Electronic Supplementary Information

Optimized iminium-catalysed 1,4-reductions inside the resorcinarene capsule: Achieving >90% *ee* with proline as catalyst

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1. General information

Experimental: All reactions were carried out using standard Schlenk techniques with Argon (Ar 4.6) as the inert gas. Unless indicated otherwise, glass equipment was dried under high vacuum (10−2 mbar) at 500-600 °C using a heat gun. Reactions at low temperatures were performed using cooling ice/water (0 °C) bath.

Sources of Chemicals: Reagents (Acros, Alfa Aesar, Fluorochem, Sigmar-Aldrich, VWR) were used without prior purification.

Solvents: Anhydrous solvents were purchased from Acros and were used without prior purification. Solvents for extractions, chromatography, filtrations, and non-anhydrous reactions were purchased from VWR as HPLC grade solvents and were used without prior purification. NMR Solvents were purchased from Cambridge Isotope Laboratories and were used without prior purification.

Thin-Layer Chromatography (TLC): Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 glass-backed plates, which were analyzed by fluorescence detection with UV-light (λ = 254 nm, [UV]) and after exposure to standard staining reagents and subsequent heat treatment. The following staining solution was used: acidic cerium ammonium molybdate solution [CAM] (40 g ammonium heptamolybdate, 1.6 g cerium sulfate in 900 mL H_2O with 100 mL conc. H_2SO_4).

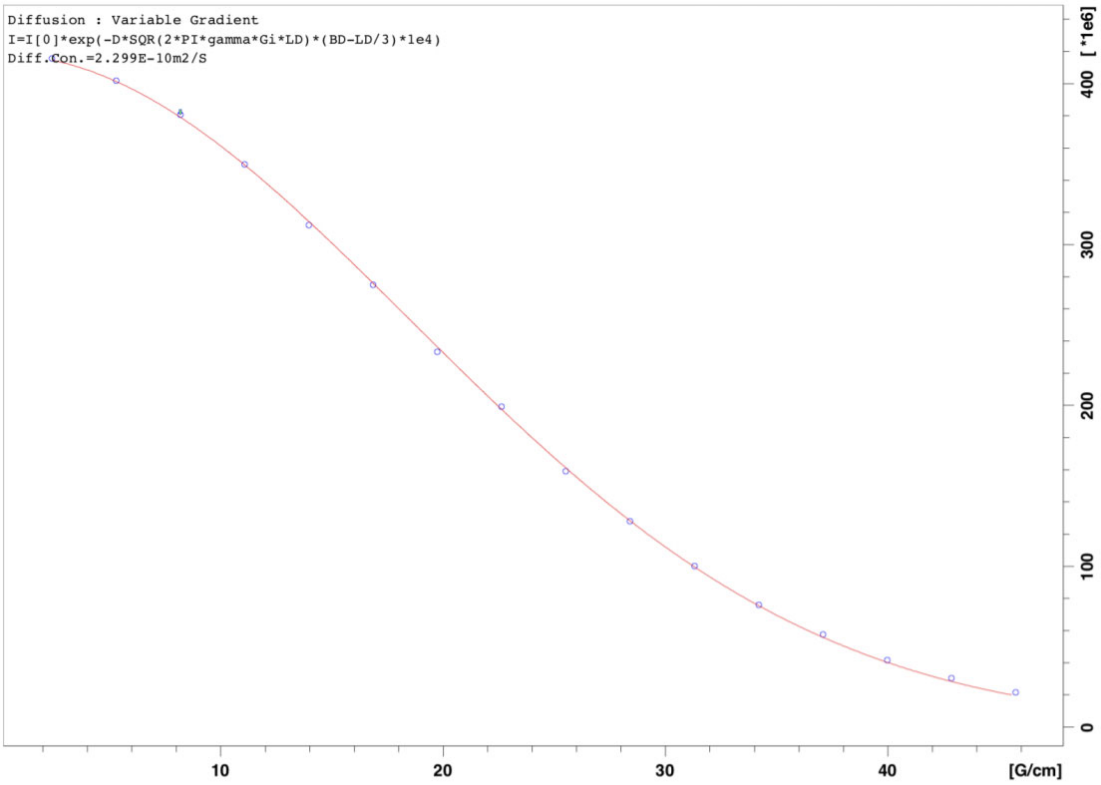
GC Analysis: GC analyses were carried out on a Shimadzu GC-2010 Plus instrument equipped with a FID detector and an Rtx-5 capillary column (length = 30 m). Hydrogen was used as the carrier gas, and the constant flow mode was used (flow rate = 40 mL/min) with a split ratio of 1:20. The following temperature program was used: 60 °C for 3 min, 15 °C min^{-1} to 250 °C, and 250 °C for 5 min.

For the determination of enantiopurity via GC, a Shimadzu GC-2010 Plus instrument equipped with a FID detector and an Rt-bDEXsm capillary column (length = 30 m) was used. Hydrogen was used as the carrier gas, and the constant-flow mode was used (flow rate = 50 mL/min) with a split ratio of 1:20. The following temperature programs were used:

- Products **P1**-**P3**: 60 °C for 1 min, 5 °C min^{-1} to 220 °C, and 220 °C for 10 min.
- Product **P4**: 60 °C for 1 min, 0.50 °C min^{-1} to 180 °C, and 180 °C for 10 min.
- Product **P5**: 60 °C for 1 min, 1.50 °C min^{-1} to 180 °C, and 180 °C for 10 min.

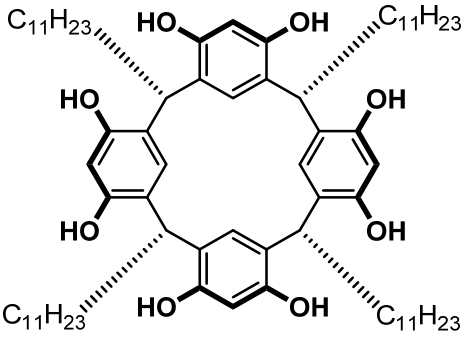
NMR Experiments: NMR experiments were performed on an UltraShield 500 spectrometer by BRUKER operating at 500 MHz proton frequency. The experiments were performed at 298 K respectively, and the temperature was calibrated using a methanol standard showing accuracy within +/− 0.2 K. The chemical shift is given in ppm (parts per million). The proton signal of the deuterated solvent was used as reference: $CDCl_3$ $\delta(^1H)$ = 7.26 ppm. The multiplicity of signals is abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint.). Broadened signals are denoted with (br). Coupling constants (*J*) are reported in Hertz (Hz). All DOSY-NMR experiments were performed on a Bruker Avance III HD four-channel NMR spectrometer operating at 600.13 MHz proton frequency. The instrument was equipped with a cryogenic 5mm four-channel QCI probe (H/C/N/F) with a self-shielded z-gradient. The experiments were performed at 298 K, and the

temperature was calibrated using a methanol standard showing accuracy within +/- 0.2 K. For the PFGSE (pulsed field gradient spin echo) diffusion experiment, the sample was placed in a 3 mm outer diameter tube and the 3 mm tube was then inserted in a standard 5 mm round-bottom tube and securely kept in place by a simple home-made device. This setup ensured a negligible temperature gradient on the sample even inside a cryogenic probe. The PFGSE experiments were performed using a bipolar gradient pulse sequence.[1] The sigmoidal intensity decrease was fitted with a two-parameter fit (I_0 and diffusion coefficient D) with the dosy routine implemented in topspin 3.6.1 [Bruker Biospin GmbH]. A typically observed intensity decrease is depicted below.



2. Synthesis

2.1. Synthesis of C-undecylcalix[4]resorcinarene (1)



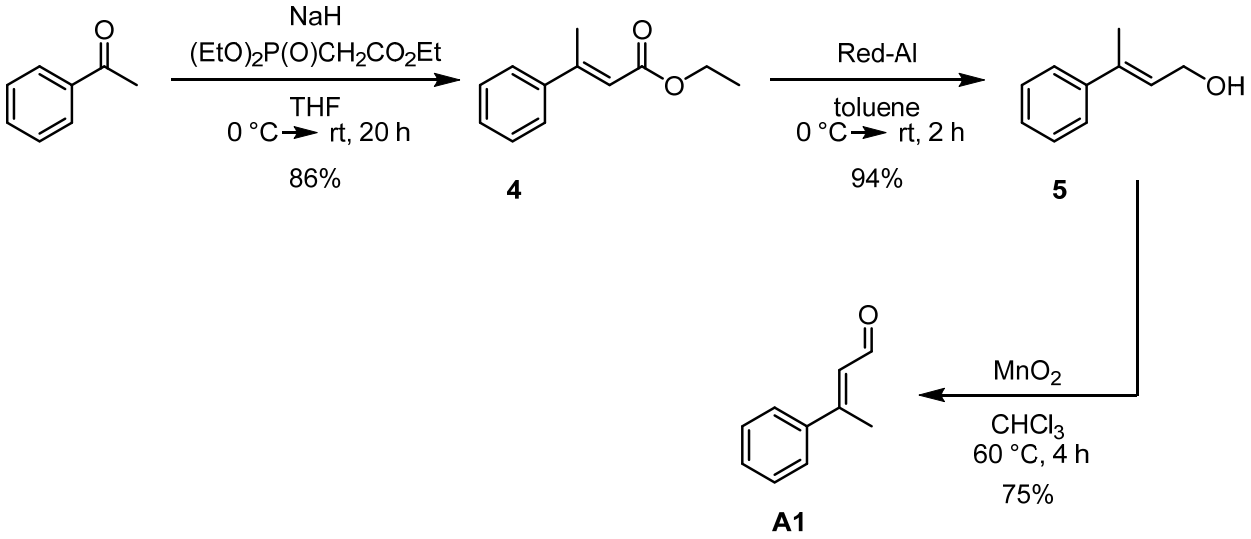
$C_{72}H_{112}O_8$
1105.68 g/mol

Resorcinarene **1** was synthesized according to modified literature procedures.[2,3] To a stirred solution of 99.9% ethanol (54 mL) and 37% aqueous HCl (18 mL), resorcinol (14.2 g, 129 mmol, 1.00 eq.) was added. After complete dissolution and cooling to 0 °C, a solution of dodecanal (28.5 mL, 23.8 g, 129 mmol, 1.00 eq.) in 99.9% ethanol (36 mL) was added dropwise into the reaction mixture over the course of 1 h. The resulting solution was allowed to warm to rt and was subsequently refluxed for 18 h. The dark red solution was then allowed to cool to rt whereby a yellow precipitate formed. The precipitate was dispersed in cold methanol, filtered, and subsequently washed with cold methanol until the washings were light yellow. The solid was recrystallized from methanol (20 mL). To remove the remaining yellow impurities, the solid was moistened with cold methanol and then washed extensively with distilled water (6 × 50 mL). The crystalline material was dried under reduced pressure (16 mbar) at rt using a rotary evaporator. The drying process was continued until the residual methanol was completely removed, and acceptable water content (11-12 eq. H_2O/hexamer **I**, see below) was obtained. Compound 1 (24.8 g, 89.9 mmol, 70%) was obtained as an off-white powder. After dissolving 1 (11.0 mg) in $CDCl_3$ (0.50 mL), the water content of 11-12 eq. H_2O/hexamer **I** was determined via integration of the corresponding peaks in the ^1H NMR spectrum. The spectroscopic data matched those reported in the literature.[4]

General remark: If the water content is too low, a gel-like mixture is obtained upon the addition of $CDCl_3$.

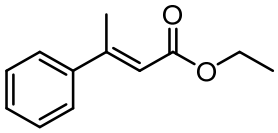
2.2. Synthesis of substrates

Synthesis of aldehyde A1



Scheme S1. Synthesis of aldehyde **A1**.

Ethyl (*E*)-3-phenylbut-2-enoate (4)



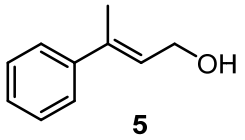
4

$C_{12}H_{14}O_2$
190.24 g/mol

To a suspension of NaH (500 mg, 60% dispersion in mineral oil, 12.5 mmol, 1.25 eq.) in anhydrous THF (25 mL) was added dropwise triethyl phosphonoacetate (2.48 mL, 2.80 g, 12.5 mmol, 1.25 eq.) over 15 min at 0 °C. After 30 min, acetophenone (1.18 mL, 1.20 g, 10.0 mmol, 1.00 eq.) was added to the reaction mixture, which was then allowed to warm to rt. After 20 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 30/1 → 20/1) to yield compound **4** (1.6 g, 8.62 mmol, 86%) as a colorless oil. The spectroscopic data matched those reported in the literature.[5]

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.51 – 7.45 (m, 2H), 7.41 – 7.32 (m, 3H), 6.14 (q, *J* = 1.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.58 (d, *J* = 1.3 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-phenylbut-2-en-1-ol (5)



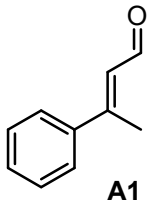
5

$C_{10}H_{12}O$
148.21 g/mol

To a stirred solution of **4** (1.6 g, 8.41 mmol, 1.00 eq.) in anhydrous toluene (9 mL) at 0 °C was added dropwise Red-Al (60 wt% solution in toluene, 3.13 mL, 3.26 g, 9.67 mmol, 1.15 eq.). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 2 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with Et_2O (20 mL), quenched by the addition of 1 M HCl (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 7/1 → 5/1) to yield compound **5** (1.17 g, 7.90 mmol, 94%) as a colorless oil. The spectroscopic data matched those reported in the literature.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.44 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 5.98 (tq, *J* = 6.7, 1.4 Hz, 1H), 4.37 (d, *J* = 6.7 Hz, 2H), 2.09 (q, *J* = 0.9 Hz, 3H).

(*E*)-3-phenylbut-2-enal (A1)



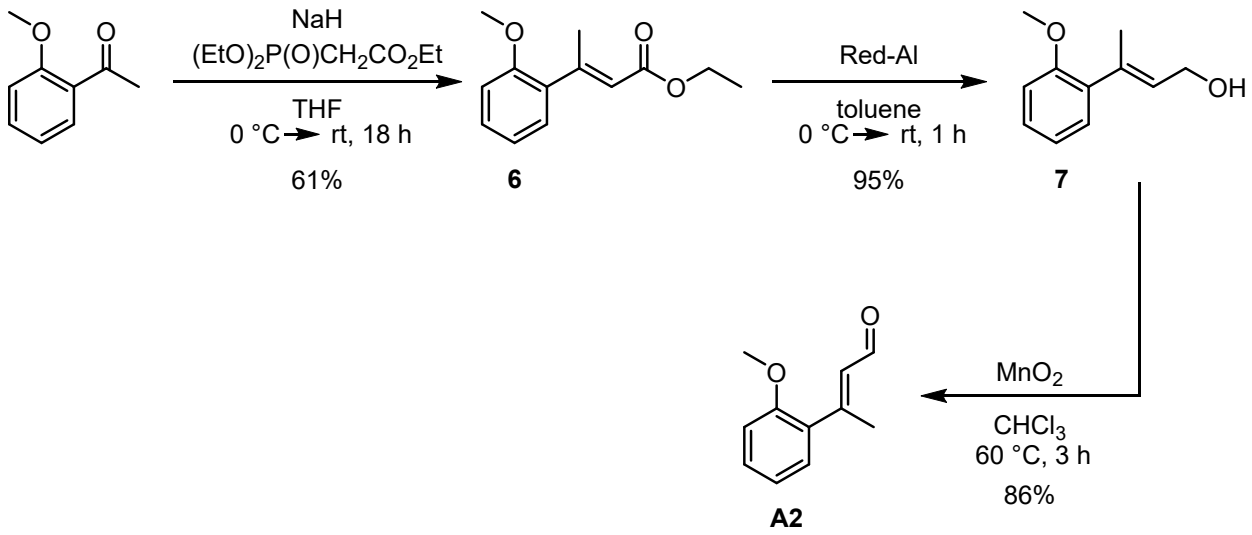
A1

$C_{10}H_{10}O$
146.19 g/mol

To a stirred solution of **5** (880 mg, 5.94 mmol, 1.00 eq.) in $CHCl_3$ (10 mL) was added manganese dioxide (2.69 g, 30.9 mmol, 5.20 eq.) in one portion. The mixture was warmed to 60 °C. After 4 h, the completion of the reaction was confirmed by TLC control. After cooling to rt, the mixture was filtered through a pad of celite using Et_2O as a rinse. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et_2O = 5/1 → 3/1) to yield compound **A1** (650 mg, 4.45 mmol, 75%) as a yellow oil. The spectroscopic data matched those reported in the literature.[7]

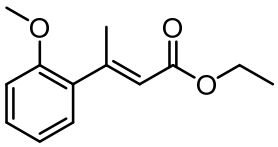
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.19 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.45 – 7.38 (m, 3H), 6.40 (dq, *J* = 7.9, 1.3 Hz, 1H), 2.58 (d, *J* = 1.2 Hz, 3H).

Synthesis of aldehyde A2



Scheme S2. Synthesis of aldehyde **A2**.

Ethyl (*E*)-3-(2-methoxyphenyl)but-2-enoate (6)



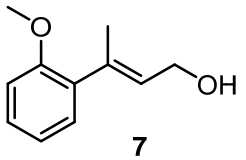
$C_{13}H_{16}O_3$
220.27 g/mol

6

To a suspension of NaH (500 mg, 60% dispersion in mineral oil, 12.5 mmol, 1.25 eq.) in anhydrous THF (25 mL) was added dropwise triethyl phosphonoacetate (2.48 mL, 2.80 g, 12.5 mmol, 1.25 eq.) over 15 min at 0 °C. After 30 min, 2-methoxyacetophenone (1.38 mL, 1.50 g, 10.0 mmol, 1.00 eq.) was added to the reaction mixture, which was then allowed to warm to rt. After 18 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 30/1 → 20/1) to yield compound **6** (1.34 g, 6.13 mmol, 61%) as a colorless oil. The spectroscopic data matched those reported in the literature.[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.30 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.89 (q, *J* = 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.49 (d, *J* = 1.4 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

(*E*)-3-(2-methoxyphenyl)but-2-en-1-ol (7)



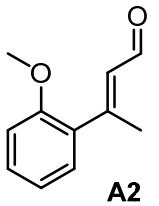
7

$C_{11}H_{14}O_2$
178.23 g/mol

To a stirred solution of **6** (1.20 g, 5.45 mmol, 1.00 eq.) in anhydrous toluene (6 mL) at 0 °C was added dropwise Red-Al (60 wt% solution in toluene, 2.03 mL, 2.11 g, 6.27 mmol, 1.15 eq.). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 1 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with Et_2O (20 mL), quenched by the addition of 1 M HCl (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 5/1 → 3/1) to yield compound **7** (920 mg, 5.16 mmol, 95%) as a colorless oil. The spectroscopic data matched those reported in the literature.[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.27 – 7.23 (m, 1H), 7.14 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.69 (tq, *J* = 6.7, 1.4 Hz, 1H), 4.34 (dd, *J* = 6.7, 0.9 Hz, 2H), 3.82 (s, 3H), 2.03 (dt, *J* = 1.6, 0.8 Hz, 3H).

(*E*)-3-(2-methoxyphenyl)but-2-enal (A2)



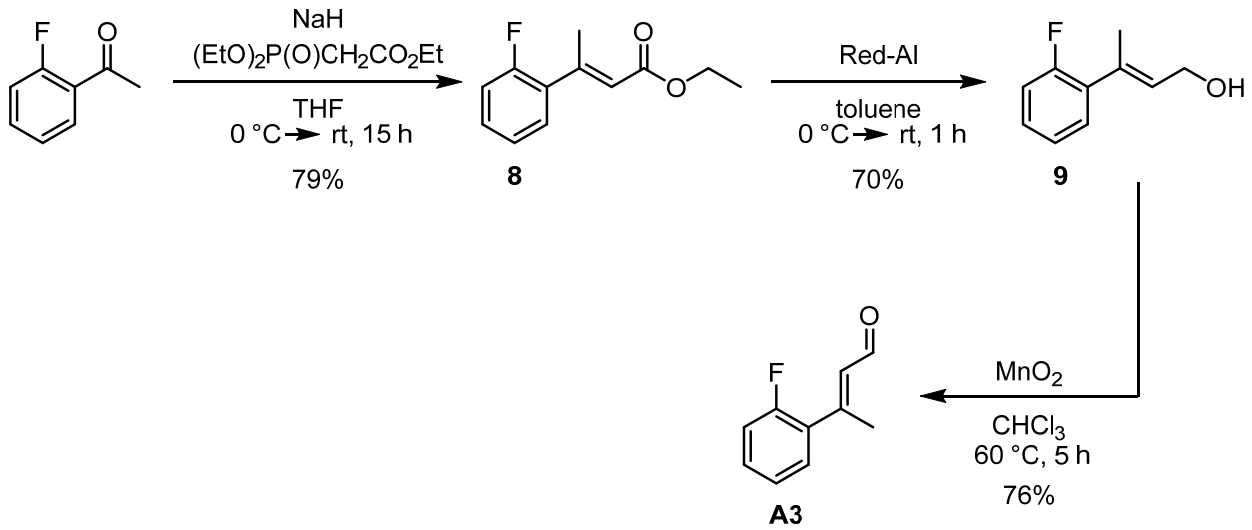
A2

$C_{11}H_{12}O_2$
176.22 g/mol

To a stirred solution of **7** (920 mg, 5.16 mmol, 1.00 eq.) in $CHCl_3$ (10 mL) was added manganese dioxide (2.33 g, 26.8 mmol, 5.20 eq.) in one portion. The mixture was warmed to 60 °C. After 3 h, the completion of the reaction was confirmed by TLC control. After cooling to rt, the mixture was filtered through a pad of celite using Et_2O as a rinse. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 15/1) to yield compound **A2** (780 mg, 4.43 mmol, 86%) as a yellow oil. The spectroscopic data matched those reported in the literature.[9]

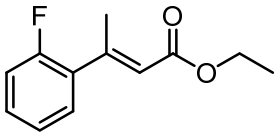
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.16 (d, J = 8.0 Hz, 1H), 7.34 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.17 (dd, J = 7.5, 1.8 Hz, 1H), 6.97 (td, J = 7.5, 1.0 Hz, 1H), 6.93 (dd, J = 8.4, 1.0 Hz, 1H), 6.12 (dq, J = 8.1, 1.3 Hz, 1H), 3.85 (s, 3H), 2.53 (d, J = 1.3 Hz, 3H).

Synthesis of aldehyde A3



Scheme S3. Synthesis of aldehyde **A3**.

Ethyl (*E*)-3-(2-fluorophenyl)but-2-enoate (8)



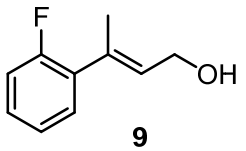
8

$C_{12}H_{13}FO_2$
208.23 g/mol

To a suspension of NaH (543 mg, 60% dispersion in mineral oil, 13.6 mmol, 1.25 eq.) in anhydrous THF (30 mL) was added dropwise triethyl phosphonoacetate (2.78 mL, 3.04 g, 13.6 mmol, 1.25 eq.) over 15 min at 0 °C. After 30 min, 2-fluoroacetophenone (1.36 mL, 1.50 g, 10.9 mmol, 1.00 eq.) was added to the reaction mixture, which was then allowed to warm to rt. After 15 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 50/1 → 30/1) to yield compound **8** (1.79 mg, 8.60 mmol, 79%) as an oil. The spectroscopic data matched those reported in the literature.[10]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.34 – 7.27 (m, 2H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H), 7.07 (ddd, *J* = 10.9, 8.2, 1.1 Hz, 1H), 6.01 – 5.98 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 1.6 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

(*E*)-3-(2-fluorophenyl)but-2-en-1-ol (9)



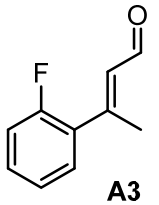
9

$C_{10}H_{11}FO$
166.20 g/mol

To a stirred solution of **8** (1.79 g, 8.60 mmol, 1.00 eq.) in anhydrous toluene (10 mL) at 0 °C was added dropwise Red-Al (70 wt% solution in toluene, 3.20 mL, 3.33 g, 9.89 mmol, 1.15 eq.). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 30 min, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with Et_2O (15 mL), quenched by the addition of 1 M HCl (25 mL), and extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 7/1 → 5/1) to yield compound **9** (1.00 g, 6.02 mmol, 70%) as an oil. The spectroscopic data matched those reported in the literature.[11]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.26 – 7.20 (m, 2H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 7.03 (ddd, *J* = 11.1, 8.1, 1.2 Hz, 1H), 5.81 (ddt, *J* = 6.6, 5.0, 1.5 Hz, 1H), 4.36 (dd, *J* = 6.7, 1.0 Hz, 2H), 2.06 (td, *J* = 1.6, 0.8 Hz, 3H).

(*E*)-3-(2-fluorophenyl)but-2-enal (A3)



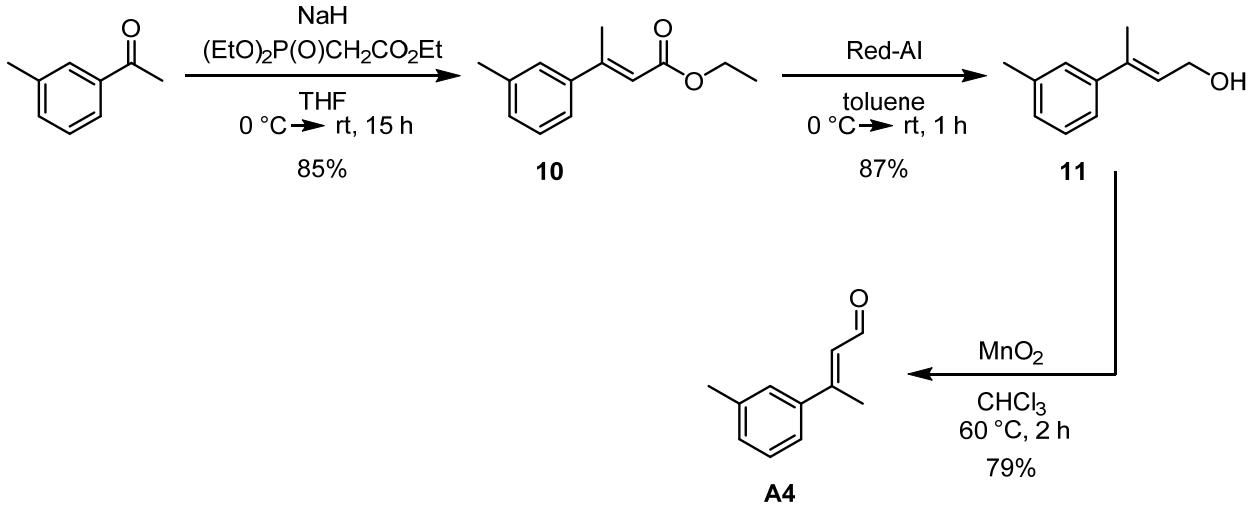
A3

$C_{10}H_9FO$
164.18 g/mol

To a stirred solution of crude product **9** (300 mg, 1.81 mmol, 1.00 eq.) in $CHCl_3$ (5 mL) was added manganese dioxide (787 mg, 9.05 mmol, 5.00 eq.) in one portion. The mixture was warmed to 60 °C. After 5 h, the completion of the reaction was confirmed by TLC control. After cooling to rt, the mixture was filtered through a pad of celite using Et_2O as a rinse. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 15/1) to yield compound **A3** (226 mg, 1.38 mmol, 76%) as an oil. The spectroscopic data matched those reported in the literature.[10]

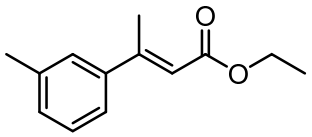
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.18 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.31 (td, *J* = 7.7, 1.8 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (ddd, *J* = 11.2, 8.2, 1.1 Hz, 1H), 6.21 (dq, *J* = 7.8, 1.5 Hz, 1H), 2.56 (t, *J* = 1.6 Hz, 3H).

Synthesis of aldehyde A4



Scheme S4. Synthesis of aldehyde **A4**.

Ethyl (*E*)-3-(m-tolyl)but-2-enoate (10)



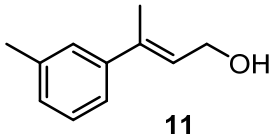
$C_{13}H_{16}O_2$
204.27 g/mol

10

To a suspension of NaH (575 mg, 60% dispersion in mineral oil, 14.4 mmol, 1.93 eq.) in anhydrous THF (18 mL) was added dropwise triethyl phosphonoacetate (2.78 mL, 3.14 g, 14.0 mmol, 1.88 eq.) over 15 min at 0 °C. After 30 min, 3-methylacetophenone (1.01 mL, 1.00 g, 7.45 mmol, 1.00 eq.) was added to the reaction mixture, which was then allowed to warm to rt. After 15 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et_2O = 15/1) to yield compound **10** (1.30 g, 6.35 mmol, 85%) as a colorless oil. The spectroscopic data matched those reported in the literature.[12]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.31 – 7.23 (m, 4H), 7.19 – 7.15 (m, 1H), 6.12 (q, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.57 (d, *J* = 1.3 Hz, 3H), 2.38 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

(*E*)-3-(m-tolyl)but-2-en-1-ol (11)



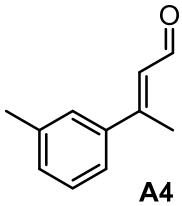
11

$C_{11}H_{14}O$
162.23 g/mol

To a stirred solution of **10** (1.30 g, 6.36 mmol, 1.00 eq.) in anhydrous toluene (8 mL) at 0 °C was added dropwise Red-Al (60 wt% solution in toluene, 2.68 mL, 2.79 g, 8.27 mmol, 1.30 eq.). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 1 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with Et_2O (20 mL), quenched by the addition of 1 M HCl (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et2O = 15/1) to yield compound **11** (900 mg, 5.55 mmol, 87%) as a colorless oil. The spectroscopic data matched those reported in the literature.[12]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.28 – 7.13 (m, 3H), 7.09 (m, 1H), 5.96 (tq, *J* = 6.7, 1.4 Hz, 1H), 4.36 (dd, *J* = 6.7, 0.9 Hz, 2H), 2.36 (s, 3H), 2.08 (m, 3H).

(*E*)-3-(m-tolyl)but-2-enal (A4)



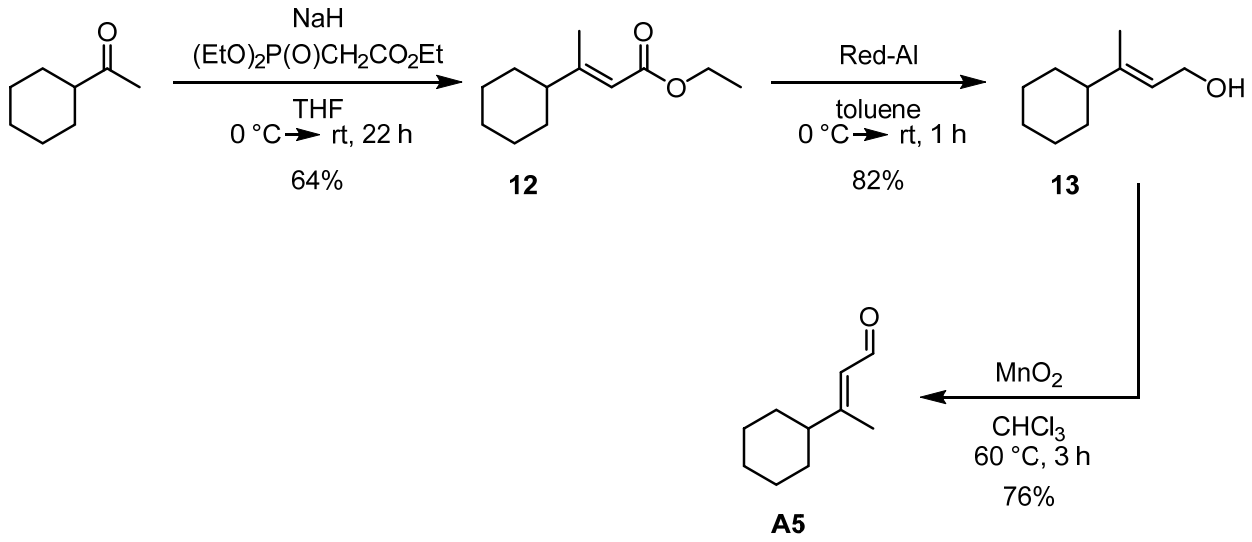
A4

$C_{11}H_{12}O$
160.22 g/mol

To a stirred solution of crude product **11** (300 mg, 1.85mmol, 1.00 eq.) in $CHCl_3$ (5 mL) was added manganese dioxide (933 mg, 10.7 mmol, 5.80 eq.) in one portion. The mixture was warmed to 60 °C. After 2 h, the completion of the reaction was confirmed by TLC control. After cooling to rt, the mixture was filtered through a pad of celite using Et_2O as a rinse. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et_2O = 6/1) to yield compound **A4** (234 mg, 1.46 mmol, 79%) as a yellow oil. The spectroscopic data matched those reported in the literature.[7]

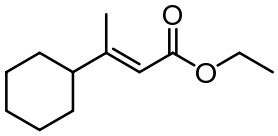
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.18 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.26 – 7.21 (m, 1H), 6.39 (dq, *J* = 7.8, 1.2 Hz, 1H), 2.56 (d, *J* = 1.3 Hz, 3H), 2.40 (s, 3H).

Synthesis of aldehyde A5



Scheme S5. Synthesis of aldehyde **A5**.

Ethyl (*E*)-3-cyclohexylbut-2-enoate (12)



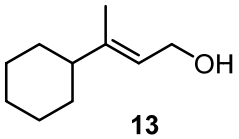
12

$C_{12}H_{20}O_2$
196.29 g/mol

To a suspension of NaH (830 mg, 60% dispersion in mineral oil, 20.8 mmol, 1.25 eq.) in anhydrous THF (40 mL) was added dropwise triethyl phosphonoacetate (4.12 mL, 4.65 g, 20.8 mmol, 1.25 eq.) over 10 min at 0 °C. After 30 min, cyclohexyl methyl ketone (2.28 mL, 2.09 g, 16.6 mmol, 1.00 eq.) was added to the reaction mixture, which was then allowed to warm to rt. After 22 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine (2 × 40 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 50/1 → 30/1) to yield compound **12** (2.10 g, 10.7 mmol, 64%) as a colorless oil. The spectroscopic data matched those reported in the literature.[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.65 (p, J = 1.2 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.14 (d, J = 1.3 Hz, 3H), 2.01 – 1.92 (m, 1H), 1.83 – 1.65 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 1.34 – 1.11 (m, 6H).

(*E*)-3-cyclo (E)-3-cyclohexylbut-2-en-1-ol (13)



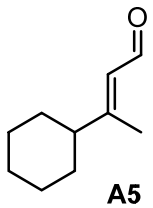
13

$C_{10}H_{18}O$
154.25 g/mol

To a stirred solution of **12** (2.10 g, 10.7 mmol, 1.00 eq.) in anhydrous toluene (15 mL) at 0 °C was added dropwise Red-Al (60 wt% solution in toluene, 3.99 mL, 4.15 g, 12.3 mmol, 1.15 eq.). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 1 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with Et_2O (20 mL), quenched by the addition of 1 M HCl (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et_2O = 5/1) to yield compound **13** (1.35 g, 8.77 mmol, 82%) as a colorless oil. The spectroscopic data matched those reported in the literature.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.39 (tt, *J* = 6.9, 1.3 Hz, 1H), 4.16 (d, *J* = 6.8 Hz, 2H), 1.85 (tt, *J* = 11.5, 3.3 Hz, 1H), 1.76 (m, 2H), 1.73 – 1.63 (m, 2H), 1.36 – 1.08 (m, 6H).

(*E*)-3-cyclohexylbut-2-enal (A5)



$C_{10}H_{16}O$
152.24 g/mol

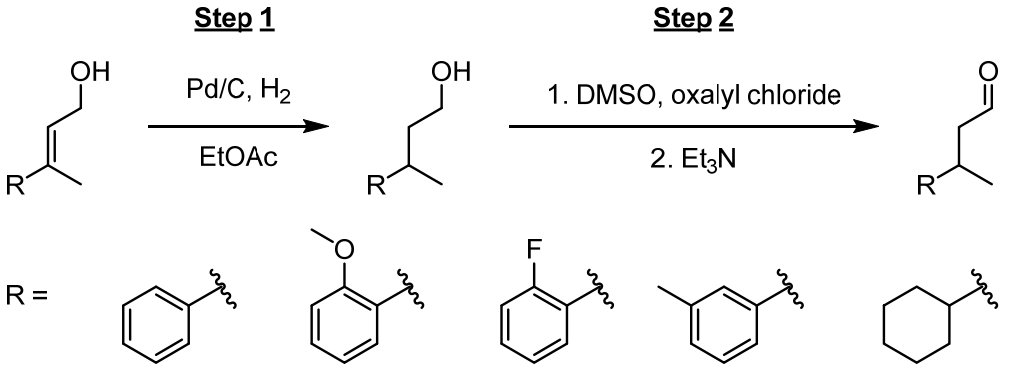
A5

To a stirred solution of **13** (400 mg, 2.59 mmol, 1.00 eq.) in $CHCl_3$ (6 mL) was added manganese dioxide (1.13 g, 13.0 mmol, 5.00 eq.) in one portion. The mixture was warmed to 60 °C. After 3 h, the completion of the reaction was confirmed by TLC control. After cooling to rt, the mixture was filtered through a pad of celite using Et_2O as a rinse. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/EtOAc = 15/1) to yield compound **A5** (301 mg, 1.98 mmol, 76%) as a yellow oil. The spectroscopic data matched those reported in the literature.[14]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] =10.05 (d, *J* = 8.0 Hz, 1H), 5.90 (dq, *J* = 8.1, 1.2 Hz, 1H), 2.18 (d, *J* = 1.3 Hz, 2H), 2.09 – 2.01 (m, 1H), 1.90 – 1.69 (m, 4H), 1.40 – 1.15 (m, 6H).

2.3. Synthesis of products

For the determination of response factors, products of the reactions of each aldehyde **A1 – A5** were synthesized according to Scheme **S6** using alcohols **5, 7, 9, 11, 13** in conformity with literature known procedures.



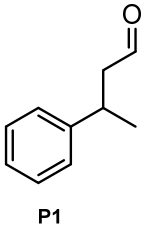
Scheme S6. Synthesis of products for the determination of response factors.

General procedure for reduction of alcohols (Step 1)

Corresponding alcohol (1.5 mmol, 1eq.) was dissolved in 5 mL of EtOAc under argon, 10 wt% of Pd/C was added to the reaction mixture, then the atmosphere was changed to hydrogen, and reaction was stirred at rt. After completion of the reaction was confirmed by TLC, the reaction was stopped by changing the atmosphere to argon. The reaction mixture was filtered through the pad of Celite to remove the catalyst and concentrated. The crude product was used in the next step without purification.[15]

General procedure for oxidation of alcohols (Step 2)

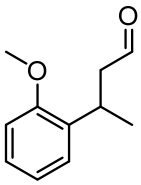
Oxalyl chloride (1.1 eq.) was added to dry DCM (5 mL) and cooled to -78 ^{o}C. A mixture of DMSO (2.2 eq.) and dry DCM (0.8 mL) was added. After being stirred for 15 min, a mixture of corresponding alcohol (1 eq.) in dry DCM (1.6 mL) was added dropwise for 5 min and stirred for 15 min. Et_3N (5.1 eq.) was added, and the reaction mixture was stirred for 5 min. After warming up to rt, H_2O (8 mL) was added, and the phases were separated. The aqueous phase was washed with brine (12.5 mL), 1% H_2SO_4 (6 mL), water (12.5 mL), 4% $NaHCO_3$ (aq.), dried over Na_2SO_4, concentrated, and purified by column chromatography (conditions for each of the products are given below).



P1

The crude product was purified by flash column chromatography (pentane/Et_2O = 5/1 → 3/1) to yield compound **P1** (70%) as a yellow oil. The spectroscopic data matched those reported in the literature.[16]

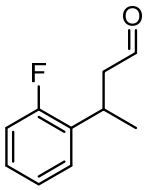
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.71 (t, *J* = 2.1 Hz, 1H), 7.31 (m, 2H), 7.25 – 7.19 (m, 3H), 3.36 (m, 1H), 2.76 (ddd, *J* = 16.6, 6.8, 1.8 Hz, 1H), 2.66 (ddd, *J* = 16.6, 7.7, 2.3 Hz, 1H), 1.32 (d, *J* = 7.0 Hz, 3H).



P2

The crude product was purified by flash column chromatography (pentane/EtOAc = 15/1) to yield compound **P2** (69%) as a yellow oil. The spectroscopic data matched those reported in the literature.[17]

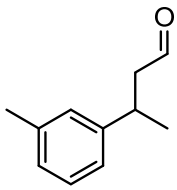
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.70 (t, *J* = 2.4 Hz, 1H), 7.24 – 7.14 (m, 2H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.83 (s, 3H), 3.75 (h, *J* = 7.0 Hz, 1H), 2.72 (ddd, *J* = 16.2, 6.4, 2.1 Hz, 1H), 2.60 (ddd, *J* = 16.2, 7.8, 2.6 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H).



P3

The crude product was purified by flash column chromatography (pentane/EtOAc = 15/1) to yield compound **P3** (81%) as a yellow oil. The spectroscopic data matched those reported in the literature.[11]

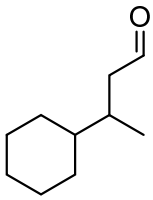
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.75 (t, *J* = 2.0 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.12 (td, *J* = 7.5, 1.3 Hz, 1H), 7.05 (ddd, *J* = 10.9, 8.0, 1.3 Hz, 1H), 3.68 (h, *J* = 7.1 Hz, 1H), 2.82 (ddd, *J* = 16.8, 6.6, 1.8 Hz, 1H), 2.73 (ddd, *J* = 16.8, 7.8, 2.1 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H).



P4

The crude product was purified by flash column chromatography (pentane/Et_2O = 6/1) to yield compound **P4** (76%) as a yellow oil. The spectroscopic data matched those reported in the literature.[18]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.73 (t, *J* = 2.1 Hz, 1H), 7.27 – 7.16 (m, 1H), 7.05 (m, *J* = 4.8, 3.8 Hz, 3H), 3.35 (h, *J* = 7.0 Hz, 1H), 2.77 (ddd, *J* = 16.6, 6.9, 1.9 Hz, 1H), 2.67 (ddd, *J* = 16.6, 7.7, 2.3 Hz, 1H), 2.36 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H).



P5

The crude product was purified by flash column chromatography (cyclohexane/EtOAc = 15/1) to yield compound **P5** (85%) as a yellow oil. The spectroscopic data matched those reported in the literature.[19]

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.75 (dd, *J* = 2.9, 1.9 Hz, 1H), 2.45 (ddd, *J* = 16.0, 4.9, 1.9 Hz, 1H), 2.19 (ddd, *J* = 16.0, 8.9, 2.9 Hz, 1H), 1.96 (m, 1H), 1.81 – 1.55 (m, 5H), 1.33 – 0.94 (m, 6H), 0.91 (d, *J* = 6.9 Hz, 3H).

3. Optimization of the reaction conditions

3.1. Chemical Procedures

General remarks:

All experiments were carried out under an air atmosphere.

The reaction progress was monitored after 24 h, 48 h, and 72 h unless otherwise indicated. The reactions were stopped after 72 h, the yields and enantiomeric excesses after 72 h for reactions under optimized conditions are given in Table 2 of the manuscript.

Preparation of water-saturated chloroform

To 10 mL of filtered over Al_2O_3 chloroform was added 0.5 mL of Milli-Q water. The mixture was sonicated for 10 seconds and was then left standing until complete phase separation. Usually, after 3-4 h standing in the dark, a clear chloroform phase was obtained, which was then decanted to a clean vial.

General Procedure A: experiments under optimized conditions

L-proline (1.26 mg, 10.9 µmol, 0.2 eq.) was weighed into a GC vial. Resorcinarene **1** (43.5 mg, 39.5 µmol, 0.72 eq.) was weighed in on the weighing paper and added to the catalyst-containing GC vial. After the addition of water-saturated chloroform (365 µL), the mixture was stirred on the stirring plate for 2 min at room temperature. Isopropanol (3.55 mg, 59.1 µmol, 4.52 µL, 1.08 eq.), n-decane (3.89 mg, 5.33 µL, 27.4 µmol, 0.50 eq.) and the respective aldehyde (54.7 µmol, 1.00 eq.) were added, and the mixture was stirred again for 2 min at room temperature. Then the Hantzsch ester (20.8 mg, 82.1 µmol, 1.5 eq.) was added. The sealed GC vial was kept at 30 °C (±1 °C) using a thermostatic heating block made from aluminum. The initial ratio (before Hantzsch ester addition) of substrate and n-decane (internal standard) and the progress of the reaction were monitored via GC. For this purpose, at specified intervals mentioned below, a small sample (approximately 10 µL) of the reaction mixture was diluted with n-hexane (0.8 mL) containing 0.05% v/v% DMSO. The diluted sample was put in the freezer for at least 15 min and centrifuged to remove compound **1** before GC analysis. The decanted clear solution was analyzed by achiral and chiral GC.

General Procedure B: capsule experiments

Chiral catalyst (10.9 µmol, 0.2 eq.) was weighed into a GC vial. The corresponding amount of resorcinarene **1** was weighed in on the weighing paper and added to the catalyst-containing GC vial. After the addition of water-saturated chloroform (365 µL), the mixture was stirred on the stirring plate for 2 min at room temperature. The corresponding amount of alcohol (if needed), n-decane (3.89 mg, 5.33 µL, 27.4 µmol, 0.50 eq.), and the respective aldehyde (54.7 µmol, 1.0 eq.) were added, and the mixture was stirred again for 2 min at room temperature. Then the Hantzsch ester (20.8 mg, 82.1 µmol, 1.5 eq.) was added. The sealed GC vial was kept at 30 °C (±1 °C) using a thermostatic heating block made from aluminum. The initial ratio (before Hantzsch ester addition) of substrate and

n-decane (internal standard) and the progress of the reaction were monitored via GC. For this purpose, at specified intervals mentioned below, a small sample (approximately 10 µL) of the reaction mixture was diluted with n-hexane (0.8 mL) containing 0.05% v/v% DMSO. The diluted sample was put in the freezer for at least 15 min and centrifuged to remove compound **1** before GC analysis. The decanted clear solution was analyzed by achiral and chiral GC.

General Procedure C: capsule free experiments

Chiral catalyst (10.9 µmol, 0.2 eq.) was weighed into a GC vial. After the addition of water-saturated chloroform (365 µL), the mixture was stirred on the stirring plate for 2 min at room temperature. Corresponding alcohol (if needed), n-decane (3.89 mg, 5.33 µL, 27.4 µmol, 0.50 eq.) and the respective aldehyde (54.7 µmol, 1.00 eq.) were added, and the mixture was stirred again for 2 min at room temperature. Then the Hantzsch ester (20.8 mg, 82.1 µmol, 1.5 eq.) was added. The sealed GC vial was kept at 30 °C (±1 °C) using a thermostatic heating block made from aluminum. The initial ratio (before Hantzsch ester addition) of substrate and n-decane (internal standard) and the progress of the reaction were monitored via GC. For this purpose, at specified intervals mentioned below, a small sample (approximately 10 µL) of the reaction mixture was diluted with n-hexane (0.8 mL) containing 0.05 v/v% DMSO. The diluted sample was put in the freezer for at least 15 min and centrifuged to remove compound **1** before GC analysis. The decanted clear solution was analyzed by achiral and chiral GC.

3.2. Optimization of the capsule I loading

To optimize the loading of capsule **I**, loadings of 8 mol% to 26 mol% with the step of 2 mol% of the capsule **I** were tested. The added amounts of resorcinarene **1**, corresponding amounts of the capsule **I** in mol%, and *ee*s for each experiment after 72h of reaction are listed in Table S1. The screening was performed according to **General Procedure B** utilizing aldehyde **A1**.

Table S1. Added amounts of resorcinarene **1** and results of optimization of the capsule **I** loading experiments.

Entry	Amount of resorcinarene **1**			**I** (mol%)	*ee* (%)
	mg	μmol	eq		
1	29.0	26.3	0.48	8	73 (*S*)
2	36.3	32.8	0.60	10	78 (*S*)
3	43.5	39.4	0.72	12	80 (*S*)
4	50.8	45.9	0.84	14	79 (*S*)
5	58.1	52.5	0.96	16	79 (*S*)
6	65.3	59.1	1.08	18	79 (*S*)
7	72.6	65.6	1.20	20	78 (*S*)
8	79.8	72.2	1.32	22	78 (*S*)
9	87.1	78.8	1.44	24	78 (*S*)
10	94.3	85.3	1.56	26	77 (*S*)

3.3. Optimization of L-proline loading

For optimization of proline loading, three different concentrations of chiral catalyst were tested in the presence of 12 mol% of capsule **I**. Conditions and *ee*s for each experiment after 72h of reaction are listed in Table S2. The screening was performed according to **General Procedure B** utilizing aldehyde **A1**.

Table S2. Results of optimization of catalyst loading experiments. Reactions were performed in triplicate and standard deviations were determined.

Entry	**L-proline** (mol%)	***ee*** (%)
1	12	73±4 (*S*)
2	20	77±1 (*S*)
3	28	77±1 (*S*)

3.4. Investigation of HCl influence

Preparation and titration of HCl stock solution in chloroform

HCl stock solution in chloroform was prepared by passing HCl gas, generated by the dropwise addition of concentrated H_2SO_4 to dry NaCl, through chloroform for approximately 30 min. The concentration of HCl in the resulting solution was determined as follows: HCl stock solution in chloroform (100 µL) was added to a solution of phenol red in EtOH (0.002 wt%, 2.5 mL) via a Microman M1 pipette equipped with a plastic tip. Upon addition, the solution turned from yellow (neutral) to pink (acidic). The resulting solution was then titrated with a 0.1 M solution of trimethylamine in ethanol. At the equivalence point, the solution turned from pink to yellow. The HCl stock solution was kept in the fridge, and the titration was repeated immediately before each use.

To check the influence of HCl, different loadings of 0, 1, 3, 5, and 10 mol% of HCl corresponding to capsule **I** were tested. The screening was performed in the presence of capsule **I** (two different loadings of optimized 12 mol% and previously reported 26 mol%), in the absence of capsule, in the absence of a chiral catalyst (proline), and absence of both capsule **I** and proline. Conditions and *ee*s for each experiment after 72h of reaction are listed in Table S3. The screening was performed according to **General Procedures B** and **C** utilizing aldehyde **A1**.

Table S3. Results of optimization of HCl content experiments.

Entry	HCl (mol%)	*ee* (%)			
		12 mol% **I**	26 mol% **I**	no **I**	no proline*
1	0	80 (*S*)	78 (*S*)	2 (*S*)	0
2	1	80 (*S*)	77 (*S*)	2 (*S*)	0
3	3	80 (*S*)	77 (*S*)	0	0
4	5	80 (*S*)	78 (*S*)	0	0
5	10	77 (*S*)	70 (*S*)	3 (*R*)	0

* 26 mol% of **I**

3.5. Optimization of alcohol additive loading

Optimization of alcohol loading was performed with three different alcohols: MeOH, EtOH, and *i*PrOH. Each of the alcohols was tested in different concentrations (3, 6, and 9 eq. corresponding to capsule) in the presence of capsule **I** in parallel with control experiments in the absence of capsule **I**. Conditions and *ee*s for each experiment after 72h of reaction are listed in Table S4. The screening was performed according to **General Procedures B** and **C** utilizing aldehyde **A1**.

Table S4. Results of experiments of optimization of alcohol loading.

Entry	ROH, eq.	**I** ?	*ee* (%)		
			MeOH	EtOH	*i*PrOH
1	0	yes		77 (*S*)	
2		no		11 (*R*)	
3	3	yes	82 (*S*)	82 (*S*)	82 (*S*)
4		no	16 (*R*)	15 (*R*)	16 (*R*)
5	6	yes	83 (*S*)	82 (*S*)	84 (*S*)
6		no	16 (*R*)	20 (*R*)	14 (*R*)
7	9	yes	83 (*S*)	84 (*S*)	85 (*S*)
8		no	21 (*R*)	17 (*R*)	17 (*R*)

3.6. Optimization of alcohol additive

Optimization of alcohol additive was performed with 5 different alcohols: MeOH, EtOH *n*PrOH, *i*PrOH, and *n*BuOH. An optimized amount (9 eq. corresponding to capsule) of each of the alcohols was used. Conditions, conversions, yields, and *ee*s for each experiment after 72h of reaction are listed in Table 1 of the manuscript. The screening was performed in triplicate according to **General Procedure B** utilizing aldehyde **A1**.

3.7. Non-linear effect study

For this experiment, different mixtures containing L- and D-proline (see Fig. S1) were prepared by mixing enantiopure L-proline and enantiopure D-proline followed by intensive grinding. Two reactions inside capsule **I** with and without *i*PrOH were conducted in parallel with the reaction in the absence of both capsule and *i*PrOH. The results are presented as graphs of the dependence of *ee* of the product on *ee* of the proline catalyst Fig. 3 of the manuscript and as Table S5. Reactions were monitored via chiral GC at the following time points: 24 h, 48 h, 72 h. The screening was performed according to **General Procedures B** and **C** utilizing aldehyde **A5**.

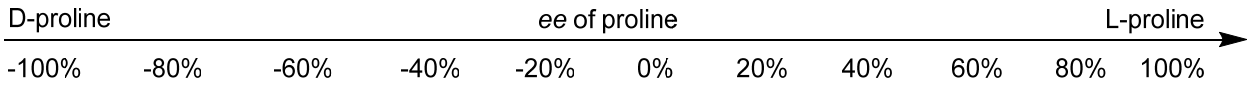


Figure S1. The enantiomeric purity of proline catalyst used for NLE studies.

Table S5. Results of non-linear effect study.

Entry	*ee* of proline (%)	*ee* of the reaction after 72 h (%)		
		I	**I**, *i*PrOH	No **I**, no *i*PrOH
1	100 (L)	55 (*S*)	59 (*S*)	34 (*S*)
2	80 (L)	44 (*S*)	48 (*S*)	27 (*S*)
3	60 (L)	33 (*S*)	36 (*S*)	23 (*S*)
4	40 (L)	22 (*S*)	25 (*S*)	19 (*S*)
5	20 (L)	11 (*S*)	11 (*S*)	8 (*S*)
6	0	0	0	0
7	20 (D)	11 (*R*)	12 (*R*)	9 (*R*)
8	40 (D)	23 (*R*)	24 (*R*)	19 (*R*)
9	60 (D)	34 (*R*)	36 (*R*)	20 (*R*)
10	80 (D)	44 (*R*)	48 (*R*)	27 (*R*)
11	100 (D)	55 (*R*)	59 (*R*)	35 (*R*)

3.8. Study of initial conversions and *ee*s

Investigation of the *i*PrOH role included the study of initial conversions and *ee*s. Two reactions inside capsule **I** with and without *i*PrOH were conducted in parallel with the same reactions in the absence of the capsule. The results are presented as graphs of the dependence of conversion/*ee* on time in Fig. 4 of the manuscript. Reactions were monitored via chiral and achiral GC at the following time points: 0 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 24 h, 48 h, 72 h. The screening was performed according to **General Procedures B** and **C** utilizing aldehyde **A2**.

4. Procedures for the analysis of experimental data

4.1. Response factor determination

Approximately 10 µL of each sample was diluted with 1 mL n-hexane and subjected to GC analysis. The response factors were calculated according to the equation below and are listed in Tables S6-S7.

$$RF = \frac{A_X \cdot C_{IS}}{A_{IS} \cdot C_X}$$

RF = response factor; A_x = GC area of analyte; A_{IS} = GC area of internal standard; C_x = concentration of analyte; C_{IS} = concentration of internal standard.

Table S6. Response factor determination for substrate **A1**.

Compound	C_x/C_{IS}	A_x/A_{IS}	RF	Mean value
	4	3.50	0.88	
A1	3	2.53	0.84	**0.85**
	2	1.66	0.83	

The response factor of **A2**-**A5** and **P1**-**P5** were calculated in the same manner. The values are listed in Table S7.

Table S7. Response factors for compounds **A2**-**A5** and **P1**-**P5**.

Compound	Mean value of the RF
A1	**0.85**
P1	**0.78**
A2	**0.73**
P2	**0.81**
A3	**0.79**
P3	**0.71**
A4	**0.77**
P4	**0.93**
A5	**0.78**
P5	**0.89**

4.2. Calculations for GC analysis

For GC analysis, conversions and yields were calculated by employing the following equations:

$$\text{yield (p)} = \left(\frac{z}{x}\right) \cdot 100\%$$

$$\text{n (sm)}_0 = \frac{(A_{sm})_0}{RF_{sm} \cdot (A_{IS})_0} = x$$

$$\text{n (sm)}_n = \frac{(A_{sm})_n}{RF_{sm} \cdot (A_{IS})_n} = y$$

$$\text{conversion (sm)} = \left(\frac{x - y}{x}\right) \cdot 100\%$$

$$\text{n (p)}_n = \frac{(A_p)_n}{RF_n \cdot (A_{IS})_n} = z$$

n $(sm)_n$ = amount of starting material in the n-th measurement; $(A_{sm})_0$ = area of starting material in the initial measurement; $(A_{IS})_0$ = area of the internal standard in the initial measurement; $(A_{sm})_n$ = area of starting material in the n-th measurement; $(A_{IS})_n$ = area of the internal standard in the n-th measurement; $(A_p)_n$ = area of the product in the n-th measurement; RF_{sm} = response factor of starting material; RF_p = response factor of product.

4.3. Mean value and standard deviation determination

The mean value was calculated by employing the following equation:

$$\text{mean value (p)} = \bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

The standard deviation was calculated by employing the following equation:

$$\text{standard deviation (p)} = \mathrm{S} = \sqrt{\frac{1}{\mathrm{n}-1}\sum_{\mathrm{i}=1}^{\mathrm{n}}(\mathrm{x_i}-\bar{\mathrm{x}})^2}$$

5. DOSY-NMR experiments

To investigate the influence of the *i*PrOH on the capsule size, DOSY-NMR experiments were performed with different amounts of *i*PrOH present at the same concentration as for the reaction conditions. Obtained D values indicate no significant change (which can be caused by concentration-effect) in capsule size and are shown in Table S8.

Table S8. D-values obtained from DOSY-NMR experiments.

Entry	*i*PrOH (eq)	$D \cdot 10^{-5}$ cm^2/s
1	0	0.15
2	1	0.15
3	3	0.16
4	6	0.16
5	9	0.16
6	18	0.17

6. Literature references

1 D. H. Wu, A. Chen and C. S. Johnson, *J. Magn. Reson. Ser. A*, 1995, 115, 260–264.

2 L. M. Tunstad, J. C. Sherman, R. C. Helgeson, J. Weiser, C. B. Knobler, D. J. Cram, J. A. Bryant, E. Dalcanale and J. A. Tucker, Host-Guest Complexation. 48. Octol Building Blocks for Cavitands and Carcerands, *J. Org. Chem.*, 1989, **54**, 1305–1312.

3 I. Elidrisi, S. Negin, P. V Bhatt, T. Govender, H. G. Kruger, G. W. Gokel and G. E. M. Maguire, Organic & Biomolecular Chemistry Pore formation in phospholipid bilayers by amphiphilic cavitands, *Org. Biomol. Chem.*, 2011,**9**, 4498-4506.

4 L. Avram and Y. Cohen, Self-Assembly of Resorcin[4]arene in the Presence of Small Alkylammonium Guests in Solution, *Proc. Natl. Acad. Sci. U.S.A*, 2002, **41**, 8.

5 W. Chen, H. Tao, W. Huang, G. Wang, S. Li, X. Cheng and G. Li, Hantzsch Ester as a Photosensitizer for the Visible-Light-Induced Debromination of Vicinal Dibromo Compounds, *Chem. - A Eur. J.*, 2016, **22**, 9546–9550.

6 M. Bernasconi, V. Ramella, P. Tosatti and A. Pfaltz, Iridium-Catalyzed Asymmetric Hydrogenation of 3,3-Disubstituted Allylic Alcohols in Ethereal Solvents, *Chem. - A Eur. J.*, 2014, **20**, 2440–2444.

7 A. Song, X. Zhang, X. Song, X. Chen, C. Yu, H. Huang, H. Li and W. Wang, Construction of Chiral Bridged Tricyclic Benzopyrans: Enantioselective Catalytic Diels-Alder Reaction and a One-Pot Reduction/Acid-Catalyzed Stereoselective Cyclization, *Angew. Chemie Int. Ed.*, 2014, **53**, 4940–4944.

8 T. N. T. Nguyen, N. O. Thiel, F. Pape and J. F. Teichert, Copper(I)-Catalyzed Allylic Substitutions with a Hydride Nucleophile, *Org. Lett.*, 2016, **18**, 2455–2458.

9 T. M. Bräuer, Q. Zhang and K. Tiefenbacher, Iminium Catalysis inside a Self-Assembled Supramolecular Capsule: Modulation of Enantiomeric Excess, *Angew. Chemie - Int. Ed.*, 2016, **55**, 7698–7701.

10 J. B. Metternich and R. Gilmour, A Bio-Inspired, Catalytic e → Z Isomerization of Activated Olefins, *J. Am. Chem. Soc.*, 2015, **137**, 11254–11257.

11 T. M. Bräuer, Q. Zhang and K. Tiefenbacher, Iminium Catalysis inside a Self-Assembled Supramolecular Capsule: Scope and Mechanistic Studies, *J. Am. Chem. Soc.*, 2017, **139**, 17500–17507.

12 A. Guzman-Martinez and A. H. Hoveyda, Enantioselective synthesis of allylboronates bearing a tertiary or quaternary B-substituted stereogenic carbon by NHC-Cu-catalyzed substitution reactions, *J. Am. Chem. Soc.*, 2010, **132**, 10634–10637.

13 B. F. Strick, D. A. Mundal and R. J. Thomson, An oxidative [2,3]-sigmatropic rearrangement of allylic hydrazides, *J. Am. Chem. Soc.*, 2011, **133**, 14252–14255.

14 S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, Enantioselective organocatalytic hydride reduction, *J. Am. Chem. Soc.*, 2005, **127**, 32–33.

15 R. Busses, H. Münsterer and G. Kresze, Ene Reaction Mechanisms. 1. Chirality Transfer to the Enophile 4-Methyl-jV-sulfinylbenzenesulfonamide, *J. Org. Chem.*, 1983, **48**, 2828–2832.

16 E. Larionov, L. Lin, L. Guénée and C. Mazet, Scope and mechanism in palladium-catalyzed isomerizations of highly substituted allylic, homoallylic, and alkenyl alcohols, *J. Am. Chem. Soc.*, 2014, **136**, 16882–16894.

17 A. F. Ward, Y. Xu and J. P. Wolfe, Synthesis of chromans via Pd-catalyzed alkene carboetherification reactions, *Chem. Commun.*, 2012, **48**, 609–611.

18 C. You, S. Li, X. Li, J. Lan, Y. Yang, L. W. Chung, H. Lv and X. Zhang, Design and application of hybrid phosphorus ligands for enantioselective Rh-Catalyzed anti-markovnikov hydroformylation of unfunctionalized 1,1-disubstituted Alkenes, *J. Am. Chem. Soc.*, 2018, **140**, 4977–4981.

19 N. Arai, K. Sato, K. Azuma and T. Ohkuma, Enantioselective Isomerization of Primary Allylic Alcohols into Chiral Aldehydes with the tol-binap/dbapen/Ruthenium(II) Catalyst, *Angew. Chemie Int. Ed.*, 2013, **52**, 7500–7504.