Supporting Information

A Complementary Pair of Enantioselective Switchable Organocatalysts

Guillaume De Bo, David A. Leigh, * Charlie T. McTernan, Shoufeng Wang

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom
Email: david.leigh@manchester.ac.uk
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1. General Methods

Unless stated otherwise, reagents were obtained from commercial sources and used without purification. Anhydrous THF (HPLC grade, Fischer scientific), CH₂Cl₂ (HPLC grade, Fischer scientific), DMF (Peptide synthesis grade, Merck) and PhMe (> 99%, Fischer scientific) were obtained by passing the solvent through an activated alumina column on a Phoenix SDS (solvent drying system; JC Meyer Solvent Systems, CA, USA). ¹H NMR spectra were recorded on a Bruker Avance III instrument with an Oxford AS600 magnet equipped with a cryoprobe [5mm CPDCH ¹³C-¹H/D] (600 MHz). Chemical shifts are reported in parts per million (ppm) from high to low frequency using the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, CD₂Cl₂ = 5.32 ppm, CD₃OD = 3.31 ppm, δ₆-Acetone = 2.05 ppm and δ₆-DMSO = 2.50 ppm). All ¹H resonances are reported to the nearest 0.01 ppm. The multiplicity of ¹H signals are indicated as: s = singlet; d = doublet; t = triplet; quint = quintet; m = multiplet; br = broad; or combinations of thereof. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. ¹³C NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference (CDCl₃ = 77.16 ppm, CD₂Cl₂ = 54.00 ppm, CD₃OD = 49.00 ppm, δ₆-Acetone = 29.84 ppm and δ₆-DMSO = 39.52 ppm). ¹⁹F NMR spectra were recorded on a Bruker Avance III instrument (376 MHz). DEPT, COSY, HSQC and HMBC experiments were used to aid structural determination and spectral assignment. Flash column chromatography was carried out using Silica 60 Å (particle size 40–63 µm, Sigma Aldrich, UK) as the stationary phase. Preparative TLC was performed using PLC 20 × 20 cm, 60 F254 Prep plates (Merck, of various thicknesses). TLC was performed on precoated silica gel plates (0.25 mm thick, 60 F254, Merck, Germany) and visualized using both short and long wave ultraviolet light in combination with standard laboratory stains (acidic potassium permanganate, acidic ammonium molybdate and ninhydrin). Low resolution ESI mass spectrometry was performed with a Thermo Scientific LCQ Fleet Ion Trap Mass Spectrometer or an Advion Compact Mass Spectrometer (CMS). High-resolution mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) or by the departmental service. Enantiomeric ratios were determined by HPLC on an Agilent 1260 Infinity system with UV detection at 210, 250 or 254 nm. A Chiralpak IA or IC (5 µm Particle size, 250×4.6 mm, Diacel Corporation) column with hexane/2-propanol (90/10) as eluent (1 ml/min flow-rate) was used for separations unless otherwise stated. Solutions were irradiated in 3.5 mL quartz cuvettes (10 × 10 mm) with a 395 nm LED source (FWHM = 15 nm, ThorLabs M395L4). Typically, solutions were irradiated for 20 minutes with an irradiance of 700 mW·cm⁻², as measured using a power meter (ThorLabs PM100D equipped with an S302C thermal sensor).

Abbreviations: DMF, dimethyl formamide. DMSO, dimethyl sulfoxide, Pd(dppf), [{1,1′-bis(diphenylphosphino)ferrocene} dichloropalladium(II), complex with CH₂Cl₂]. PE, petroleum ether. HRMS (ESI⁺), high resolution electrospray mass spectrometry. MS (ESI⁻), low resolution electrospray mass spectrometry. pTSA, para-toluenesulfonic acid. DIPEA, diisopropylethylamine. THF, tetrahydrofuran. Phenyl triflimide, N-Phenyl-bis(trifluoromethanesulfonimide). Boc₂O, Di-tert-butyl dicarbonate.
2. Synthesis of 1 and 2

Reagents and conditions. i) 1-Bromodecane, Cs$_2$CO$_3$, MeCN, reflux, 16 h. ii) BH$_3$-THF, THF, reflux, 16 h. iii) Boc$_2$O, CH$_2$Cl$_2$, DIPEA r.t., 1 h. iv) 4-Hydroxyphenylboronic acid, Pd(dppf), THF, 2 M Na$_2$CO$_3$, 16 h. v) Phenyl triflimide, DIPEA, DMF, r.t., 16 h. vi) Bispinocolatodiboron, Pd(dppf), KOAc, dioxane, 100 °C, 16 h.

Reagents and conditions: vii) 2-Bromo-6-(dimethoxymethyl)pyridine (7), Pd(PPh$_3$)$_4$, THF, 2 M Na$_2$CO$_3$, 60 °C, 4 d. viii) pTSA, THF, H$_2$O, 50 °C, 3 h. ix) 4-Nitrobenzohydrazide (21), aniline, CH$_2$Cl$_2$, r.t., 16 h. x) TFA, CH$_2$Cl$_2$, r.t., 1 h. xi) 3-Amino-4-(((S)-{(1S,2R,4S,5R)-5-ethylquinuclidin-2-yl}(7-methoxynaphthalen-1-yl)methyl)amino)cyclobut-3-ene-1,2-dione (4), DMF, Et$_3$N, MeOH, r.t., 16 h.
xii) 3-bromo-2-(dimethoxymethyl)pyridine (6), Pd(PPh₃)₄, THF, 2 M Na₂CO₃, 60 °C, 4 d. xiii) 3-Nitrobenzohydrazide (22), aniline, CH₂Cl₂, r.t., 16 h. xiv) 3-amino-4-(((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(7-methoxynaphthalen-1-yl)methyl)amino)cyclobut-3-ene-1,2-dione (5), DMF, Et₃N, MeOH, r.t., 16 h.

7, S₁, 6, S², 4, S³, S⁵, S¹, S⁵ and 22 were synthesized according to literature procedures.

**S1. tert-Butyl (3-bromo-4-(decyloxy)benzyl)carbamate**

![Structure](Image)

To a stirred suspension of 3-bromo-4-hydroxybenzonitrile (5.00 g, 25.2 mmol) and caesium carbonate (8.21 g, 25.2 mmol) in MeCN (100 ml) was added 1-bromodecane (5.53 g, 25.0 mmol). The suspension was then heated to reflux for 16 h then the reaction was cooled to r.t., and partitioned between Et₂O (500 ml) and 1 M NaOH (500 ml). The organic phase was washed with 1 M NaOH (500 ml), dried over MgSO₄, filtered and concentrated in vacuo to afford the crude product. The crude product was then dissolved in THF (50 ml) and cooled to 0 °C. To this stirred solution, BH₃·THF (1 M in THF, 40 ml) was added dropwise. The reaction was heated to reflux for 16 h then cooled to 0 °C and quenched with H₂O (2 ml) followed by 1 M NaOH (2 ml). The solvent was removed in vacuo and the residue dissolved in CH₂Cl₂ (200 ml). This solution was then washed with 2 M NaOH (200 ml), dried over MgSO₄, filtered and concentrated in vacuo to afford the crude product. The crude was then dissolved in CH₂Cl₂ (200 ml) and diisopropylethylamine (7.5 ml). To this was added di-tert-butyl dicarbonate (4.20 g, 19.2 mmol) all at once. The reaction was stirred at r.t. for 1 h and the solvent removed in vacuo. Imidazole (3.00 g, 44.0 mmol) was added to the residue, which was then dissolved in EtOH (75 ml), and stirred at r.t. for 5 min. The solvent removed in vacuo and the residue partitioned between CHCl₃ and 1 M HCl. The organic phase was dried over MgSO₄, filtered, and the solvent removed in vacuo to afford the crude product. Purification by flash column chromatography [EtOAc:PE 7:3] afforded 5 (5.51 g, 12.1 mmol, 50%) as a pale yellow oil.

³¹H NMR (600 MHz, CDCl₃) δ: 7.45 (1H, s, H₂O), 7.16 (1H, d, J = 7.9 Hz, H₁₃), 6.82 (1H, d, J = 8.2 Hz, H₁₂), 4.79 (1H, s, br, H₁₅), 4.20 (2H, d, J = 6.0 Hz, H₁₄), 4.00 (3H, t, J = 6.9 Hz, H₁₀), 1.85–1.72 (2H, m, H₉), 1.51–1.41 (11H, m, H₈ + H₁₈), 1.39–1.22 (12H, m, H₇–H₉), 0.88 (3H, t, J = 7.3 Hz, H₆). ¹³C NMR (150 MHz, CDCl₃) δ: 155.6, 154.8, 132.4, 132.3, 127.6, 113.2, 112.3, 79.6, 69.3, 43.7, 31.9, 29.6, 29.6, 29.3, 29.1, 28.4, 26.0, 22.7, 14.2. MS (ESI⁺): m/z = 442.2 [M+H⁺], 464.3 [M+Na⁺]; HRMS (ESI⁺): [C₉₂H₄₈BrN₂O₃]⁺ predicted 459.2217, found 459.2207 (Δ = 2.1 ppm).
S2. tert-Butyl ((6-(decyloxy)-4'-hydroxy-[1,1'-biphenyl]-3-yl)methyl)carbamate

Bromide S1 (6.00 g, 13.6 mmol) was dissolved in DMF (60 ml) and 2 M Na₂CO₃(aq) (20 ml). The reaction was sparged with argon for 15 minutes, then 4-hydroxyphenylboronic acid (3.50 g, 25.4 mmol) and Pd(dppf) (800 mg, 0.980 mmol) were added. The reaction was heated under argon to 80 °C for 16 h then cooled to r.t. and the solvent removed in vacuo. The residue was partitioned between CH₂Cl₂ and NaCl(sat), and the aqueous phase washed once with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography [EtOAc:PE 1:19 grading to 1:4] to furnish S2 (5.97 g, 13.1 mmol, 96%) as a pale yellow oil.

^1H NMR (600 MHz, CDCl₃) δ: 7.41 (2H, d, J = 8.5 Hz, H₂23), 7.20 (1H, s, H₁₀), 7.17 (1H, d, J = 8.1 Hz, H₁₃), 6.90 (1H, d, J = 8.4 Hz, H₁₂), 6.85 (2H, d, J = 8.5 Hz, H₂₄), 5.01 (1H, s, H₂₁), 4.80 (1H, s, br, H₁₅), 4.28 (2H, d, J = 4.9 Hz, H₁₄), 3.92 (3H, t, J = 6.7 Hz, H₁₀), 1.72–1.68 (2H, m, H₉), 1.46 (9H, s, H₁₈), 1.40–1.34 (2H, m, H₈), 1.31–1.20 (12H, m, H₇–H₂), 0.88 (3H, t, J = 7.1 Hz, H₃); ^13C NMR (150 MHz, CDCl₃) δ: 156.0, 155.5, 154.8, 154.0, 131.0, 131.0, 130.7, 130.1, 129.8, 127.5, 114.9, 112.8, 79.6, 68.7, 44.4, 32.0, 29.7, 29.7, 29.5, 28.6, 26.2, 22.8, 14.3; MS (ESI⁺): m/z = 456.3 [100, (M+H)⁺], 478.3 [25, (M+Na)⁺]; HRMS (ESI⁺): [C₆H₁₄NO₃]+ predicted 456.3108, found 456.3102 (Δ – 1.4 ppm).

S3. 5’-(((tert-Butoxycarbonyl)amino)methyl)-2’-(decyloxy)-[1,1’-biphenyl]-4-yl trifluoromethanesulfonate

To a stirred solution of S2 (5.50 g, 12.1 mmol) in DMF (150 ml) and diisopropylethylamine (8 ml) was added N-phenyl-bis(trifluoromethanesulfonimide) (5.00 g, 14.0 mmol). The reaction was stirred at r.t. for 16 h before the solvent was removed in vacuo. The residue was partitioned between CH₂Cl₂ (200 ml) and 2 M HCl(aq) (200 ml). The organic phase was washed with 2 M NaOH(aq) (200 ml) then LiCl(sat), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography [EtOAc:PE 1:9] to furnish S3 (6.72 g, 11.8 mmol, 97%) as a yellow oil.

^1H NMR (600 MHz, CDCl₃) δ: 7.63 (2H, d, J = 8.8 Hz, H₂₂), 7.35 (2H, d, J = 8.4 Hz, H₂₄), 7.24 (1H, d, J = 8.6 Hz, H₃₀), 7.22 (1H, s, H₁₅), 6.96 (1H, d, J = 8.3 Hz, H₁₂), 4.94 (1H, s, br, H₁₅), 4.25 (2H, d, J = 5.2 Hz, H₁₄), 3.96 (3H, t, J = 7.2 Hz, H₁₀), 1.72–1.67 (2H, m, H₉), 1.43 (9H, s, H₁₈), 1.38–1.32 (2H, m, H₈), 1.31–1.21 (12H, m, H₇–H₂), 0.88 (3H, t, J = 8.1 Hz, H₃); ^13C NMR (150 MHz, CDCl₃) δ: 155.1, 148.5, 139.1, 131.6, 131.4, 129.8, 128.6, 128.3, 123.9, 120.6, 118.8 (q, J = 320 Hz), 112.5, 79.1, 68.6, 43.9, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.1, 26.1, 22.7, 13.9; ^19F NMR (376 MHz, CDCl₃): -72.83;
to furnish
The crude residue was purified by flash column chromatography [EtOAc:CH2OAc, 0.1 under argon for 4 days. The reaction was cooled to r.t. and partitioned between EtOAc and water. The organic phase was dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on Al2O3 (Brockmann II). EtOAc:PE 1:99 to 1:2 to furnish 3 (209 mg, 0.370 mmol, 81%) as a colorless oil.

\[\text{ms (esi)}: \text{m/z} = 588.6 \ [100, (m+H)^+], 610.7 \ [15, (m+Na)^+]; \text{hrms (esi)}: [c_{20}h_{44}n_{2}o_{5}s]^+ \text{predicted 605.2867, found 605.2861 (}\Delta - 0.9 \text{ ppm).}\]

3. tert-Butyl ((6-decyl)-4′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1′-biphenyl]-3-yl)methyl)carbamate

![Image of molecule](image)

To a stirred solution of S3 (270 mg, 0.459 mmol) in dioxane (12 ml) were added KOAc (200 mg, 2.02 mmol) and bis(pinocloanto)diboron (270 mg, 1.06 mmol). The suspension was sparged with argon for 15 min, then [1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with CH2Cl2 (60 mg, 7.35 µmol) was added. The reaction was heated to 100 °C for 16 hours under argon, then cooled to r.t. and concentrated in vacuo. The residue was purified by flash column chromatography on Al2O3 (Brockmann II), EtOAc:PE 1:99 to 1:2 to furnish 3 (209 mg, 0.370 mmol, 81%) as a colorless oil.

\[\text{1h nmr (600 MHz, cdcl3)}: \delta: 7.83 \ (2h, d, j = 8.3 \text{ Hz, h}_{23}), 7.55 \ (2h, d, j = 8.1 \text{ Hz, h}_{24}), 7.24 \ (1h, d, j = 1.9 \text{ Hz, h}_{13}), 7.21 \ (1h, d, j = 8.6 \text{ Hz, h}_{12}), 6.92 \ (1h, d, j = 8.6 \text{ Hz, h}_{12}), 4.78 \ (1h, s, br, h_{15}), 4.29 \ (2h, d, j = 6.3 \text{ Hz, h}_{14}), 3.92 \ (3h, t, j = 8.4 \text{ Hz, h}_{10}), 1.72–1.65 \ (2h, m, h_{8}), 1.46 \ (9h, s, h_{16}), 1.39–1.34 \ (14h, m, h_{8}+h_{27}), 1.31–1.21 \ (12h, m, h_{7}–h_{9}), 0.88 \ (3h, t, j = 8.1 \text{ Hz, h}_{11}); {}^{13}\text{c nmr (150 MHz, cdcl3)}: \delta: 155.9, 155.4, 141.3, 134.3, 131.0, 130.8, 130.2, 128.9, 128.0, 112.7, 83.7, 79.5, 68.7, 44.2, 31.9, 29.6, 29.6, 29.3, 29.3, 29.2, 29.1, 28.5, 26.0, 24.9, 22.7, 14.1; \text{ms (esi)}: \text{m/z} = 565.4 [100, (m+H)^+], 588.3 [35, (m+Na)^+]; \text{hrms (esi)}: [c_{34}h_{50}n_{2}o_{5}s]^+ \text{predicted 582.4313, found 582.4306 (}\Delta - 1.2 \text{ ppm).}\]

S4. tert-Butyl ((6-decyl)-4′-(6-(dimethoxymethyl)pyridin-2-yl)-[1,1′-biphenyl]-3-yl)methyl)carbamate

![Image of molecule](image)

To a stirred solution of 3 (170 mg, 0.301 mmol) in THF (5 ml) and 2 M Na2CO3 (aq) (2 ml) was added 2-Bromo-6-(dimethoxymethyl)pyridine (7) (160 mg, 0.689 mmol). The solution was sparged with argon for 15 min. Pd(PPh3)4 (120 mg, 0.104 mmol) was added, and the reaction heated to 60 °C under argon for 4 days. The reaction was cooled to r.t. and partitioned between EtOAc (50 ml) and 0.1 M EDTA (aq) (50 ml). The organic phase was dried over MgSO4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography [EtOAc:CH2Cl2 1:99 grading to 1:24] to furnish S4 (162 mg, 0.274 mmol, 91%) as a pale yellow oil.

S7
**1H NMR** (600 MHz, CDCl₃) δ: 8.06 (2H, d, J = 8.1 Hz, H₂₂), 7.83–7.80 (1H, m, H₂₈), 7.75 (1H, d, J = 8.2 Hz, H₂₀), 7.65 (2H, d, J = 7.8 Hz, H₂₄), 7.51 (1H, d, J = 7.8 Hz, H₂₇), 7.28 (1H, d, J = 2.6 Hz, H₂₀), 7.23 (1H, d, J = 8.4 Hz, H₁₃), 6.94 (1H, d, J = 8.4 Hz, H₁₂), 5.48 (1H, s, H₃₁), 4.81 (1H, s, br, H₁₅), 4.31 (2H, d, J = 5.4 Hz, H₁₄), 3.95 (3H, t, J = 6.9 Hz, H₁₀), 1.74–1.68 (2H, m, H₇), 1.46 (9H, s, H₁₈), 1.41–1.35 (2H, m, H₆), 1.31–1.19 (12H, m, H₂–H₁₂), 0.86 (3H, t, J = 7.2 Hz, H₁); **13C NMR** (150 MHz, CDCl₃) δ: 157.3, 156.5, 155.9, 155.5, 139.2, 137.5, 134.5, 131.1, 130.5, 130.1, 129.9, 128.0, 126.6, 120.3, 119.3, 112.7, 104.9, 79.5, 68.7, 54.2, 44.2, 31.9, 29.6, 29.6, 29.3, 29.3, 29.2, 28.4, 28.1, 22.7, 14.1; **MS (ESI⁺)**: m/z = 591.4 [100, (M+H)⁺], 613.4 [15, (M+Na)⁺]; **HRMS (ESI⁺)**: [C₃₆H₄₅N₂O₅]⁺ predicted 591.3792, found 591.3779 (Δ – 2.3 ppm).

**9. tert-Butyl ((6-decylloxy)-4′-(6-formylpyridin-2-yl)-[1,1′-biphenyl]-3-yl)methyl carbamate**

![Chemical Structure Image]

To a stirred solution of 54 (78.0 mg, 0.132 mmol) in THF (3 ml) was added H₂O (100 μl) and p-toluenesulfonic acid (78.0 mg, 0.411 mmol). The reaction was heated under argon to 50 °C for 3 h. The reaction was partitioned between CH₂Cl₂ (30 ml) and 2 M NaOH (aq) (30 ml). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography [EtOAc:CH₂Cl₂ 1:99 grading to 1:24] to furnish 9 (72 mg, 0.132 mmol, quant.) as a pale yellow oil.

**1H NMR** (600 MHz, CDCl₃) δ: 10.20 (1H, s, H₃₁), 8.13 (2H, d, J = 8.1 Hz, H₂₃), 8.01 (1H, d, d, J = 7.6, 1.1 Hz, H₂₉), 7.95 (1H, t, J = 7.6 Hz, H₂₈), 7.91 (1H, d, d, J = 7.6, 1.1 Hz, H₂₇), 7.70 (2H, d, J = 8.4 Hz, H₁₄), 7.30 (1H, d, J = 2.2 Hz, H₂₀), 7.26–7.22 (1H, d, J = 8.6 Hz, H₁₃), 6.95 (1H, d, J = 8.4 Hz, H₁₂), 4.82 (1H, s, br, H₁₅), 4.31 (2H, d, J = 5.2 Hz, H₁₄), 3.97 (3H, t, J = 6.2 Hz, H₁₀), 1.75–1.69 (2H, m, H₆), 1.47 (9H, s, H₃₁), 1.42–1.35 (2H, m, H₆), 1.31–1.18 (12H, m, H₂–H₁₂), 0.85 (3H, t, J = 6.9 Hz, H₁); **13C NMR** (150 MHz, CDCl₃) δ: 194.1, 157.8, 155.9, 155.5, 152.7, 139.9, 137.8, 136.5, 131.1, 130.2, 130.2, 128.2, 126.5, 124.4, 119.7, 112.7, 79.5, 68.7, 44.2, 38.1, 31.9, 29.6, 29.5, 29.3, 29.3, 29.2, 28.4, 26.1, 22.7, 14.1; **MS (ESI⁺)**: m/z = 545.3 [100, (M+H)⁺], 567.2 [45, (M+Na)⁺]; **HRMS (ESI⁺)**: [C₃₆H₄₅N₂O₅]⁺ predicted 545.3374, found 545.3374 (Δ – 1.4 ppm).
11. **tert-Butyl** (E)-((6-(decyloxy)-4'-(6-((2-(4-nitrophenyl)hydrazono)methyl)pyridin-2-yl)-[1,1'-biphenyl]-3-yl)methyl)carbamate

![Chemical Structure](image)

To a stirred solution of 9 (740 mg, 1.36 mmol) in CH$_2$Cl$_2$ (100 ml) was added 4-nitrobenzohydrazide (296 mg, 1.63 mmol, 21) and aniline (6.33 mg, 0.0680 mmol). The reaction was stirred for 16 h then concentrated *in vacuo*. The crude residue was purified by flash column chromatography [MeOH:CH$_2$Cl$_2$ 1:19 grading to 1:9] to furnish 11 (800 mg, 1.13 mmol, 83%) as a yellow oil.

$^1$H NMR (600 MHz, DMSO-$d_6$) δ: 15.39 (1H, s, H$_{32}$), 8.24–8.19 (3H, m, H$_{29} + H_{33}$), 8.09 (1H, d, J = 7.4 Hz, H$_2$), 8.06 (2H, d, J = 9.5 Hz, H$_{34}$), 7.89–7.84 (4H, m, H$_{24} + H_{28} + H_{31}$), 7.54 (2H, d, J = 7.4 Hz, H$_3$), 7.26–7.21 (2H, m, H$_{13} + H_{20}$), 7.09 (1H, d, J = 7.4 Hz, H$_1$), 4.16 (2H, d, J = 5.0 Hz, H$_{14}$), 3.94 (2H, t, J = 5.0 Hz, H$_{10}$), 1.55–1.49 (2H, m, H$_9$), 1.39 (9H, s, H$_{18}$), 1.20–1.17 (2H, m, H$_8$), 1.12–1.06 (4H, m, H$_7 + H_6$), 0.83 (3H, t, J = 6.6 Hz, H$_1$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 162.7, 156.5, 156.2, 155.0, 152.3, 149.8, 140.9, 140.3, 139.5, 136.7, 132.9, 130.2, 129.7, 129.5, 129.1, 128.3, 127.3, 126.1, 124.4, 123.1, 113.4, 68.7, 41.8, 31.6, 29.4, 29.2, 29.0, 29.0, 28.7, 28.7, 26.0, 22.5, 14.3; MS (ESI$^+$): m/z = 708.1 [100, (M+H)$^+$], 730.1 [15, (M+Na)$^+$]; HRMS (ESI$^+$): [C$_{41}$H$_{49}$N$_5$O$_6$]$^+$ predicted 708.3756, found 708.3751 (Δ −0.7 ppm).

1. **N'-(E)-(6-(2'-(Decyloxy)-5'-(2-(((S)-(1S,2R,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquionolin-4-yl)methyl)amo)no)-3,4-dioxocyclobutyl)amino)methyl)-[1,1'-biphenyl]-4-yl)pyridin-2-yl)methylene)-4-nitrobenzohydrazide**

![Chemical Structure](image)
Hydrazide 11 (51.1 mg, 0.0721 mmol) was dissolved in 
CH₂Cl₂ (4 ml) and TFA (1 ml) was added. The reaction was stirred at r.t. for 1 h and concentrated in 
vacuo with the addition of toluene (5 ml). The residue was azeotroped 5 x with toluene:CH₂Cl₂ (1:1, 10 ml). The crude residue was dissolved in DMF (2 ml), MeOH (2 ml) and Et₃N (0.5 ml), then 4 (85.2 mg, 0.195 mmol) was added. The reaction was stirred at r.t. for 16 h, concentrated in 
vacuo, and purified by preparatory thin layer chromatography (4 x 500 μm, eluted with Et₃N:MeOH:CH₂Cl₂ 0.1:1:10) to afford 1 (46 mg, 0.0455 mmol, 63%) as a 
yellow powder.

¹H NMR (600 MHz, DMSO-d₆) δ: 12.40 (1H, s, H₆a), 8.75 (1H, s, H₂a), 8.61 (1H, s, H₆a), 8.41 (2H, d, J = 9.3 Hz, H₆b), 8.20 (2H, d, J = 9.3 Hz, H₅b), 8.16–8.10 (1H, m, H₁b), 8.06–7.93 (5H, m, H₂c + H₄c + H₅c + H₈c), 7.63–7.54 (3H, m, H₃c + H₆c), 7.42 (1H, dd, J = 9.3, 2.3 Hz, H₁c), 7.34–7.31 (2H, m, H₂h + H₃h), 7.29–7.23 (1H, m, H₄h), 7.11–7.05 (1H, m, H₁h), 5.94 (2H, br, H₁e + H₂e), 4.74–4.70 (2H, m, H₁f), 3.99–3.87 (5H, m, H₁o + H₂o), 3.15–3.07 (1H, m, H₁i), 2.42–2.35 (1H, m, H₃i), 1.65–1.58 (2H, m, H₇), 1.56–1.44 (3H, m, H₈ + H₉), 1.12–1.06 (4H, m, H₇ + H₈), 1.42–1.10 (23H, m, H₂j + H₃j + H₄j + H₅j + H₆j + H₇j + H₈j + H₉j + H₁₀j).

¹³C NMR (150 MHz, DMSO-d₆) δ: 182.8, 182.5, 162.3, 156.2, 156.6, 153.4, 149.9, 149.8, 148.2, 144.8, 140.9, 140.2, 139.4, 139.3, 138.5, 137.0, 132.0, 131.3, 130.5, 130.0, 129.8, 129.5, 129.4, 129.2, 128.7, 127.3, 126.6, 125.8, 124.2, 123.4, 121.4, 119.3, 113.6, 101.9, 68.6, 59.1, 56.2, 48.6, 40.7, 31.7, 31.6, 29.4, 29.3, 29.2, 29.1, 29.1, 29.0, 29.0, 28.9, 25.9, 25.9, 22.5, 22.5, 14.4, 14.3.

To a stirred solution of 3 (170 mg, 0.301 mmol) in THF (5 ml) and 2 M Na₂CO₃(aq) (2 ml) was added 6 (160 mg, 0.689 mmol). The solution was sparged with argon for 15 min, Pd(PPh₃)₄ (120 mg, 0.104 mmol) was added, and the reaction heated to 60 °C under argon for 4 days. The reaction was cooled to r.t. and partitioned between EtOAc (50 ml) and 0.1 M EDTA(aq) (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography [EtOAc:CH₂Cl₂ 1:99 grading to 1:24] to furnish S5 (162 mg, 0.274 mmol, 91%) as a pale yellow oil.

¹H NMR (600 MHz, CDCl₃) δ: 8.08 (2H, d, J = 8.4 Hz, H₂a), 7.84–7.81 (1H, m, H₂a), 7.76 (1H, d, J = 7.7 Hz, H₆b), 7.69 (2H, d, J = 8.4 Hz, H₃a), 7.52 (1H, d, J = 7.7 Hz, H₄a), 7.30 (1H, d, J = 2.1 Hz, H₅a), 7.25 (1H, d, J = 8.4 Hz, H₆a), 6.96 (1H, d, J = 8.4 Hz, H₇a), 5.47 (1H, s, H₁a), 4.83 (1H, s, br, H₁a), 4.33 (2H, d, J = 5.8 Hz, H₃a), 3.98 (2H, t, J = 6.7 Hz, H₄a), 3.50 (6H, s, H₅a), 3.17–1.71 (2H, m, H₇a), 1.49 (9H, s, H₈a), 1.44–1.38 (2H, m, H₈a), 0.88 (3H, t, J = 7.2 Hz, H₁a); ¹³C NMR (150 MHz, CDCl₃) δ: 157.3, 156.6, 155.9, 155.5, 139.1, 137.6, 137.3,
131.0, 130.5, 130.1, 129.9, 128.0, 126.6, 120.2, 119.2, 112.7, 105.0, 68.8, 54.1, 44.2, 31.9, 29.6, 29.5, 29.3, 29.1, 28.4, 26.1, 22.7, 14.1; MS (ESI'): m/z = 591.4 [100, (M+H')], 613.3 [20, (M+Na')]; HRMS (ESI'): [C_{36}H_{50}N_{10}O_{5}]^+ predicted 591.3792, found 591.3779 (Δ = 2.3 ppm).

8. tert-Butyl ((6-(decyloxy)-4'-{(2-formylpyridin-3-yl)-[1,1'-biphenyl]-3-yl)methyl)carbamate

To a stirred solution of 55 (60.0 mg, 0.102 mmol) in THF (3 ml) was added H₂O (100 µl) and p-toluenesulfonic acid (60.0 mg, 0.316 mmol). The reaction was heated under argon to 50 °C for 3 h. The reaction was partitioned between CH₂Cl₂ (30 ml) and 2 M NaOH (aq) (30 ml). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography [EtOAc:CH₂Cl₂ 1:99 grading to 1:24] to furnish 8 (44.7 mg, 0.0822 mmol, 81%) as a pale yellow oil.

H NMR (600 MHz, Acetone-d₆) δ: 10.14 (1H, s, H₁₁), 8.32–8.26 (3H, m, H₂₃ + H₂₉), 8.15–8.11 (1H, m, H₂₈), 7.90 (1H, d, J = 7.7 Hz, H₂₇), 7.74 (2H, d, J = 7.7 Hz, H₂₈), 7.39 (1H, d, J = 2.2 Hz, H₂₀), 7.29 (2H, dd, J = 7.8, 2.2 Hz, H₁₃), 7.07 (1H, d, J = 8.4 Hz, H₁₂), 6.47 (1H, s, br, H₁₅), 4.28 (2H, d, J = 6.4 Hz, H₁₄), 4.04 (2H, t, J = 6.8 Hz, H₁₀), 1.76–1.70 (2H, m, H₁₃), 1.46–1.40 (11H, m, H₁₈ + H₈), 1.34–1.16 (12H, m, H₇–H₉), 0.83 (3H, t, J = 6.3 Hz, H₃); ¹³C NMR (150 MHz, Acetone-d₆) δ: 193.4, 157.2, 155.9, 155.2, 152.9, 140.3, 138.4, 136.3, 132.7, 130.0, 129.7, 129.6, 128.1, 126.3, 124.3, 119.4, 112.7, 77.8, 68.3, 43.4, 31.7, 29.5, 29.2, 29.0, 29.0, 28.8, 27.8, 26.0, 22.4, 13.5; MS (ESI'): m/z = 545.3 [100, (M+H')], 567.3 [10, (M+Na')]; HRMS (ESI'): [C₃₄H₄₅N₅O₄]⁺ predicted 545.3374, found 545.3366 (Δ = 1.4 ppm).

10. tert-Butyl (E)-((6-(decyloxy)-4'-{(2-{(2-{3-nitrobenzoyl}hydrazono)methyl}pyridin-3-yl)-[1,1'-biphenyl]-3-yl)methyl)carbamate

To a stirred solution of 8 (42.0 mg, 0.0773 mmol) in CH₂Cl₂ (100 ml) was added 3-nitrobenzohydrazide (18.0 mg, 0.0928 mmol, 22) and aniline (0.360 mg, 3.87 µmol). The reaction was stirred for 16 h then concentrated in vacuo. The crude residue was purified by flash column
chromatography [MeOH:CH₂Cl₂ 1:19 grading to 1:9] to furnish 10 (43.7 mg, 0.617 mmol, 80%) as a yellow oil.

¹H NMR (600 MHz, CDCl₃) δ: 15.82 (1H, s, H₃₂), 8.75 (1H, s, H₃₉), 8.36 (1H, d, J = 8.2 Hz, H₁₃₂), 8.13 (1H, d, J = 8.2 Hz, H₃₅₂), 8.05–8.01 (1H, m, H₂₈), 7.81 (1H, d, J = 8.2 Hz, H₂₉), 7.74–7.70 (3H, m, H₂₃ + H₂₀), 7.54–7.49 (3H, m, H₂₄ + H₂₇), 7.47–7.43 (1H, m, H₃₆), 7.28 (1H, d, J = 8.5 Hz, H₁₃₁), 6.96 (1H, d, J = 8.5 Hz, H₁₂₁), 4.96 (1H, s, br, H₁₅₁), 4.35 (2H, d, J = 4.8 Hz, H₁₄₄), 3.98 (2H, t, J = 6.7 Hz, H₁₂₀), 1.72–1.65 (2H, m, H₆), 1.47 (9H, s, H₁₈₈), 1.36–1.30 (2H, m, H₈), 1.27–1.14 (12H, m, H₂–H₁₂), 0.83 (3H, t, J = 6.6 Hz, H₃₁) ¹³C NMR (150 MHz, CDCl₃) δ: 162.9, 157.6, 156.0, 155.4, 152.2, 148.3, 140.5, 140.0, 138.9, 136.7, 135.1, 133.4, 131.3, 130.2, 130.1, 129.9, 129.7, 128.5, 126.9, 126.6, 124.6, 123.5, 122.5, 112.7, 68.7, 44.2, 31.9, 29.6, 29.5, 29.3, 29.9, 29.2, 29.1, 26.0, 22.7, 14.1; MS (ESI⁺): m/z = 708.1 [100, (M+H)⁺], 730.1 [10, (M+Na)⁺]; HRMS (ESI⁺): [C₄₁H₄₀N₅O₆Na]⁺ predicted 730.3575, found 730.3581 (Δ = 0.8 ppm).

2. **N’-((E)-(3-(2’-(decyloxy))-5’-(((2’-((R)-(1S,2S,4S,5R)-5-ethylquinoclidin-2-yl)(6-methoxyquinolin-4-yl)(methyl)amino)-3,4-dioxocyclobutyl)(amino)methyl)-[1,1’-biphenyl]-4-yl)pyridin-2-yl)methylene)-3-nitrobenzohydrazide**

![Chemical Structure of 2](image)

10 (43.7 mg, 0.617 mmol) was dissolved in CH₂Cl₂ (4 ml) and TFA (1 ml) was added. The reaction was stirred at r.t. for 1 h and concentrated in vacuo with the addition of toluene (5 ml). The residue was azeotroped 5 x with toluene:CH₂Cl₂ (1:1, 10 ml). The crude residue was dissolved in DMF (2 ml), MeOH (2 ml) and Et₃N (0.5 ml), then 5 (85 mg, 0.195 mmol) was added. The reaction was stirred at r.t. for 16 h, concentrated in vacuo, and purified by preparatory thin layer chromatography (4 x 500 µm, eluted with Et₃N:MeOH:CH₂Cl₂ 0.1:1:10) to afford 2 (33.1 mg, 0.327 mmol, 53%) as a yellow powder.

³H NMR (600 MHz, DMSO-d₆) δ: 12.42 (1H, s, H₅₃), 8.80 (1H, s, H₅₅), 8.75 (1H, s, H₂₄₆), 8.63 (1H, s, H₅₄), 8.49 (1H, d, J = 8.1 Hz, H₅₀), 8.41 (1H, d, J = 8.1 Hz, H₂₅₀), 8.15 (2H, d, J = 8.1 Hz, H₅₁), 8.07 (1H, d, J = 6.9 Hz, H₅₀), 8.04–7.94 (3H, m, H₅₁ + H₅₂ + H₆₁), 7.91–7.87 (1H, m, H₂₇), 7.86–7.79 (1H, m, H₂₃), 7.65–7.55 (3H, m, H₁₃ + H₆₆), 7.43 (1H, d, J = 8.1, H₂₈), 7.36–7.33 (1H, m, H₁₁), 7.29–7.25 (1H, m, H₄₃), 7.11–7.07 (1H, m, H₂₄), 6.29 (1H, br, H₁₅ or H₂₀), 6.05 (1H, br, H₁₅ or H₂₀), 4.70–4.61 (2H, m, H₂₄), 3.99–3.95 (2H, m, H₁₀), 3.94–3.87 (4H, m, H₂₁ + H₃₂), 2.90–2.84 (1H, m, H₃₃), 1.65–1.59 (2H, m, H₈), 1.56–1.45 (5H, m, H₂ + H₈ + H₃₅₅), 1.38–1.10 (20 H, m, H₂–H₁₂–H₁₃–H₂₄ + H₃₅₅ + H₁₃₂ + H₁₃₁ + H₁₄₀ + H₁₄₁), 0.84–0.80 (3H, m, H₇), 0.77 (3H, t, J = 7.4, H₃₈); ¹³C NMR (150 MHz, DMSO-d₆) δ: 182.4, 182.1, 167.0, 157.9, 155.1, 147.8,
147.7, 146.7, 145.2, 144.3, 141.2, 139.6, 138.5, 137.9, 137.3, 134.2, 133.8, 131.6, 131.1, 130.2, 129.9, 129.7, 129.6, 129.4, 129.3, 128.9, 127.5, 126.0, 125.6, 125.2, 122.5, 122.1, 113.2, 101.3, 68.2, 59.0, 55.6, 49.0, 48.1, 46.4, 31.3, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.7, 28.6, 28.6, 25.7, 25.6, 25.4, 22.1, 13.9, 13.9; **MS (ESI⁺):** \( m/z = 1011.1 \) [100, (M+H)⁺], 1033.2 [5, (M+Na)⁺]; **HRMS (ESI⁺):** \([C_{60}H_{67}N_8O_7]^+\) predicted 1011.5127, found 1011.5096 (\( \Delta = 3.1 \text{ ppm} \)).
3. Catalysis tests

Addition of malonitrile to chalcone to form S6

\[
\text{Malonitrile } 12 \ (1.0 \text{ mg, } 0.015 \text{ mmol}), \text{ chalcone } S7 \ (32 \text{ mg, } 0.15 \text{ mmol}) \text{ and catalyst } 1 \text{ or } 2 \ (0.75 \text{ mg, } 0.75 \mu\text{mol}) \text{ were dissolved in CDCl}_3 \ (0.7 \text{ ml}). \text{ Conversion was measured periodically by } ^1\text{H NMR spectroscopy and comparison with authentic spectra of starting materials and product. Upon completion, the crude was purified by TLC, and the chirality of the product ascertained by HPLC (chiralpak IC, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 } t_r = 18.4 \text{ min, for catalyst 2 } t_r = 29.9 \text{ min).}
\]

Addition of 1,4-dithiane-2,5-diol to chalcone to form S8

\[
\text{1,4-dithiane-2,5-diol } S9 \ (2.3 \text{ mg, } 0.015 \text{ mmol}), \text{ chalcone } S7 \ (32 \text{ mg, } 0.15 \text{ mmol}) \text{ and catalyst } 1 \text{ or } 2 \ (0.75 \text{ mg, } 0.75 \mu\text{mol}) \text{ were dissolved in toluene } (0.7 \text{ ml}) \text{ then heated to 50 °C. Conversion was measured periodically by } ^1\text{H NMR spectroscopy and comparison with authentic spectra of starting materials and product. Upon completion, the crude was purified by TLC, and the chirality of the product ascertained by HPLC (chiralpak IA, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 } t_r = 13.6 \text{ min, for catalyst 2 } t_r = 19.3 \text{ min).}
\]

Addition of malonitrile to (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one to form 14

\[
\text{Malonitrile } 12 \ (1.0 \text{ mg, } 0.015 \text{ mmol}), \text{ (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one } 13 \ (30 \text{ mg, } 0.15 \text{ mmol}) \text{ and catalyst } 1 \text{ or } 2 \ (0.75 \text{ mg, } 0.75 \mu\text{mol}) \text{ were dissolved in CDCl}_3 \ (0.7 \text{ ml}). \text{ Conversion was measured periodically by } ^1\text{H NMR spectroscopy and comparison with authentic spectra of starting materials and product. Upon completion, the crude was purified by TLC, and the chirality of the product ascertained by HPLC (chiralpak IA, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 } t_r = 19.9 \text{ min, for catalyst 2 } t_r = 23.9 \text{ min).}
\]
Addition of diethyl malonate to trans-β-nitrostyrene to form S10

\[
\text{O} \quad \begin{array}{c}
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\text{H}
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\xrightarrow{\text{O} \quad \begin{array}{c}
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\end{array} } 
\text{O} \quad \begin{array}{c}
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\text{H}
\end{array}
\]

Diethyl malonate S11 (24 mg, 0.15 mmol), trans-β-nitrostyrene S12 (2.2 mg, 0.015 mmol) and catalyst 1 or 2 (3.75 mg, 3.75 μmol) were dissolved in CDCl₃ (0.7 ml). Conversion was measured periodically by ¹H NMR spectroscopy and comparison with authentic spectra of starting materials and product. Upon completion, the crude was purified by TLC, and the chirality of the product ascertained by HPLC (chiralpak IA, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 tᵣ = 13.7 min, for catalyst 2 tᵣ = 18.4 min).

Addition of diethyl malonate to trans-β-nitrostyrene to form S13

\[
\text{O} \quad \begin{array}{c}
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\text{H} \\
\text{H}
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\xrightarrow{\text{O} \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{H}
\end{array} } 
\text{O} \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{H}
\end{array}
\]

1,3-Diphenylpropane-1,3-dione S14 (3.4 mg, 0.015 mmol), trans-β-nitrostyrene S12 (22 mg, 0.15 mmol) and catalyst 1 or 2 (3.75 mg, 3.75 μmol) were dissolved in CDCl₃ (0.7 ml). Conversion was measured periodically by ¹H NMR spectroscopy and comparison with authentic spectra of starting materials and product. Upon completion, the crude was purified by TLC, and the chirality of the product ascertained by HPLC (chiralpak IA, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 tᵣ = 18.5 min, for catalyst 2 tᵣ = 36.8 min).

Addition of malonitrile to (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one to form S15

\[
\text{O} \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{H}
\end{array} 
\xrightarrow{\text{O} \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{H}
\end{array} } 
\text{O} \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{H}
\end{array}
\]

2-(Methoxymethoxy)malononitrile S16 (8.0 mg, 0.063 mmol, prepared according to literature procedure), (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one 13 (62 mg, 0.32 mmol) and catalyst 1 or 2 (3.2 mg, 3.2 μmol) were dissolved in CDCl₃ (1 ml). Upon completion, the crude was purified by PTLC, furnishing a colourless oil (24.1 mg, 0.0744 mmol, 74%) and the chirality of the product ascertained by HPLC (chiralpak IA, 90:10 Hexane:iPrOH, major enantiomer produced by catalyst 1 tᵣ = 12.1 min, for catalyst 2 tᵣ = 9.8 min). ¹H NMR (600 MHz, CDCl₃) δ: 7.60 (1H, d, J = 1.9 Hz, H₁₁), 7.49 (2H, dd, J = 7.8, 1.3 Hz, H₄ + H₆), 7.38-7.34 (3H, m, H₁-H₃), 7.21 (1H, d, J = 3.6 Hz, H₁₃), 6.54
(1H, dd, J = 3.6, 1.7 Hz, H1a),  5.06–5.01  (2H, m, H20),  4.21  (1H, dd, J = 9.2, 3.9 Hz, H1),  3.72  (1H, dd, J = 15.8, 9.7 Hz, H8a),  3.55  (1H, dd, J = 16.7, 3.9 Hz, H8b),  3.46  (3H, s, H22); 13C NMR (150 MHz, CDCl3) δ: 184.4, 152.2, 146.8, 133.9, 129.6, 129.3, 128.9, 117.6, 112.7, 96.5, 70.0, 57.5, 49.1, 38.4; MS (ESI⁺): m/z = 347.1 [100, (M+Na)⁺]; HRMS (ESI⁺): [C18H16N2O4Na⁺] predicted 347.1002, found 347.1002 (Δ −0.1 ppm).
4. Optimisation of light switching conditions for catalyst 1

The degree of isomerisation was monitored by following the integral ratio of the E and Z states of hydrazone proton H(55) (at c. 12 ppm and c. 16 ppm, see characterisation for full numbering).

A brief initial screen of light sources showed a 395 nm source to be the most efficient in promoting hydrazone isomerization. Initially problems with decomposition, particularly hydrazone hydrolysis, were observed. This could be prevented by the addition of molecular sieves, which also improved the E:Z ratio achieved. A significant improvement in final switching ratio was achieved by the addition of EtOAc to the solvent mixture (pure EtOAc could not be used due to insufficient solubility). Increasing the concentration of solution was deleterious to conversion. The timescale of switching could be accelerated to 20 min of irradiation by increasing the power and using CH₂Cl₂:EtOAc as solvent. This switching system also alleviated the previously observed decomposition, obviating the need for molecular sieves.

Table S1

| Mass/mg | Solvent | Additive | Wavelength/nm | Time/min | Power/mW | Ratio E:Z | Decomp. |
|---------|---------|----------|---------------|----------|----------|-----------|---------|
| 1       | CH₂Cl₂  | -        | 365           | 30       | 215      | 60:40     | 20%     |
| 1       | Toluene | -        | 365           | 30       | 215      | 57:43     | 20%     |
| 1       | EtOAc   | -        | 365           | 30       | 215      | 43:57     | 20%     |
| 1       | CHCl₃   | -        | 395           | 30       | 215      | 58:42     | 10%     |
| 1       | Toluene: CH₂Cl₂:9:1 | -  | 395     | 30       | 215      | 60:40     | 10%     |
| 1       | EtOAc: CH₂Cl₂:9:1 | -  | 395     | 30       | 215      | 40:60     | 10%     |
| 1       | CH₂Cl₂  | Cold White | 395 | 30       | 215      | 87:13     | 10%     |
| 1       | EtOAc: CH₂Cl₂ 9:1 | - Cold White | 395 | 30       | 215      | 90:10     | 10%     |
| 1       | EtOAc CH₂Cl₂ 9:1 | - Cold White | 395 | 900      | 215      | 45:55     | 25%     |
| 1       | EtOAc: CH₂Cl₂ 4:1 | - Cold White | 395 | 300      | 380      | 54:46     | 35%     |
| 1       | CHCl₃   | MS       | 395           | 60       | 380      | 40:60     | -        |
| 1       | CHCl₃   | MS       | 395           | 140      | 380      | 46:54     | 5%       |
| 1       | EtOAc: CHCl₃ 4:1 | MS, 10 Eq Chalcone | 395 | 60       | 380      | 29:71     | -        |
| 1       | EtOAc: CHCl₃ 4:1 | MS, Rose Bengal | 395 | 60       | 380      | 87:13     | -        |
| 1       | EtOAc: CHCl₃ 4:1 | MS, 2 Eq TFA | 395 | 60       | 380      | 52:48     | 5%       |
| 1       | EtOAc: CHCl₃ 4:1 | MS, 2 Eq TFA, Chalcone | 395 | 60       | 380      | 42:58     | 5%       |
| 1       | EtOAc: CHCl₃ 4:1 | MS, Et₃N MS, Chalcone, Malo- | 395 | 90       | 380      | 27:73     | -        |
| 1       | EtOAc: CHCl₃ 4:1 | MS, Chalcone, Malo- | 395 | 90       | 380      | 34:66     | -        |
| 1 | EtOAc: CHCl$_3$ 4:1 | MS, Zn$^{2+}$ | 395 | 90 | 380 | 84:16 | - |
| 3 | EtOAc: CHCl$_3$ 4:1 | MS | 395 | 90 | 380 | 39:61 | - |
| 1 | EtOAc: CHCl$_3$ 4:1 | Nitrostyrene, diethylmalonate | 395 | 90 | 380 | 48:52 | Some |

| 1 | EtOAc: MeOH 4:1 | MS | 395 | 90 | 380 | Too broad to integrate at 12 ppm | - |
| 1 | DCE | MS | 395 | 60 | 380 | 50:50 | - |
| 1 | CH$_2$Cl$_2$ | MS | 395 | 110 | 380 | 50:50 | Limited |
| 1 | CHCl$_3$ | MS | 395 | 70 | 380 | 47:53 | - |
| 1 | EtOAc: CHCl$_3$ 2:3 | MS | 395 | 120 | 380 | 25:75 | - |
| 1 | EtOAc: CHCl$_3$ 4:1 | MS | 395 | 120 | 380 | 22:78 | - |
| 1 | EtOAc: CH$_2$Cl$_2$ 4:1 | MS | 395 | 70 | 380 | 25:75 | - |
| 1 | Toluene: CH$_2$Cl$_2$ 4:1 | MS | 395 | 70 | 380 | 53:47 | - |
| 1 | EtOAc: CHCl$_3$ 4:1 | MS | 395 | 90 | 380 | 30:70 | - |
| 1 | TCE | 395 | 20 | 700 | 47:53 | - |
| 1 | TCE: CH$_2$Cl$_2$:EtOAc 1:1:5 | 395 | 20 | 700 | 32:68 | - |
| 1 | CH$_2$Cl$_2$:EtOAc 1:4 | 395 | 20 | 700 | 21:79 | - |

All entries run in 3.5 ml total solvent, with switching ratios obtained after removal of solvent and $^1$H NMR in $d_6$-DMSO.
5. Optimisation of thermal switching of catalyst 1

The degree of isomerisation was monitored by following the integral ratio of the \( E \) and \( Z \) states of hydrazone proton H(55) (at c. 12 ppm and c. 16 ppm, see characterisation for full numbering).

Initial isomerization of catalyst 1 focused on pure thermal switching. More polar solvents were found to promote isomerization, and pleasing ratios could be obtained in DMF at 90 °C. However, the extended reaction time and high temperature required prompted us to search for effective acid catalysed switching conditions. The addition of TFA to EtOAc allowed virtually quantitative switching after one hour.

Table S2

| Entry | Solvent       | \( T/°C \) | Concentration mg/ml | Additive | Time/hr | Ratio  |
|-------|---------------|------------|---------------------|----------|---------|--------|
| 1     | CHCl\(_3\)    | 65         | 0.01                | -        | 3       | 25:75  |
| 2     | EtOAc/DMF 9:1 | 60         | 0.01                | -        | 3       | 40:60  |
| 3     | DMF           | 60         | 0.01                | -        | 3       | 46:54  |
| 4     | DMSO          | 60         | 0.01                | -        | 3       | 34:66  |
| 5     | DMF           | 90         | 0.02                | -        | 3       | 84:16  |
| 6     | DMF           | 90         | 0.2                 | -        | 3       | 84:16  |
| 7     | DMF           | 90         | 0.2                 | -        | 5       | 90:10  |
| 8     | CHCl\(_3\)    | 40         | 0.02                | 0.02% TFA| 1       | 62:38  |
| 9     | EtOAc         | 50         | 0.02                | 0.04% TFA| 1       | 83:17  |
| 10    | EtOAc         | 50         | 0.02                | 0.1% TFA | 1       | 98:2   |
### 6. Literature Catalysis Examples

| Entry | Reagents | Product | Catalyst | Catalyst loading (mol%) | Solvent | Temp. | Time (h) | Conversion (S:R) |
|-------|----------|---------|----------|-------------------------|---------|-------|----------|-----------------|
| 1     | ![Reagent Image](image1.png) | ![Product Image](image2.png) | ![Catalyst Image](image3.png) | 0.5 | CHCl₃ | rt | 24 | 82% (95:5)³⁶ |
| 2     | ![Reagent Image](image4.png) | ![Product Image](image5.png) | ![Catalyst Image](image6.png) | 1 | Toluene | 60°C | 6 | 81% (6:94)³⁷ |
| 3     | ![Reagent Image](image7.png) | ![Product Image](image8.png) | ![Catalyst Image](image9.png) | 10 | m-Xylene | rt | 18 | 96%* (93:7)³⁸ |
| 4     | ![Reagent Image](image10.png) | ![Product Image](image11.png) | ![Catalyst Image](image12.png) | 1 | CH₂Cl₂ | rt | 180 | 83% (95:5)³⁹ |
| 5     | ![Reagent Image](image13.png) | ![Product Image](image14.png) | ![Catalyst Image](image15.png) | 1 | CH₂Cl₂ | rt | 6 | 89% (95:5)³⁹ |
7. *in situ* Switching Experiments

Procedure for switching of catalyst state during the course of reaction

Malonitrile (1.0 mg, 0.015 mmol), (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (9 mg, 0.045 mmol) and catalyst 2 (0.75 mg, 0.75 μmol) were dissolved in CDCl₃ (0.7 ml). Conversion was measured periodically by ¹H NMR spectroscopy and comparison with authentic spectra of starting materials and product. After a given time, the reaction was diluted with 10 ml Et₂O. The precipitate was collected via syringe filtration, and dissolved in CH₂Cl₂. The filtrate was stored at − 20 °C for the duration of the switching procedure. The relevant heat or light switch was performed on the catalyst, followed by aqueous extraction with saturated Na₂CO₃ (aq). After drying, the catalyst was recombined with the diluted reaction mixture. Solvent was removed *in vacuo* whilst the flask was cooled to 0 °C. The reaction mixture was immediately dissolved in CDCl₃ (0.7 ml) and monitored by NMR. This process was repeated using the alternate switching conditions after a suitable time had passed. No erosion of stereochemistry in the product was observed, as compared to the continuous reaction.

![Figure S1. Relative reactivity of ON and OFF states of catalyst 2 towards the addition of malonitrile to chalcone 22 by starting with the OFF state (left) or ON state (right, solid lines are a guide to the eye). A full switching cycle could be carried out during this reaction, starting from either ‘ON’ or ‘OFF’ catalyst, using 3.5 mol% of 2 (initial E:Z ratio 99:1 (ON) or 2:98 (OFF)). After 6 h the E-to-Z, or vice versa, stimulus was applied (0.1% CF₃CO₂H, 60 min, 50 °C or 395 nm, 700 mW, 20 min) and the reaction continued. After 24 h (for initially OFF 2) or 21 h (for initially ON 2) the opposing stimulus was applied reverting catalyst 2 to its initial state.](image-url)
8. HPLC Traces

**Formation of S6 using catalyst 1** (Chiralpak IC, 90:10 Hexane:iPrOH, 1mL/min).

![HPLC Trace 1](image1)

| Peak RetTime Type Width | Area (mAU’s) | Height | Area % |
|-------------------------|--------------|--------|--------|
| 1 18.360 BB | 0.5819 1179.75647 | 30.59268 16.9746 |
| 2 29.923 BB | 0.8660 5770.36914 | 101.39162 03.0254 |

**Formation of S6 using catalyst 2** (Chiralpak IC, 90:10 Hexane:iPrOH, 1mL/min).

![HPLC Trace 2](image2)

| Peak RetTime Type Width | Area (mAU’s) | Height | Area % |
|-------------------------|--------------|--------|--------|
| 1 19.155 BB | 0.7002 1228.80835 | 28.09811 77.1590 |
| 2 32.989 BB | 0.8728 363.75751 | 5.23420 22.8410 |

**Formation of S8 using catalyst 1** (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

![HPLC Trace 3](image3)

| Peak RetTime Type Width | Area (mAU’s) | Height | Area % |
|-------------------------|--------------|--------|--------|
| 1 13.631 BB | 0.4678 1657.34219 | 56.57403 74.6692 |
| 2 19.132 BB | 0.5704 562.23755 | 14.76140 25.3308 |
Formation of S8 using catalyst 2 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

Signal 3: DAD1 C, Sig=210.4 Ref=500,100

| Peak RetTime Type Width Area Height Area % |
|-----------------------------------------|---------------------------------|-------------------------------|-------------|
| # [min] [min] [mAU's] [mAU]          |                                |                               |             |
| 1 13.783 BB 0.3569 2804.13420 121.64997 29.5406 |
| 2 19.261 BB 0.5065 6688.33691 205.05865 70.4594 |

Formation of 14 using catalyst 1 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

Signal 2: DAD1 B, Sig=254.4 Ref=500,100

| Peak RetTime Type Width Area Height Area % |
|-----------------------------------------|---------------------------------|-------------------------------|-------------|
| # [min] [min] [mAU's] [mAU]          |                                |                               |             |
| 1 28.252 MM 0.5563 39,87947 1.19485 4.5869 |
| 2 23.881 BB 0.5819 829,54236 21.51132 95.4131 |

Formation of 14 using catalyst 2 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

Signal 2: DAD1 B, Sig=254.4 Ref=500,100

| Peak RetTime Type Width Area Height Area % |
|-----------------------------------------|---------------------------------|-------------------------------|-------------|
| # [min] [min] [mAU's] [mAU]          |                                |                               |             |
| 1 19.943 BB 0.5209 6671.54150 194.21600 92.5924 |
| 2 23.805 BB 0.5804 533,89978 13.79792 7.4076 |

Totals :
7287.44128 208.03483
Formation of S10 using catalyst 1 (Chiralpak IC, 90:10 Hexane:iPrOH, 1mL/min).

Signal 3: DAD1 C, Sig=210,4 Ref=500,100

| Peak | RetTime | Width | Area  | Height | Area  |
|------|---------|-------|-------|--------|-------|
| 1    | 13.715  | 0.3133| 1069.02795 | 53.009949 | 89.2687 |
| 2    | 19.452  | 0.4296| 128.51219   | 4.38077   | 10.7313 |

Formation of S10 using catalyst 2 (Chiralpak IC, 90:10 Hexane:iPrOH, 1mL/min).

Signal 3: DAD1 C, Sig=210,4 Ref=500,100

| Peak | RetTime | Width | Area  | Height | Area  |
|------|---------|-------|-------|--------|-------|
| 1    | 13.218  | 0.3000| 85.15978  | 4.39684   | 19.6072   |
| 2    | 18.370  | 0.4224| 349.16968  | 12.63498  | 80.3928   |

Formation of S13 using catalyst 1 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

Signal 1: DAD1 A, Sig=250,4 Ref=500,100

| Peak | RetTime | Width | Area  | Height | Area  |
|------|---------|-------|-------|--------|-------|
| 1    | 18.461  | 0.7091| 478.63751  | 10.05877  | 90.5574   |
| 2    | 36.193  | 1.2775| 49.90842   | 6.51126e-1| 9.4426    |
Formation of S\textsubscript{13} using catalyst 2 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

| Peak RetTime Type | Width | Area  | Height | Area % |
|-------------------|-------|-------|--------|--------|
| 1                 | 18.72 | 0.49  | 73.87  | 9.86   |
| 2                 | 36.80 | 0.99  | 668.49 | 90.01  |

Formation of S\textsubscript{15} using catalyst 1 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

| Peak RetTime Type | Width | Area  | Height | Area % |
|-------------------|-------|-------|--------|--------|
| 1                 | 9.76  | 0.24  | 91.24  | 14.34  |
| 2                 | 12.14 | 0.29  | 545.00 | 85.65  |

Formation of S\textsubscript{15} using catalyst 2 (Chiralpak IA, 90:10 Hexane:iPrOH, 1mL/min).

| Peak RetTime Type | Width | Area  | Height | Area % |
|-------------------|-------|-------|--------|--------|
| 1                 | 9.74  | 0.23  | 809.25 | 84.52  |
| 2                 | 12.14 | 0.29  | 148.12 | 15.47  |
9. NMR Spectra

Spectra of intermediate S1

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate S1

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate S1
NMR spectra of intermediate $S_2$

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate $S_2$

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate $S_2$
NMR spectra of intermediate S3

$^1$H NMR (600 MHz, CD$_2$Cl$_2$) of intermediate S3

$^{13}$C NMR (150 MHz, CD$_2$Cl$_2$) of intermediate S3
$^{19}$F NMR (376 MHz, CDCl$_3$) of intermediate S3
NMR spectra of intermediate 3

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate 3

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate 3
NMR spectra of intermediate S4

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate S4

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate S4
NMR spectra of intermediate 9

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate 9

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate 9
NMR spectra of intermediate 11

$^1$H NMR (600 MHz, $d_6$-DMSO) of intermediate 11

$^{13}$C NMR (150 MHz, $d_6$-DMSO) of intermediate 11
NMR spectra of bifunctional catalyst 1

$^1$H NMR (600 MHz, $d_6$-DMSO) of bifunctional catalyst 1

$^{13}$C NMR (150 MHz, $d_6$-DMSO) of bifunctional catalyst 1
NMR spectra of intermediate S5

$^1$H NMR (600 MHz, CDCl$_3$) of intermediate S5

$^{13}$C NMR (150 MHz, CDCl$_3$) of intermediate S5
NMR spectra of intermediate 8

$^1$H NMR (600 MHz, $d_6$-Acetone) of intermediate 8

$^{13}$C NMR (150 MHz, $d_6$-Acetone) of intermediate 8
NMR spectra of intermediate 10

$^{1}H$ NMR (600 MHz, CDCl$_3$) of intermediate 10

$^{13}C$ NMR (150 MHz, CDCl$_3$) of intermediate 10
NMR spectra of bifunctional catalyst 2

$^1$H NMR (600 MHz, $d_6$–DMSO) of bifunctional catalyst 2

$^{13}$C NMR (150 MHz, $d_6$–DMSO) of bifunctional catalyst 2
NMR spectra of addition product S15

$^1$H NMR (600 MHz, CDCl$_3$) of addition product S15

$^{13}$C NMR (150 MHz, CDCl$_3$) of addition product S15
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