Supporting Information

Removing the superfluous: a supported squaramide catalyst with a minimalistic linker applied to the enantioselective flow synthesis of pyranonaphthoquinones

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Table of Contents

1. General information S2
2. Preparation of Morita-Baylis-Hillman acetates 6 S3
3. Preparation of catalytic resins 2-5 S4
4. General procedure for the synthesis of 8a in batch S8
5. Optimization of the cyclization reaction in flow S9
6. Preparation of the library of enantioenriched pyranonaphthoquinones in flow (GP1) S10
7. Stereochemical model to account for the observed selectivity S10
8. Characterization of 7a S11
9. Characterization of compounds 8a-8g S12
10. $^1$H and $^{13}$C NMR spectra S14
11. HPLC chromatograms S29
1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with p-anisaldehyde or phosphomolybdic acid dip. NMR spectra were recorded at 298 K on a Fourier 300 MHz Bruker, a Bruker Avance 400 Ultrashield or a Bruker Avance 500 Ultrashield apparatus. \(^1\)H NMR spectroscopy chemical shifts are quoted in ppm relative to tetramethylsilane (TMS). CDCl\(_3\) was used as internal standard for \(^{13}\)C NMR spectra. Chemical shifts are given in δ and coupling constants in Hz. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid (Spain) or at MEDAC Ltd. (Surrey, UK). High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralpak columns and guard columns. ESI mass spectra were obtained on a Waters LCT Premier Instrument. Specific optical rotation measurements were carried out on a Jasco P-1030 polarimeter. Racemic standard products were prepared using the same general procedures but with 10 mol% of DABCO as catalyst in order to establish HPLC conditions.
2. Preparation of Morita-Baylis-Hillman acetates 6a-6g

The MBH acetates 6 were prepared according to a procedure described in the literature.\(^1\) In the same reference, 6a and 6e are characterized. Spectroscopic data for all the MBH acetates are given below and the corresponding \(^1\)H and \(^{13}\)C NMR spectra can be found in Section 9.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.36 (s, 1H), 7.51-7.43 (m, 5H), 5.22 (s, 2H), 2.15 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 170.2, 145.3, 139.9, 131.3, 130.9, 130.0 (×2), 129.2 (×2), 57.8, 20.7.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.33 (s, 1H), 7.48-7.42 (m, 2H), 7.01-6.96 (m, 2H), 5.25 (s, 2H), 3.87 (s, 3H), 2.15 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 170.4, 162.4, 143.0, 140.0, 132.5 (×2), 123.2, 114.9 (×2), 58.1, 55.5, 20.8.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 8.27 (s, 1H), 7.03 (dd, J = 8.1, 1.8 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.07 (s, 2H), 5.23 (s, 2H), 2.15 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 170.4, 162.4, 143.0, 140.0, 132.5 (×2), 123.2, 114.9 (×2), 58.0, 20.8.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.29 (s, 1H), 7.49-7.44 (m, 2H), 7.43-7.38 (m, 2H), 5.19 (s, 2H), 2.14 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 170.2, 145.6, 138.5, 137.7, 131.2 (×2), 129.7 (×2), 139.3, 57.5, 20.7.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.03 (s, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.01 (d, J = 3.5 Hz, 1H), 6.63 (dd, J = 3.5, 1.8 Hz, 1H), 5.51 (s, 2H), 2.09 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 170.5, 148.0, 146.6, 141.3, 125.0, 122.6, 113.4, 57.9, 20.8.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.49 (s, 1H), 7.73 (dd, J = 5.1, 1.2 Hz, 1H), 7.54 (dd, J = 3.8, 1.2 Hz, 1H), 7.22 (dd, J = 5.1, 3.8 Hz, 1H), 5.40 (s, 2H), 2.12 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 170.6, 141.7, 136.7, 134.2, 133.3, 132.6, 128.7, 57.9, 20.6.
**3. Preparation of catalytic resins 2-5**

*General synthetic scheme for the preparation of resins 2-4*

Merrifield resin (Novabiochem, 1% DVB, 0.53 mmol/g of active chlorine, 0.50 g) was charged in a screw cap Schlenk flask and was suspended in 3.3 mL of dry DMF under Ar atmosphere. Then, Cs₂CO₃ (0.13 g, 0.40 mmol) and 4-aminobenzoic acid (0.055 g, 0.40 mmol) were added to the previous suspension and the reaction mixture was shaken at rt for 1 h and at 80 °C for 10 more hours. The resulting resin was allowed to cool down to rt, filtered and washed successively with water (60 mL), water/MeOH 1:1 (60 mL), MeOH/CH₂Cl₂ 1:1 (60 mL) and CH₂Cl₂ (60 mL). After drying it overnight under vacuum at 45 °C, 0.50 g of 13a were isolated.

**N elemental analysis (%)**: 0.72 ± 0.25.

**f**: 0.51 mmol/g (quantitative anchoring, **f**ₘₐₓ: 0.48 mmolₘₒₙₒₜₑₐₙₖ/resin).

**IR (ATR)**: ν 1707 cm⁻¹ (carbonyl band).
Merrifield resin (Novabiochem, 1% DVB, $f = 0.53$ mmol/g of active chlorine, 0.55 g) was charged in a screw cap Schlenk flask and was suspended in 3.6 mL of dry DMF under Ar atmosphere. Then, Cs$_2$CO$_3$ (0.14 g, 0.44 mmol) and 4-amino-2-(trifluoromethyl)benzoic acid (0.090 g, 0.44 mmol) were added to the previous suspension and the reaction mixture was shaken for 1 h at rt and subsequently at 80 °C for 10 more hours. The resulting resin was allowed to cool down to rt, filtered and washed successively with water (60 mL), water/MeOH 1:1 (60 mL), MeOH/CH$_2$Cl$_2$ 1:1 (60 mL) and CH$_2$Cl$_2$ (60 mL). After drying it overnight under vacuum at 45 °C, 0.63 g of 13b were isolated.

F elemental analysis (%): 2.73 ± 0.25.

$f$: 0.49 mmol/g (quantitative anchoring, $f_{\text{max}}$: 0.46 mmol$_{\text{monomer/g resin}}$).

IR (ATR): ν 1728 cm$^{-1}$ (carbonyl band).

3,4-Dimethoxy-3-cyclobutene-1,2-dione (0.06 g, 0.43 mmol) was added to a suspension of 13a (0.45 g, 0.23 mmol) in 3.5 mL of MeOH. The reaction mixture was shaken overnight at rt, filtered and washed successively with MeOH (60 mL), MeOH/CH$_2$Cl$_2$ 1:1 (60 mL) and CH$_2$Cl$_2$ (60 mL). After drying it overnight under vacuum at 45 °C, 0.42 g of 14a were isolated.

N elemental analysis (%): 0.69 ± 0.25.

$f$: 0.49 mmol/g (quantitative anchoring, $f_{\text{max}}$: 0.45 mmol$_{\text{monomer/g resin}}$).

IR (ATR): ν 1802, 1714 cm$^{-1}$ (carbonyl bands).

3,4-Dimethoxy-3-cyclobutene-1,2-dione (0.08 g, 0.52 mmol) was added to a suspension of 13b (0.57 g, 0.26 mmol) in 3.6 mL of MeOH. The reaction mixture was shaken overnight at rt, filtered and washed successively with MeOH (60 mL), MeOH/CH$_2$Cl$_2$ 1:1 (60 mL) and CH$_2$Cl$_2$ (60 mL). After drying it overnight under vacuum at 45 °C, 0.49 g of 14b were isolated.

F elemental analysis (%): 2.60 ± 0.25.

$f$: 0.46 mmol/g (quantitative anchoring, $f_{\text{max}}$: 0.44 mmol$_{\text{monomer/g resin}}$).

IR (ATR): ν 1804, 1733 cm$^{-1}$ (carbonyl bands).
General procedure for the preparation of resins 2-4 from 14a or 14b

Resins 14a or 14b (0.15 mmol) were suspended in 2 mL of CH₂Cl₂ and then a solution of the corresponding diamine, either (1R,2R)-trans-2-(1-piperidinyl)cyclohexylamine or epi-aminoquinine, in CH₂Cl₂ (0.30 mmol, 0.37 M) was added. The reaction mixture was shaken at rt for 3 days, filtered and washed successively with MeOH (60 mL), MeOH/CH₂Cl₂ 1:1 (60 mL) and CH₂Cl₂ (60 mL). Then it was allowed to dry overnight under vacuum at 45 °C.

**N elemental analysis (%)**: 0.90 ± 0.25.

- f: 0.21 mmol/g (51% functionalization, \( f_{\text{max}} \): 0.43 mmol_{monomer}/g_{resin}).
- IR (ATR): \( \nu \) 1792, 1708 cm⁻¹ (carbonyl bands).

**N elemental analysis (%)**: 0.94 ± 0.25.

- f: 0.22 mmol/g (52% functionalization, \( f_{\text{max}} \): 0.42 mmol_{monomer}/g_{resin}).
- IR (ATR): \( \nu \) 1792, 1727 cm⁻¹ (carbonyl bands).

**N elemental analysis (%)**: 1.03 ± 0.25

- f: 0.24 mmol/g (54% functionalization, \( f_{\text{max}} \): 0.44 mmol_{monomer}/g_{resin}).
- IR (ATR): \( \nu \) 1707 cm⁻¹ (carbonyl bands).

**Synthetic scheme for the preparation of resin 5**

```latex
\begin{align*}
\text{Wang resin} & \quad \text{DCC, DMAP} \\
\text{CH}_2\text{Cl}_2/\text{DMF} & \quad \text{CH}_2\text{Cl}_2\text{Cl}_2
\end{align*}
```

Scheme S2
A mixture of 4-aminobenzoic acid (11.6 g, 84.0 mmol) and 3,4-dimethoxy-3-cyclobutene-1,2-dione (12.0 g, 84.0 mmol) was suspended in 184 mL of MeOH and stirred at rt for 3 days. The resulting pale yellow solid was isolated by filtration and used in the next step without any further purification (19.6 g, 79.0 mmol, 94% yield).

\( ^{1}H\) NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.00 (s, 1H), 7.91 (d, \( J = 8.4 \) Hz, 2H), 7.47 (d, \( J = 8.3 \) Hz, 2H), 4.41 (s, 3H);

\( ^{13}C\) NMR (101 MHz, DMSO-\(d_6\)): \( \delta \) 188.1, 184.9, 180.0, 169.6, 167.2, 142.45, 131.1 (×2), 126.1, 119.2 (×2), 61.2;

IR (ATR): \( \nu \) 3247, 3190, 3098, 2969, 1799, 1709, 1675, 1607, 1569, 1374, 1280 cm\(^{-1}\); mp: 282-285 °C; HRMS (ESI–): \( m/z \) calcd. for C\(_{12}\)H\(_8\)NO\(_5\) [M–H]: 246.0408, found: 246.0404.

The Wang resin (Iris Biotech, \( f = 1.2 \) mmol/g, 5 g) and DMAP (0.15 g, 1.2 mmol) were suspended in 40 mL of dry CH\(_2\)Cl\(_2\) and a solution of 9 (1.79 g, 7.2 mmol) in 10 mL of dry DMF was added under N\(_2\) atmosphere. The mixture was cooled to 0 °C and a solution of dicyclohexylcarbodiimide (DCC, 1.86 g, 9.0 mmol) in 10 mL of dry DMF was added. It was allowed to slowly reach rt and shaken overnight. Then, the resin was filtered and washed with DMF (100 mL), DMF/H\(_2\)O 1:1 (200 mL), H\(_2\)O (100 mL), H\(_2\)O/MeOH 1:1 (200 mL), MeOH (200 mL), MeOH/CH\(_2\)Cl\(_2\) 1:1 (200 mL) and CH\(_2\)Cl\(_2\) (200 mL) and dried under vacuum at 45 °C. After this, 5.75 g of a deep orange resin were obtained.

**N** elemental analysis (%): 1.30 ± 0.25.

\( f \): 0.94 mmol/g (quantitative anchoring, \( f_{\text{max}} \): 0.93 mmol\text{monomer/gresin}).

IR (ATR): \( \nu \) 1802, 1715 cm\(^{-1}\) (carbonyl bands).

Resin 10 (2.3 g, 2.1 mmol) was swollen in 14 mL of CH\(_2\)Cl\(_2\) and (1R,2R)-trans-2-(1-piperidinyl)cyclo-hexylamine\(^5\) (0.78 g, 4.3 mmol), dissolved in 4 mL of CH\(_2\)Cl\(_2\), was added. It was shaken at rt for two days. Then, it was filtered and washed with CH\(_2\)Cl\(_2\) (150 mL), CH\(_2\)Cl\(_2\)/MeOH 1:1 (150 mL), MeOH (120 mL), CH\(_2\)Cl\(_2\)/MeOH 1:1 (120 mL) and CH\(_2\)Cl\(_2\) (150 mL) and dried under vacuum at 45 °C. After this, 2.4 g of a yellow resin were obtained.
**N elemental analysis** (%): 2.45 ± 0.25.

*f*: 0.58 mmol/g (72% functionalization, *f*\(_{max}\): 0.82 mmol\text{monomer/g}\text{resin}).

IR (ATR): \(\nu\) 1792, 1710 cm\(^{-1}\) (carbonyl bands).

### 4. General procedure for the synthesis of 8a in batch

PS-squaramide 5 (5.5 mg, 3.2 \(\mu\)mol) was charged in a vial and it was swollen with 0.25 mL of solvent. Subsequently, \((E)\)-2-nitro-phenylallyl acetate (6a, 14 mg, 0.06 mmol) and hydroxynaphthoquinone (12 mg, 0.07 mmol) were added to the suspension and the reaction mixture was shaken at rt until total consumption of the starting nitroacetate 6a (TLC monitoring). Then, the resin was filtered and washed with the specific solvent. After this, 0.5 mL of aqueous NaHCO\(_3\) (sat) solution were added to the filtrate and the biphasic mixture was stirred for 1 h. The phases were then separated and the aqueous layer was washed with CH\(_2\)Cl\(_2\) twice. The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and evaporated under vacuum to dryness. The crude was finally purified by silica gel column chromatography (cyclohexane/EtOAc 80:20) to give a yellow solid.

### Screening of solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Reaction time</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>1 h</td>
<td>87%</td>
<td>&gt;95:5</td>
<td>98%</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>1 h</td>
<td>90%</td>
<td>91:9</td>
<td>92%</td>
</tr>
<tr>
<td>DCE</td>
<td>1.5 h</td>
<td>73%</td>
<td>&gt;95:5</td>
<td>98%</td>
</tr>
<tr>
<td>dioxane</td>
<td>2 h</td>
<td>67%</td>
<td>90:10</td>
<td>90%</td>
</tr>
<tr>
<td>toluene</td>
<td>5 h</td>
<td>77%</td>
<td>91:9</td>
<td>82%</td>
</tr>
<tr>
<td>THF</td>
<td>3 h</td>
<td>88%</td>
<td>&gt;95:5</td>
<td>96%</td>
</tr>
<tr>
<td>EtOAc</td>
<td>3 h</td>
<td>89%</td>
<td>92:8</td>
<td>97%</td>
</tr>
</tbody>
</table>

Table S1
5. Optimization of the cyclization reaction in flow

A solution of Michael adduct 7a in a 9:1 mixture of CH₂Cl₂/THF (0.1 M, flow 1 = 0.2 mL/min; HPLC pump AZURA P 4.1S from KNAUER) and the solution of aqueous base (flow 2; syringe pump Legato 200 from KDSCIENTIFIC) were mixed in a T-junction (PTFE). The reaction mixture was circulated through the coil (Ø = 0.8 mm, 10 mL, PTFE) at rt. The solution with the starting material was pumped for 2 min. After this time, the 3-position valve was switched to the reservoir of solvent (CH₂Cl₂/THF 9:1; Scheme S3) and it was passed through the system at equal flow rate. The organic phase at the outlet of the liquid-liquid separator was collected and evaporated under reduced pressure. Conversion was determined by ¹H NMR. Subsequently, new conditions were tested utilizing the same procedure (Table S2 and Table 3 main text).

![Scheme S3](image)

**Screening of basic aqueous solutions for the cyclization reaction**

<table>
<thead>
<tr>
<th>Aqueous base</th>
<th>Flow 2 (mL/min)</th>
<th>Conversion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO₃</td>
<td>0.45</td>
<td>100%</td>
<td>–</td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>0.3</td>
<td>100%</td>
<td>A precipitate is formed.</td>
</tr>
<tr>
<td>Na₂CO₃/NaHCO₃ buffer pH = 9.3</td>
<td>0.3</td>
<td>13%</td>
<td>–</td>
</tr>
<tr>
<td>Na₃PO₄ (0.3 M)</td>
<td>0.3</td>
<td>100%</td>
<td>Only deprotonation (aqueous phase), no cyclized product observed.</td>
</tr>
<tr>
<td>Tris buffer pH = 8</td>
<td>0.3</td>
<td>50%</td>
<td>–</td>
</tr>
<tr>
<td>Na₂HPO₄ (0.35 M)</td>
<td>0.4</td>
<td>80%</td>
<td>–</td>
</tr>
</tbody>
</table>

Table S2
6. Preparation of the library of enantioenriched pyranonaphthoquinones in flow (GP1)

Catalyst 5 (400 mg, 0.23 mmol) was introduced in a PTFE column (Ø = 3.9 mm diameter) and this was connected to the flow set-up depicted in Scheme S4. Then, the resin was swollen by circulating a mixture of CH₂Cl₂/THF 9:1 (HPLC pump AZURA P 4.1S from KNAUER). Solutions containing hydroxynaphthoquinone (1.1 mmol, 1.1 equiv.) and the corresponding nitroalkene (1 mmol, 1.0 equiv.) in CH₂Cl₂ (9 mL) and THF (1 mL) were sequentially circulated through the column (0.2 mL/min, syringe pump Legato 200 from KDSCIENTIFIC equipped with a gastight syringe from Hamilton, ca. 50 min for each run). A solution of sat. aq. NaHCO₃ was circulated downstream of the column to carry out the cyclization step in a 10-mL coil (0.45 mL/min, syringe pump as above equipped with plastic syringes). At the end, the biphasic mixture was separated with the aid of a liquid-liquid separator. When each combination of reagents was consumed, the system was rinsed with the solvent mixture for 1 h (0.2 mL/min) to ensure all organic materials were collected before the next combination was introduced in the flow set-up.

![Scheme S4](image)

7. Stereochemical model to account for the observed selectivity

![Stereochemical model](image)

S10
8. Characterization of 7a

Orange foam; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.10 (dd, $J = 7.8, 1.3$ Hz, 1H), 8.01 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.90 (br s, 1H), 7.74 (td, $J = 7.6, 1.3$ Hz, 1H), 7.65 (td, $J = 7.6, 1.3$ Hz, 1H), 7.57-7.53 (m, 2H), 7.35-7.30 (m, 2H), 7.29-7.24 (m, 1H), 6.30 (ddd, $J = 12.0, 8.5, 2.9$ Hz, 1H), 5.09 (d, $J = 12.0$ Hz, 1H), 4.47 (dd, $J = 12.3, 2.9$ Hz, 1H), 4.30 (dd, $J = 12.3, 8.5$ Hz, 1H), 2.06 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 188.3, 180.9, 170.0, 153.1, 136.1, 135.4, 133.3, 132.5, 129.3 ($\times$2), 128.9 ($\times$2), 128.8, 128.3, 127.2, 126.2, 120.0, 85.8, 63.6, 42.2, 20.5; $\left[\alpha\right]_{D}^{25}$: $+23.4$ (c 1.12, CHCl$_3$); HRMS (ESI$^+$): $m/z$ calcd. for C$_{21}$H$_{17}$NNaO$_7$ [M+Na]$^+$: 418.0897, found: 418.0904; IR (ATR): $\nu$ 1750, 1672, 1649, 1594, 1556, 1459, 1370, 1227 cm$^{-1}$; HPLC (Daicel Chiralpak IA column, Hx/CH$_2$Cl$_2$/EtOH/TFA 90:5:5:0.1; flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_R$(maj) = 20.0 min; $t_R$(min) = 32.6 min.

The relative configuration of 7a was determined by X-ray diffraction:

The corresponding CIF file has been deposed with the CCDC and has reference number 1456999.
9. Characterization of compounds 8a-8g

Compound 8a was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene 6a (0.221 g, 1.0 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 71% yield (0.237 g, 0.71 mmol), 87:13 dr and 98% ee. 

\(^1\)H and \(^{13}\)C NMR data match with those reported in the literature.\(^4\) HPLC (Daicel Chiralpak IC column, hexane/i-PrOH (75:25), flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_{\text{major}} = 20.0\) min; \(t_{\text{minor}} = 15.5\) min.

Compound 8b was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene 6b (0.251 g, 1.0 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 83% yield (0.300 g, 0.83 mmol), 85:15 dr and 97% ee.

\(^1\)H and \(^{13}\)C NMR data match with those reported in the literature.\(^4\) HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_{\text{major}} = 51.2\) min; \(t_{\text{minor}} = 10.0\) min.

Compound 8c was prepared in flow from hydroxynaphthoquinone (0.163 g, 0.94 mmol) and nitroalkene 6c (0.225 g, 0.85 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 74% yield (0.239 g, 0.63 mmol), 87:13 dr and 97% ee.

\(^1\)H and \(^{13}\)C NMR data match with those reported in the literature.\(^4\) HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, \(\lambda = 254\) nm): \(t_{\text{major}} = 52.9\) min; \(t_{\text{minor}} = 12.3\) min.

Compound 8d was prepared in flow from hydroxynaphthoquinone (0.176 g, 1.01 mmol) and nitroalkene 6d (0.235 g, 0.92 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 80% yield (0.273 g, 0.74 mmol), 92:8 dr and 96% ee.
$^1$H and $^{13}$C NMR data match with those reported in the literature.\textsuperscript{4} HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 46.1$ min; $t_{\text{minor}} = 9.1$ min.

Compound 8e was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene 6e (0.211 g, 1.0 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 62% yield (0.203 g, 0.62 mmol), 84:16 dr and 97% ee.

$^1$H and $^{13}$C NMR data match with those reported in the literature.\textsuperscript{4} [a]$^{25}$D: +103 (c 1.00, CHCl$_3$); HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 19.5$ min; $t_{\text{minor}} = 8.1$ min.

Compound 8f was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene 6f (0.227 g, 1.0 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 65% yield (0.223 g, 0.65 mmol), 78:22 dr and 98% ee.

$^1$H and $^{13}$C NMR data match with those reported in the literature.\textsuperscript{4} HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 31.7$ min; $t_{\text{minor}} = 8.9$ min.

Compound 8g was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene 6g (0.256 g, 1.0 mmol) according to the General Procedure GP1. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 81% yield (0.299 g, 0.81 mmol), >99:1 dr and 98% ee.

$^1$H and $^{13}$C NMR data match with those reported in the literature.\textsuperscript{4} HPLC (Daicel Chiralpak IA column, hexane/i-PrOH (70:30), flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 30.8$ min; $t_{\text{minor}} = 8.8$ min.

10. $^1$H and $^{13}$C NMR spectra

![NMR spectra of compound 6a](image-url)
11. HPLC chromatograms
Sample Info: IC hex/IPA 75/25 1 ml/min 254nm

Additional Info: Peak(s) manually integrated

### Chart 1

**DAD1 A, Sig=254.4 Ref=360.100 (LAURA/LOP10874COL_9.D)**

<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>15.486</td>
<td>BB</td>
<td>0.4365</td>
<td>984.17529</td>
<td>34.53581</td>
<td>49.0592</td>
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<td>2</td>
<td>20.263</td>
<td>BB</td>
<td>0.5570</td>
<td>985.73480</td>
<td>27.04044</td>
<td>50.1408</td>
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</table>

![Chart 1 Image]

**Chart 1 Image**

8a (rac)

### Chart 2

**DAD1 A, Sig=254.4 Ref=360.100 (LAURA/LOP10877COL_4.D)**

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<tr>
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<td>20.045</td>
<td>BB</td>
<td>0.5613</td>
<td>8651.60547</td>
<td>236.19977</td>
<td>99.1305</td>
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![Chart 2 Image]

**Chart 2 Image**

8a

---

S30
Sample Info: IA hex/IPA 70/30 1 mL/min 230 nm

Additional Info: Peak(s) manually integrated

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<th>Area %</th>
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<td>1</td>
<td>BB</td>
<td>0.5202</td>
<td>1.1907e4</td>
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<td>2</td>
<td>BB</td>
<td>2.3267</td>
<td>1.1589e6</td>
<td>60.55875</td>
<td>49.3245</td>
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**Chemical Structure:**

![Chemical Structure](image)

(rac)
Sample Info: IA hex/IPA 70/30 1 mL/min 230 nm

Additional Info: Peak(s) manually integrated

DAD1 A, Sig=2544 Ret-off (C:\Chem32\Data\Laurallop2_1016od_2.D)

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(rac)

DAD1 B, Sig=2544 Ret-off (C:\Chem32\Data\Laurallop2_1016od_2.D)

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<tbody>
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8e
Sample Info: IA hex/IPA 70/30 1.0 ml/min 230 nm thienyl racemic

Additional Info: Peak(s) manually integrated

<table>
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<tr>
<th>#</th>
<th>RetTime</th>
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<th>Area</th>
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<tbody>
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<td>2443.68140</td>
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<td>49.2988</td>
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</table>

**8f (rac)**

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Sample Info: IA hex/IPA 70/30 1.0 ml/min 230 nm thienyl racemic

Additional Info: Peak(s) manually integrated

<table>
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<tr>
<th>#</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>BB</td>
<td>0.4437</td>
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<tr>
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