.25, CHCl3): + 44.4 (e.r. = 89:11);

SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO2 to 50 % iPrOH in CO2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tR = 4.2 min (major), 4.7 (minor).

7.2. 1-Methyl-3-phenylpiperazine (11)

Racemic 1-methyl-3-phenylpiperazine (350 mg, 2.00 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.40 g, 1.50 mmol/g, ~1.10 equiv) for 24 hours. The amide products (12a and 12b) were not separable by column chromatography, however the amines could be obtained by sequential hydrolysis protocol.

(R)-1-methyl-3-phenylpiperazine

The mixture of the amides (500 mg) was treated with I2 (760 mg, 3.00 mmol) in 10 mL (1:1) H2O:THF mixture for 3 h. The resulting products were separated by column chromatography (hexanes:EtOAc 1:1) for (S)-1-(4-methyl-2-phenylpiperazin-1-yl)-3-(2-nitrophenyl)propan-1-one and EtOAc 100% (+0.1% Et3N) for (R)-1-methyl-3-phenylpiperazine. The amine was obtained as a white amorphous solid (60 mg, 18% (over two steps)) in e.r. = 84:16

[α]D24 (c = 1.5, CHCl3): − 49.6 (e.r. = 84:16); lit: [α]D28 (c = 1.2, CHCl3) = −23.6 (e.r. = 79:21)

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et3NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tR = 9.0 min (minor), 9.8 min (major).
(S)-1-(4-methyl-2-phenylpiperazin-1-yl)-3-(2-nitrophenyl)propan-1-one (11b)

The amide product after the hydrolysis was obtained as a pale yellow oil (250 mg, 35%) in e.r. = 91:9.

SFC column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % iPrOH in CO$_2$ to 50 % iPrOH in CO$_2$ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 8.5$ min (major), 9.6 (minor).

(S)-1-methyl-3-phenylpiperazine

(S)-1-(4-methyl-2-phenylpiperazin-1-yl)-3-(2-nitrophenyl)propan-1-one (30 mg, 0.1 mmol, 1.0 equiv) was hydrolyzed according to general method A using Zn (33 mg, 0.6 mmol, 6.0 equiv). Product was purified by column chromatography – CH$_2$Cl$_2$ : MeOH 9:1 and title material obtained as a white amorphous solid (12 mg, 85%) in e.r. = 91:9. [$\alpha$]$^b$ (c = 0.50, CHCl$_3$): +38.1 (e.r. = 91:9)

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et$_2$NH flow: 1.0 mL/min; detection: 254 nm. Retention time: $t_R = 9.0$ min (minor), 9.8 min (major).
7.3. Trans-decahydroquinoline (6)

Racemic trans-decahydroquinoline (210 mg, 1.50 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.50 g, ~1.50 equiv.) for 18 h. The amide products were separated via column chromatography (Hex:EtOAc 6:1 ➔ 3:1), to yield 1) 1-((4aR,8aS)-octahydroquinolin-1(2H)-yl)pent-4-en-1-one (13a) as a colorless oil (90 mg, 27%) in **87:13** e.r. and 2) 3-(2-nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (180 mg, 38%) e.r. = **91:9**

(4aR,8aS)-Decahydroquinoline (13c)

1-((4aR,8aS)-octahydroquinolin-1(2H)-yl)pent-4-en-1-one (80.0 mg, 0.36 mmol, 1.00 equiv) was hydrolyzed according to the general method using I₂ (274 mg, 1.08 mmol, 3.00 equiv) in 2 mL (1:1) H₂O:THF mixture for 4 h. The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a white amorphous solid (13 mg, 25%) in **e.r. = 87:13**. The product was converted to its Fmoc- derivative using FmocCl and DIPEA to measure the enantiopurity on SFC.

(4aR,8aS)-(9H-fluoren-9-yl)methyl octahydroquinoline-1(2H)-carboxylate

[α]²⁴_D (c = 0.25, CHCl₃): +22.0 (e.r. = 87:13); ^1H NMR (400 MHz, CDCl₃) δ 7.78 (m, 2H), 7.63 (m, 2H), 7.43 (m, 2H), 7.35 (m, 2H), 4.55 (m, 2H), 4.26 (t, J = 6.0Hz, 1H), 3.62 (m, 1H), 3.25 (m, 1H), 2.87 (td, J = 10.9, 3.3Hz, 1H), 1.85 (m, 1H), 1.75 – 1.50 (m, 6H), 1.42 (m, 1H), 1.30 – 1.15 (m, 3H), 1.10 – 0.95 (m, 2H); ^13C NMR (101 MHz, CDCl₃) δ 156.0, 144.3, 144.3, 141.5, 141.4, 127.6, 127.5, 127.0, 124.0, 124.9, 124.8, 119.9, 119.9, 66.4, 62.2, 47.6, 39.6, 38.3, 33.1, 31.2, 27.3, 26.1, 25.6, 22.9; HRMS (ESI) calculated for [C₂₄H₂₈NO₂]⁺ m/z = 362.2115; found m/z = 362.2114; IR (ν/cm⁻¹, neat) 2925, 2855, 1696, 1449, 1418, 1276, 1244, 1146, 758, 739.
SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_r = 5.6 min (major), 5.9 (minor).

3-(2-Nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one (6b)

\[ \text{e.r.} = 91:9 \]

SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5% iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_r = 4.8 min (minor), 5.1 (major).

(4aS,8aR)-Decahydroquinoline (16c)

3-(2-Nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one (170 mg, 0.54 mmol, 1.00 equiv) was hydrolyzed according to the general method B using Pd/C (40 mg). The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as an amorphous white solid (40 mg, 52%) in \text{e.r.} = 91:9. The product was converted to its Fmoc- derivative using Fmoc-Cl and DIPEA to measure the enantio purity on SFC.

(4aS,8aR)-(9H-Fluoren-9-yl)methyl octahydroquinoline-1(2H)-carboxylate

\[ [\alpha]^{24}_D (c = 2.0, \text{CHCl}_3) = -48.4 \ (\text{e.r.} = 91:9) \]
**SFC** column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5% iPrOH in CO₂ to 50% iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 5.6 \) min (minor), 5.9 (major).

7.4. 4-(4-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (12)

Racemic 4-(4-fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (200 mg, 0.86 mmol, 1.00 equiv.) was resolved according to the general procedure using 1:1 polymer mixture (1.00 g, 1.50 mmol/g, ~2.00 equiv.) in THF (15 mL) for 24 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 2:1), to yield 1) (R)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)pent-4-en-1-one as a colorless oil (100 mg, 37%) in **e.r. = 86:14** and 2) (S)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-(2-nitrophenyl)propan-1-one as a pale yellow oil (180 mg, 50%) **e.r. = 90:10**.

(R)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)pent-4-en-1-one (12a)

\([\alpha]^2_D\) (c = 0.15, CHCl₃): \( -200.4 \) (e.r. = 86:14); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.30 (m, 2H), 7.20 (d, \( J = 5.2 \)Hz, 1H), 7.00 (ap.t, \( J = 8.7 \)Hz, 2H), 6.92 (s, 1H), 6.71 (ap.d, \( J = 5.2 \)Hz, 1H), 5.88 (m, 1H), 5.05 (m, 2H), 3.93 (m, 1H), 3.35 (m, 1H), 3.05 – 2.90 (m, 2H), 2.55 – 2.40 (m, 4H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 170.7, 162.3 (d, \( J = 247 \)Hz), 137.3, 134.1 (d, \( J = 20 \)Hz), 130.3 (d, \( J = 8 \)Hz), 126.5, 123.5, 115.4, 115.1 (d, \( J = 21 \)Hz), 52.9, 39.3, 32.9, 29.3, 25.8; \(^{19}\)F NMR (282 MHz, CDCl₃) –114.1, –114.7; **HRMS** (ESI) calculated for \([C_{18}H_{19}NOFS]^{+}\) m/z = 316.1166; found m/z = 316.1164; **IR** (v/cm\(^{-1}\)) neat 2939, 1639, 1603, 1506, 1432, 1221, 1206, 1185, 1158, 913. **SFC** column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5% iPrOH in CO₂ to 50% iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 7.5 \) min (major), 8.8 (minor).
(R)-4-(4-fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (13e)

(R)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)pent-4-en-1-one (e.r. 86:14) (90 mg, 0.32 mmol, 1.00 equiv) was hydrolyzed according to the general procedure using I₂ (220 mg, 0.86 mmol, 3.00 equiv) in 3 mL (1:1) H₂O:THF mixture for 2 h. The product was purified by column chromatography CH₂Cl₂ : MeOH (9:1) to afford the product as a white amorphous solid (56.0 mg, 80%, e.r. = 86:14).

[α]₂⁵ D (c = 0.20, CHCl₃): −8.2 (e.r. = 86:14)

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 6.4 min (minor), 7.8 min (major).

(S)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-(2-nitrophenyl)propan-1-one (12b)

[α]¹⁹ D (c = 0.30, CHCl₃): +129.6 (e.r. = 90:10); ¹H NMR (400 MHz, CDCl₃) δ 7.95 (m, 0.8H), 7.90 (m, 0.2H), 7.50 – 7.42 (m, 2H), 7.38 (m, 0.8H), 7.30 (m, 2H), 7.15 (m, 1.2H), 7.00 (m, 2H), 6.90 (s, 0.8H), 6.70 (m, 1H), 5.95 (s, 0.2H), 4.85 (m, 0.2H), 3.90 (m, 0.8H), 3.25 (m, 2.8H), 3.10 (m, 0.2H), 2.95 – 2.65 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 162.3 (d, J = 247Hz), 149.3, 137.0, 136.2, 134.1 (d, J = 7Hz), 133.3, 132.8, 130.4 (d, J = 8Hz), 127.6, 126.4, 124.8, 124.7, 123.5, 123.4, 115.1 (d, J = 21Hz), 53.1, 39.2, 34.5, 29.3, 25.8; ¹⁹F NMR (282 MHz, CDCl₃) −114.1, −114.5; HRMS (ESI) calculated for [C₂₂H₂₀N₂O₃FS]⁺ m/z =
411.1173; found m/z = 411.1164; IR (υ/cm⁻¹, neat) 2945, 2843, 1638, 1523, 1506, 1434, 1346, 1222, 1206, 1158. SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 6.1 min (minor), 7.0 (major).

(S)-4-(4-fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (16e)

(S)-1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-(2-nitrophenyl)propan-1-one (e.r. = 90:10) (150 mg, 0.37 mmol, 1.00 equiv) was hydrolyzed according to the general procedure A using Zn (166 mg, 2.55 mmol, 7.00 equiv) in AcOH. The product was purified by column chromatography using CH₂Cl₂: MeOH (9:1) to afford the product as a white amorphous solid (55.0 mg, 64% e.r. 90:10). [α]²⁵D (c = 0.25, CHCl₃): +20.7 (e.r. = 90:10)

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 6.4 min (major), 7.8 min (minor).

7.5. 3-(4-Fluorobenzyl)morpholine (7)

Racemic 3-(4-fluorobenzyl)morpholine (300 mg, 1.54 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (2.00 g, ~1.50 mmol/g, 2.00 equiv) for 24 hours. The amide products were separated via column chromatography hexanes:EtOAc (4:1 → 2:1) to yield 1) (R)-1-(3-(4-fluorobenzyl)morpholino)pent-
4-en-1-one (120 mg, 28%) in e.r. = 93:7 and 2) (S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one (200 mg, 35%) in e.r. = 92:8.

(R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one (7a)

\[
\begin{array}{c}
\text{SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5% iPrOH in CO} \\
\text{2 to 50% iPrOH in CO}_2 \text{ over 10 min; flow: 3.0 mL/min; detection: 254 nm.}
\end{array}
\]

Retention time: \(t_R = 2.9 \text{ min (minor), 3.4 (major).}\)

(R)-3-(4-fluorobenzyl)morpholine (13b)

(R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one (120 mg, 0.43 mmo, 1.00 equiv) was hydrolyzed according to the general method using I\(_2\) (330 mg, 1.30 mmol, 3.00 equiv) in in 4 mL (1:1) H\(_2\)O:THF mixture for 3 h. The product was purified by column chromatography CH\(_2\)Cl\(_2\):MeOH 9:1 (+0.1% Et\(_3\)N) to afford the title compound as a colorless oil (70 mg, 83%) in e.r. = 93:7.

\[\alpha\]^D\(_{24}\)(c = 0.45, CHCl\(_3\)): +28.0 (e.r. = 93:7); HPLC column: Daicel Chiralpak ASH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et\(_2\)NH flow: 1.0 mL/min; detection: 254 nm. Retention time: \(t_R = 4.9 \text{ min (major), 5.5 min (minor).}\)
(S)-3-(4-fluorobenzyl)morpholine (16b)

(S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one (180 mg, 0.48 mmol, 1.00 equiv) was hydrolyzed according to the method B using Pd/C (30 mg). The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a colorless oil (70 mg, 83%) in e.r. = 92:8.

[α]²⁴ᵇ (c = 0.35, CHCl₃): −25.0 (e.r. = 92:8); HPLC column: Daicel Chiralpak ASH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 4.9 min (minor), 5.5 min (major).

7.6. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline

Racemic dimethyl 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (300 mg, 1.11 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (2.00 g, 1.50 mmol/g, 3.00 equiv.) for 18 h. The amide products were separated via column chromatography (hexanes:EtOAc 5:1 → 2:1), to yield 1) (R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one as a colorless oil (200 mg, 49%) in e.r. 90:10 and 2) (S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one (150 mg, 30%) in e.r. = 95:5.

(R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one (9a) e.r. = 90:10

SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 5.6 min (minor), 5.9 (major).
(R)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (13d)

(R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one (190 mg, 0.54 mmol, 1.00 equiv) was hydrolyzed according to the general method using I₂ (434 mg, 1.70 mmol, 3.00 equiv) in 6 mL (1:1) H₂O:THF mixture for 8 h. The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a white amorphous solid (130 mg, 89%) in e.r. = 90:10.

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 9.6 min (minor), 14.0 min (major).

(S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one (9b)

e.r. = 95:5

SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 7.2 min (major), 7.6 (minor).
(S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (16d)

(S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (150 mg, 0.33 mmol, 1.00 equiv) was hydrolyzed according to the method B using Pd/C (30 mg). The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a colorless oil (35 mg, 40%) in e.r. = 95:5.

HPLC column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 20% iPrOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 9.6 min (major), 14.0 min (minor).

7.7 2,8-Bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (10)

Racemic 2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (580 mg, 1.50 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.50 g, 1.50 mmol/g, ~1.50 equiv.) for 18 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 2:1), to yield 1) 1-((S)-2-((R)-2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one as a colorless oil (55 mg, 8%) in e.r. = 97:3 and 2) 3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (150 mg, 27 %) e.r. = 94:6 After column chromatography 80 mg of compound was obtained as a mixture of both amides.
1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one (10a)  

**e.r. = 97:3**

**SFC** column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: $t_R = 5.2$ min (major), 5.5 (minor).

(R)-(2,8-bis(trifluoromethyl)quinolin-4-yl)((S)-piperidin-2-yl)methanol (17)

The mixture of both amides (~1:1) obtained from the kinetic resolution (80 mg, 0.17 mmol, 1.00 equiv) was treated with I₂ (132 mg, 0.52 mmol, 3.00 equiv) in 4 mL (1:1) H₂O:THF mixture for 4 h. The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a white amorphous solid (30 mg, 46%) (90% yield based on pure 1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one) in **e.r. = 97:3**.

**HPLC** column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 4% EtOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: $t_R = 7.0$ min (major), 12.2 min (minor).
1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one (10b)

The unreacted 1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one amide was obtained as a pale yellow oil (25 mg, 30%) (60% yield based on pure 1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one).

e.r. = 94:6

SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R = 6.9 \text{ min (major), 7.4 (minor)} \).

(S)-(2,8-bis(trifluoromethyl)quinolin-4-yl)((R)-piperidin-2-yl)methanol (18)

1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one (150 mg, 0.27 mmol, 1.00 equiv) was hydrolyzed according to the general method B using Pd/C (30 mg). The product was purified by column chromatography CH₂Cl₂:MeOH 9:1 (+0.1% Et₃N) to afford the title compound as a colorless oil (80 mg, 78%) in e.r. = 94:6.

HPLC column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 4% EtOH in hexanes + 0.1% Et₂NH flow: 1.0 mL/min; detection: 254 nm. Retention time: \( t_R = 7.0 \text{ min (minor), 12.2 min (major)} \).
8. Parallel Kinetic Resolution in Flow

Two separate glass columns were charged with (500 mg, ~1.50 mmol/g, ~0.50 equiv) of each of the polymeric reagents. Column length was fixed with the adjustable plastic seals to keep the column volume minimal, while maintaining sufficient space for polymers to swell (~5mL). The polymers were allowed to swell by flushing the system with THF at a flow rate 3 mL/min at 45 °C for 15 – 20 min. The amine (1.5 mmol, 1.00 equiv) was flushed through the system for 18 – 24 h at a flow rate 2 – 3 mL/min and temperature of 45 °C. After the reaction the polymers were washed with THF (3 × three column volumes) and Et₂O (2 × three column volumes). The amide products were
separated by column chromatography and the polymers were regenerated by treatment with the corresponding anhydride as described above.

8.1. Obtained products

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (9)

Racemic dimethyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (400 mg, 1.50 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.00 g, 1.50 mmol/g, 1.00 equiv.) for 18 h. The amide products were separated via column chromatography (hexanes EtOAc 5:1 → 2:1), to yield 1) (R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one as a colorless oil (210 mg, 40%) in e.r. = 97:3 and 2) (S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one (320 mg, 48%) in e.r. = 96:4.

(R)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one (9a)

SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 5.6 min (minor), 5.9 (major).

(S)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one (9b)

SFC column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 7.2 min (major), 7.6 (minor).
3-(4-Fluorobenzyl)morpholine (7)

Racemic dimethyl 3-(4-fluorobenzyl)morpholine (150 mg, 0.77 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (900 mg, 2.00 equiv.) for 25 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 1:1), to yield 1) (R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one as a colorless oil (60 mg, 28%) in e.r. = 96:4 and 2) (S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one as a pale yellow oil (100 mg, 35%) e.r. = 94:6

(R)-1-(3-(4-fluorobenzyl)morpholino)pent-4-en-1-one (7a)

\[
\text{SFC column: Daicel Chiralpak OJH (4.6} \times \text{250 mm); gradient: 5 % } iPrOH \text{ in } CO_2 \text{ to 50 % } iPrOH \text{ in } CO_2 \text{ over 10 min; flow: 3.0 mL/min; detection: 254 nm.}
\]

Retention time: \( t_R = 2.9 \text{ min (minor), 3.4 (major).} \)

(S)-1-(3-(4-fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one (7b)

\[
\text{SFC column: Daicel Chiralpak OJH (4.6} \times \text{250 mm); gradient: 5 % } iPrOH \text{ in } CO_2 \text{ to 50 % } iPrOH \text{ in } CO_2 \text{ over 10 min; flow: 3.0 mL/min; detection: 254 nm.}
\]

Retention time: \( t_R = 5.1 \text{ min (major), 5.5 (minor).} \)
Racemic ethyl piperidine-2-carboxylate (235 mg, 1.50 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.00 g, 1.50 mmol/g, 1.00 equiv) for 24 h. The amide products were separated via column chromatography hexanes EtOAc (4:1 → 2:1) to yield 1) (S)-ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate as a colorless oil (180 mg, 50% yield) in e.r. = 95:5 and 2) (R)-ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate as a pale yellow oil (240 mg, 48% yield) in e.r. = 93:7.

(S)-ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate (2a)

\[\text{e.r.} = 95:5\]

![Graph](image1)

SFC column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient: 5 % iPrOH in CO\(_2\) to 50 % iPrOH in CO\(_2\) over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \(t_R = 4.0\) min (minor), 4.6 (major).

(R)-ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate (2b)

\[\text{e.r.} = 93:7\]

![Graph](image2)

SFC column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient: 5 % iPrOH in CO\(_2\) to 50 % iPrOH in CO\(_2\) over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \(t_R = 4.0\) min (minor), 4.6 (major).
Cis-Decahydroquinoline (5)

Racemic cis-decahydroquinoline (140 mg, 1.00 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (900 mg, 1.50 mmol/g, 1.50 equiv.) for 18 h. The amide products were separated via column chromatography (hexanes EtOAc 9:1 → 3:1), to yield 1) 1-((4aR,8aR)-octahydroquinolin-1(2H)-yl)pent-4-en-1-one as a colorless oil (100 mg, 45%) in e.r. = 89:11 and 2) 3-(2-nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (110 mg, 35%) e.r. = 95:5

1-((4aR,8aR)-Octahydroquinolin-1(2H)-yl)pent-4-en-1-one (5a)

e.r. = 89:11

SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 3.2 min (major), 3.7 (minor).

3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one (5b)

e.r. = 95:5

SFC column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵣ = 5.3 min (minor), 5.7 (major).
2,8-Bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (mefloquine) (10)

Racemic 2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl)methanol (mefloquine) (540 mg, 1.50 mmol, 1.00 equiv) was resolved according to the general procedure using 1:1 polymer mixture (1.00 g, 1.50 mmol/g, 1.00 equiv.) for 24 h. The amide products were separated via column chromatography (hexanes:EtOAc 4:1 → 2:1), to yield 1) 1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one as a colorless oil (120 mg, 18%) in e.r. = 94:6 and 2) 3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one as a pale yellow oil (140 mg, 17%) e.r. = 96:4. After column chromatography 50 mg of compound was obtained as a mixture of both amides.

1-((S)-2-((R)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one (10a) e.r. = 94:6

SFC column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % iPrOH in CO₂ to 50 % iPrOH in CO₂ over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: tᵦ = 5.2 min (major), 5.5 (minor).
1-((R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one (10b)

\[
\text{e.r.} = 96:4
\]

**SFC** column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % \text{iPrOH} in CO\textsubscript{2} to 50 % \text{iPrOH} in CO\textsubscript{2} over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: \( t_R \) = 6.9 min (major), 7.4 (minor).
9. Spectral Data

9.1. Benzyl ((4aS,9aR)-6-bromo-3-oxo-2,3,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-4(4aH)-yl) carbonate 1a
9.2. \((4aS,9aR)-6\text{-Bromo-3-oxo-2,3,9,9a-tetrahydroindeno}[2,1-b][1,4]\text{-oxazin-4(4aH)-yl benzylicarbamate} \ 1b\)
9.3. 3-(2-Nitrophenyl)propanoic acid
9.4. 3-(4-Fluorobenzyl)morpholine

\[
\text{\includegraphics{structure.png}}
\]
9.5. 7-(2-fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane
9.6. \((S)\)-Ethyl 1-(pent-4-enoyl)piperidine-2-carboxylate 2a
9.7. (R)-Ethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2-carboxylate 2b

\[
\text{Chemical Structure Image}
\]

\[
\text{NMR Spectra Image}
\]
9.8. (2S,3R)-Dimethyl 1-(pent-4-enoyl)piperidine-2,3-dicarboxylate 3a
9.9. (2R,3S)-Dimethyl 1-(3-(2-nitrophenyl)propanoyl)piperidine-2,3-dicarboxylate 3b
9.10. (R)-1-(1-Phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pent-4-en-1-one 4a
9.11. (S)-3-(2-Nitrophenyl)-1-(1-phenyl-3,4-dihydropyrrolo[1,2-\text{a}]pyrazin-2(1H)-yl)propan-1-one 4b
9.12. 1-((4aR,8aR)-Octahydroquinolin-1(2H)-yl)pent-4-en-1-one 5a
9.13. 3-(2-Nitrophenyl)-1-((4aS,8aS)-octahydroquinolin-1(2H)-yl)propan-1-one 5b
9.15. 1-((4aR,8aS)-Octahydroquinolin-1(2H)-yl)pent-4-en-1-one 6a
9.16. 3-(2-Nitrophenyl)-1-((4aS,8aR)-octahydroquinolin-1(2H)-yl)propan-1-one 6b
9.17. (R)-1-(3-(4-Fluorobenzyl)morpholino)pent-4-en-1-one 7a
9.18. (S)-1-(3-(4-Fluorobenzyl)morpholino)-3-(2-nitrophenyl)propan-1-one 7b
9.19. (R)-1-(7-(2-Fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pent-4-en-1-one 8a
9.20. (S)-1-(7-(2-Fluorobenzyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-(2-nitrophenyl)propan-1-one 8b
9.21. (R)-1-(6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)pent-4-en-1-one 9a
9.22. (S)-1-(6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-(2-nitrophenyl)propan-1-one 9b

\[
\text{MeO} \quad \begin{array}{c}
\text{MeO} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{O_2N} \\
\text{Ph}
\end{array} 
\]
9.23. 1-((S)-2-((R)-(2,8-Bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)pent-4-en-1-one 10a
9.24. 1-((R)-2-((S)-(2,8-Bis(trifluoromethyl)quinolin-3-yl)(hydroxy)methyl)piperidin-1-yl)-3-(2-nitrophenyl)propan-1-one 10b
9.25. (R)-1-(4-(4-Fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)pent-4-en-1-one \textbf{11a}
9.26. (S)-1-(4-(4-Fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-(2-nitrophenyl)propan-1-one 12b
9.27. (4aR,8aS)-(9H-Fluoren-9-yl)methyl octahydroquinoline-1(2H)-carboxylate