Catalytic Enantioselective Synthesis of 1,4-Dihydropyridines via the Addition of C(1)-Ammonium Enolates to Pyridinium Salts

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1. General experimental

All reagents and solvents were obtained from commercial suppliers and were used as received without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods. Tetramisole (TM) HCl 3 was purchased from Sigma-Aldrich, benzotetramisole (BTM) 4 and HyperBTM 5 were prepared in house. All diastereomeric ratios (dr) of crude reaction mixtures analysed by $^1$H NMR are reported to the nearest multiple of 5.

1.1. Purification of solvents

Anhydrous solvents (CH$_2$Cl$_2$, THF, PhMe) were obtained after passing through an alumina column (Mbraun SPS-800). Anhydrous MeCN was purchased from Sigma-Aldrich and used without further purification. Anhydrous DMF was purchased from Acros and used without further purification. Petrol is defined as petroleum ether 40-60 °C. EtOAc, Et$_2$O, CH$_2$Cl$_2$ and petrol for purification purposes were used as obtained from suppliers without further purification.

1.2. Purification of reagents

Dry Hunig’s base was obtained by distillation over KOH and transferred to and stored in a screw-top vial over KOH and purged with and stored under nitrogen.

1.3. Experimental details

Reactions were carried out in flame-dried glassware under an inert atmosphere (N$_2$) using standard vacuum line techniques. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature (RT) refers to 20-25 °C. Temperatures of 0 °C and were obtained using an ice/water. Temperatures of 0 °C, −10 °C and −40 °C for catalysis reactions were obtained using an immersion cooler (HAAKE EK 90). Reactions involving heating were performed using DrySyn blocks, sand, and a contact thermocouple. Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and
ILMVIC vacuum controller, or an IKA RV10 rotary evaporator with an IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to –5 °C. In vacuo refers to the use of a Schlenk line manifold and high vacuum pump.

1.4. Purification of products

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with either aqueous KMnO₄ solution or ethanolic Vanillin solution followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Kieselgel 60 silica. Purification of catalysis products using a gradient between 0-10% Et₂O in CH₂Cl₂ was carried out using a stock solution of 10% Et₂O in CH₂Cl₂, diluted appropriately with CH₂Cl₂.

1.5. Analysis of products

Melting points (mp) were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations [α]₀²⁰ were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-20A₃ degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-20A₃R degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using either DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.
Infrared spectra ($\nu_{\text{max}}$) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers ($\nu_{\text{max}}$) reported in cm$^{-1}$.

$^1$H, $^{13}$C($^1$H), and $^{19}$F NMR spectra were acquired on either a Bruker AV400 with a BBFO probe ($^1$H 400 MHz; $^{13}$C($^1$H) 101 MHz; $^{19}$F($^1$H) 377 MHz), a Bruker AVII 400 with a BBFO probe ($^1$H 400 MHz; $^{13}$C($^1$H) 101 MHz; $^{19}$F($^1$H) 376 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe ($^1$H 500 MHz, $^{13}$C($^1$H) 126 MHz, $^{19}$F($^1$H) 470 MHz), or a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe ($^1$H 500 MHz, $^{13}$C($^1$H) 126 MHz, $^{19}$F 470 MHz), in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, $J$, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic and app denotes apparent. NMR peak assignments were confirmed using 2D $^1$H correlated spectroscopy (COSY), 2D $^1$H-$^{13}$C heteronuclear single quantum coherence (HSQC), 2D $^1$H-$^{13}$C heteronuclear multiple-bond correlation spectroscopy (HMBC), 2D $^1$H total correlation spectroscopy (TOCSY) and 2D $^1$H nuclear Overhauser effect spectroscopy (NOESY), where necessary.

High resolution mass spectrometry (HRMS) data were acquired by either electrospray ionisation (ESI), electron impact (EI), atmospheric solids analysis probe (ASAP), or nanospray ionisation (NSI) at either the University of St Andrews Mass Spectrometry Facility, the EPSRC UK National Mass Spectrometry Facility at Swansea University, or at the School of Chemistry University of Edinburgh mass spectrometry service.
2. General procedures

2.1. General procedure A: synthesis of esters

\[
\begin{align*}
R^1 \overset{\text{EDCI-HCl (1.3 equiv)}}{\longrightarrow} & \quad R^1 \overset{\text{CH}_2\text{Cl}_2 (0.6 \text{ M})}{\longrightarrow} \quad R^2 \\
\text{CH}_2\text{Cl}_2 (0.6 \text{ M}) \quad \text{RT, 16 h} & \quad \text{CH}_2\text{Cl}_2 (3 \times) \\
& \quad \text{MgSO}_4 , \quad \text{filtered,} \\
& \quad \text{concentrated under reduced pressure} \\
\end{align*}
\]

The appropriate acetic acid (1.0 equiv) and EDCI·HCl (1.3 equiv) were dissolved in anhydrous CH₂Cl₂ (0.6 M) and the reaction mixture was stirred at room temperature. After 10 mins, the appropriate phenol (1.5 equiv) was added, and the reaction stirred at room temperature for 16 h. The reaction mixture was diluted with H₂O and extracted with CH₂Cl₂ (3 ×). The organic layer was dried with MgSO₄, filtered, and concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography.

2.2. General procedure B: synthesis of pyridinium salts

\[
\begin{align*}
\text{R}^2 \text{X} (1.5 \text{ equiv}) & \quad \text{MeCN (0.5 M)} \\
\quad \text{reflux, 18 h} & \quad \text{MeCN (0.5 M)} \\
\end{align*}
\]

The appropriate electrophile (1.5 equiv) was added to the appropriate pyridine (1.0 equiv) in MeCN (0.5 M) and the reaction was refluxed for 18 h. The reaction mixture was cooled to 0 °C and cold Et₂O was added with stirring until a precipitate formed. The solid was filtered, washed with cold Et₂O and dried in vacuo.

2.3. General procedure C: optimisation of the dearomatisation reaction

\[
\begin{align*}
R^1 \overset{\text{catalyst base, solvent temp. (°C), time}}{\longrightarrow} & \quad \text{R}^2 \overset{\text{NuH (5 equiv) temp (°C), time}}{\longrightarrow} \\
\text{R}^1 \overset{\text{NuH (5 equiv) temp (°C), time}}{\longrightarrow} & \quad \text{R}^2 \\
\end{align*}
\]

The appropriate ester, pyridinium salt, base (if solid) and catalyst were dissolved in solvent. The appropriate base (if liquid) was added, and the reaction was stirred at the stated temperature for the required time. The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at the stated temperature for the required time. The
reaction mixture was quenched with 1 M NaOH (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography.

2.4. General procedure D: isothiourea-catalysed dearomatisation of pyridinium salts

The appropriate ester (1.5 equiv), electrophile (1.0 equiv), DABCO (1.5 equiv) and catalyst (20 mol%) were weighed into a 20 mL test tube. The test tube was sealed, purged, lowered into a cryostat bath at 0 °C. PhMe (0.15 M) was added and the reaction was stirred at 0 °C for 24 h. The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at 0 °C for a further 24 h. The reaction mixture was quenched with 1 M NaOH (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.
3. Synthesis of aryl esters

4''-Nitrophenyl 2-(4'-tolyl)acetate (1)

Following general procedure A, using 2-(p-tolyl)acetic acid (5.00 g, 34 mmol, 1.0 equiv), EDCI·HCl (8.40 g, 44 mmol, 1.3 equiv), 4-nitrophenol (7.00 g, 50 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (56 mL, 0.6 M) for 22 h gave, after purification by column chromatography (CH$_2$Cl$_2$, R$_f$ 0.58), the title compound (5.81 g, 64%) as a colourless solid with spectroscopic data in accordance with the literature.$^{[3]}$ mp 60-62 °C [Lit.$^{[4]}$ 60-62 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δH: 2.39 (3H, s, C$_3$H$_3$), 3.88 (2H, s, C(2)H$_2$), 7.22 (2H, d, J 8.0, ArC(3',5')H), 7.24 – 7.32 (4H, m, ArC(2',6')H and ArC(2'',6'')H), 8.27 (2H, d, J 9.2, ArC(3'',5'')H).

4''-Nitrophenyl 2-phenylacetate (10)

Following general procedure A, using phenylacetic acid (5.44 g, 40 mmol, 1.0 equiv), EDCI·HCl (9.97 g, 52 mmol, 1.3 equiv), 4-nitrophenol (8.35 g, 60 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (67 mL, 0.6 M) for 21 h gave, after purification by column chromatography (CH$_2$Cl$_2$, R$_f$ 0.6), the title compound (7.28 g, 71%) as a colourless solid with spectroscopic data in accordance with the literature.$^{[5]}$ mp 58-60 °C [Lit.$^{[4]}$ 58-60 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δH: 3.90 (2H, s, C(2)H$_2$), 7.26 (2H, d, J 9.2, ArC(2',6')H), 7.28 – 7.46 (5H, m, ArC), 8.25 (2H, d, J 9.2, C(3'',5'')H).

4''-Nitrophenyl 2-(naphthalen-2'-yl)acetate (11)

Following general procedure A, using 2-naphthylacetic acid (1.86 g, 10 mmol, 1.0 equiv), EDCI-HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-
Sil 50 g, 100 mL min⁻¹, CH₂Cl₂ in Petrol (50% 5 CV, 50-75% 10 CV), Rf 0.68 at 100% CH₂Cl₂] the title compound (2.21 g, 72%) as a colourless solid with spectroscopic data in accordance with the literature./Button mp 96-98 °C [Lit.[7] 95-97 °C]; ¹H NMR (400 MHz, CDCl₃) δH: 4.09 (2H, s, C(2)'H₂), 7.28 (2H, d, J 9.3, C(2'',6'')H), 7.45 – 7.62 (3H, m, ArC'H), 7.79 – 7.97 (4H, m, ArCH), 8.27 (2H, d, J 9.2, C(3'',5'')H).

Following general procedure A, using 4-methoxyphenylacetic acid (0.66 g, 4 mmol, 1.0 equiv), EDCI·HCl (1.0 g, 5.2 mmol, 1.3 equiv), 4-nitrophenol (0.84 g, 6 mmol, 1.5 equiv) and CH₂Cl₂ (6.7 mL, 0.6 M) for 21 h gave, after purification by column chromatography (CH₂Cl₂, Rf 0.56), the title compound (0.61 g, 53%) as a colourless solid with spectroscopic data in accordance with the literature.[4] mp 89-91 °C [Lit.[4] 88-90 °C]; ¹H NMR (400 MHz, CDCl₃) δH: 3.82 (3H, s, C'H₃), 3.84 (2H, s, C(2)'H₂), 6.92 (2H, d, J 8.7, C(3',5')H), 7.25 (2H, d, J 9.2, C(2'',6'')H), 7.29 (2H, d, J 8.8, C(2',6')H), 8.24 (2H, d, J 9.2, C(3'',5'')H).

Following general procedure A, using 3,4-methoxyphenylacetic acid (3.9 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.00 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.2 g, 30 mmol, 1.5 equiv) and CH₂Cl₂ (34 mL, 0.6 M) for 20 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min⁻¹, CH₂Cl₂ in petrol (70% 5 CV, 70-80% 7 CV), Rf 0.40 at 100% CH₂Cl₂] the title compound (3.1 g, 49%) as a colourless solid with spectroscopic data in accordance with the literature./Button mp 77-79 °C [Lit.[8] 126-128 °C]; ¹H NMR (500 MHz, CDCl₃) δH: 3.86 (2H, s, C(2)'H₂), 3.91 (3H, s, C(4')OCH₃), 3.92 (3H, s, C(3')OCH₃), 6.89 (1H, d, J 8.2, C(5')H), 6.91 (1H, d, J 1.9, C(2')H), 6.94 (1H, dd, J 8.1, 2.0, C(6')H), 7.28 (2H, d, J 9.2,
C(2'',6'')H, 8.27 (2H, d, J 9.2, C(3'',5'')H); $^{13}$C($^1$H) NMR (126 MHz, CDCl$_3$) δ: 40.9 (C(2)H$_2$), 56.0 (C(3')OCH$_3$), 56.0 (C(4')OCH$_3$), 111.4 (C(5')H), 112.4 (C(2')H), 121.7 (C(6')H), 122.5 (C(2'',6'')H), 125.1 (C(1')), 125.3 (C(3'',5'')H), 145.4 (C(4'')), 148.6 (C(4')OCH$_3$), 149.2 (C(3')OCH$_3$), 155.5 (C(1'')), 169.5 (C(1)=O). The observed melting point was significantly lower than the one reported. However, we are satisfied that the structure of the compound is correct and of high purity based on the other characterisation data.

4''-Nitrophenyl 2-(thiophen-3''-yl)acetate (14)

Following general procedure A, using 3-thiophene acetic acid (1.42 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.10 g, 15 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min$^{-1}$, CH$_2$Cl$_2$ in petrol (40-100% 21 CV), R$_f$ 0.62 at 100% CH$_2$Cl$_2$] the title compound (1.73 g, 66%) as a colourless solid with spectroscopic data in accordance with the literature.$^{[4]}$ mp 55-57 °C {Lit.$^{[4]}$ 55-57 °C}; $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.95 (2H, s, C(2)H$_2$), 7.13 (1H, dd, J 5.0, 1.2, C(4')H), 7.24 – 7.30 (3H, m, C(2'',6'')H and C(2')H), 7.36 (1H, dd, J 4.9, 3.0, C(5')H), 8.26 (2H, d, J 9.1, C(3'',5'')H).

4''-Nitrophenyl 2-(4'-(trifluoromethyl)phenyl)acetate (15)

Following general procedure A, using 4-(trifluoromethyl)phenylacetic acid (1.63 g, 8 mmol, 1.0 equiv), EDCI·HCl (2.00 g, 10.4 mmol, 1.3 equiv), 4-nitrophenol (1.67 g, 12 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (13 mL, 0.6 M) for 21 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min$^{-1}$, CH$_2$Cl$_2$ in petrol (40% 5 CV, 50-60% 6 CV), R$_f$ 0.72 at 100% CH$_2$Cl$_2$] the title compound (1.41 g, 54%) as a colourless solid with spectroscopic data in accordance with the literature.$^{[4]}$ mp 71-73 °C {Lit.$^{[4]}$ 65-67 °C}; $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.98 (2H, s, C(2)H$_2$), 7.27 (2H, d, J 9.2, C(2'',6'')H), 7.51 (2H,
d, J 8.1, C(2’,6’)H), 7.65 (2H, d, J 8.1, C(3’,5’)H), 8.26 (2H, d, J 9.1, C(3’’,5’’)H); ¹⁹F NMR (471 MHz, CDCl₃) δF: −62.6 (s).
4. Synthesis of pyridinium salts

1-Benzyl-3-cyanopyridin-1-ium bromide (2)

Following general procedure B, using benzyl bromide (5.0 mL, 42 mmol, 1.5 equiv), 3-pyridine carbonitrile (2.9 g, 28 mmol, 1.0 equiv) and MeCN (56 mL, 0.5 M) for 18 h gave the title compound (6.10 g, 79%) as a beige solid with spectroscopic data in accordance with the literature.\textsuperscript{[9]} mp 144-148 °C [Lit.\textsuperscript{[9]} 151-153 °C]; \textsuperscript{1}H NMR (500 MHz, D\textsubscript{2}O) δ: 5.91 (2H, s, CH\textsubscript{2}), 7.38 – 7.60 (5H, m, C(2',6')H, C(3',5')H and C(4')H), 8.26 (1H, app t, J 14.4, C(5)H), 8.93 (1H, d, J 8.2, C(4)H), 9.21 (1H, d, J 6.3, C(6)H), 9.46 (1H, s, C(2)H).

1-Benzyl-3-cyanopyridin-1-ium chloride (7)

1-Benzylpyridin-1-ium bromide 2 (138 mg, 0.5 mmol, 1.0 equiv) and potassium chloride (37 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL, 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (115 mg, quant.) as a beige solid. mp 130-132 °C; ν\textsubscript{max} (solid): 2992 (C-H), 2918 (C-H), 1632, 1493, 1470, 1443, 1206, 1142, 721, 675; \textsuperscript{1}H NMR (500 MHz, DMSO) δ: 5.94 (2H, s, CH\textsubscript{2}), 7.19 – 7.50 (3H, m, C(3',5')H and C(4')H), 7.62 (2H, dd, J 7.3, 2.1, C(2',6')H), 8.38 (1H, dd, J 7.9, 6.4, C(5)H), 9.13 (1H, app dt, J 8.0, 1.2, C(4)H), 9.48 (1H, d, J 6.3, C(6)H), 10.06 (1H, s, C(2)H); \textsuperscript{13}C{\textsuperscript{1}H} NMR (126 MHz, DMSO) δ: 63.9 (CH\textsubscript{2}), 113.3 (C(3)), 113.9 (C(3)CN), 128.9 (C(5)H), 129.2 (C(2',6')H), 129.3 (C(3',5')H), 129.6 (C(4')H), 133.4 (C(1)), 148.1 (C(6)H), 149.0 (C(4)H or C(6)H), 149.1 (C(4)H or C(6)H); HRMS (ESI\textsuperscript{+}) C\textsubscript{13}H\textsubscript{11}N\textsubscript{2} [M–Cl]\textsuperscript{+} found 195.0914, requires 195.0917 (–1.5 ppm).
1-Benzyl-3-cyanopyridin-1-ium hexafluorophosphate(V) (8)

![Structure of compound 8]

1-Benzylpyridin-1-ium bromide 2 (138 mg, 0.5 mmol, 1.0 equiv) and potassium hexafluorophosphate (92 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL, 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (170 mg, quant.) as a peach solid. mp 118-120 °C; νmax (solid): 1502, 1495, 1458, 1447, 1200, 1140, 825 (P-F); 1H NMR (500 MHz, DMSO) δH: 5.87 (2H, s, CH2), 7.35 – 7.52 (3H, m, C(3',5')H and C(4')H), 7.58 (2H, dd, J 7.4, 2.0, C(2',6')H), 8.36 (1H, dd, J 8.0, 6.4, C(5)H), 9.11 (1H, app dt, J 8.1, 1.3, C(4)H), 9.39 (1H, d, J 6.3, C(6)H), 9.97 (1H, s, C(2)H); 19F{1H} NMR (470 MHz, DMSO) δF: -70.1 (d, J 711.3); 13C{1H} NMR (126 MHz, DMSO) δC: 64.2 (CH2), 113.4 (C(3)), 113.9 (C(3)CN), 128.9 (C(5)H), 129.2 (C(2',6')H), 129.2 (C(3',5')H), 129.7 (C(4')H), 133.4 (C(1')), 148.1 (C(6)H), 149.0 (C(2)H), 149.2 (C(4)H); 31P{1H} NMR (202 MHz, DMSO) δP: -144.2 (sept, J 711.3); HRMS (ESI+) C13H11N2[M−PF6]+ found 195.0912, requires 195.0917 (−2.6 ppm).

1-Benzyl-3-cyanopyridin-1-ium tetrafluoroborate (9)

![Structure of compound 9]

1-Benzylpyridin-1-ium bromide 2 (138 mg, 0.5 mmol, 1.0 equiv) and sodium tetrafluoroborate (55 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL, 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (127 mg, 90%) as a white gum. νmax (film): 3088 (ArC-H), 1634, 1497 (ArC=C), 1456, 1206, 1024, 723, 675; 1H NMR (500 MHz, DMSO) δH: 5.88 (2H, s, CH2), 7.41 – 7.51 (3H, m, C(3',5')H and C(4')H),
7.58 (2H, dd, J 7.4, 2.0, C(2',6')H), 8.36 (1H, dd, J 8.0, 6.4, C(5)H), 9.11 (1H, d, J 8.1, C(4)H), 9.40 (1H, d, J 6.3, C(6)H), 9.98 (1H, s, C(2)H); *^1^H NMR (471 MHz, CD$_3$CN) δ: –151.9, –151.8; *^1^H NMR (126 MHz, DMSO) δ: 64.1 (CH$_2$), 113.4 (C(3)), 113.9 (CN), 128.9 (C(5)H), 129.2 (C(2',6')H and C(3',5')H), 129.7 (C(4')H), 133.4 (C(1')H), 141.8 (C(4)H), 149.0 (C(2)H or C(6)H), 149.2 (C(2)H or C(6)H); HRMS (ESI$^+$) C$_{13}$H$_{11}$N$_2$ [M–BF$_4$]$^+$ found 195.0914, requires 195.0917 (–1.5 ppm).

1-Benzyl-3-(ethoxycarbonyl)pyridin-1-ium bromide (16)

Following general procedure B, using benzyl bromide (2.7 mL, 22.5 mmol, 1.5 equiv), ethyl nicotinate (2.0 mL, 5 mmol, 1.0 equiv) and MeCN (30 mL, 0.5 M) for 18 h. Upon completion, the reaction mixture was concentrated in vacuo to give the title compound (4.80 g, quant.) as a beige solid with spectroscopic data in accordance with the literature.$^{[10]}$

mp 140-144 °C {no Lit. mp}; *^1^H NMR (400 MHz, acetone) δH: 1.41 (3H, t, J 7.1, CO$_2$CH$_2$CH$_3$), 4.48 (2H, q, J 7.1, CO$_2$CH$_2$CH$_3$), 6.49 (2H, s, CH$_2$), 7.21 – 7.64 (3H, m, C(3',5')H and C(4')H), 7.87 (2H, dd, J 6.7, 3.0, C(2',6')H), 8.42 (1H, dd, J 7.8, 6.4, C(5)H), 9.12 (1H, app dt, J 8.1, 1.5, C(4)H), 10.01 (1H, s, C(2)H), 10.09 (1H, app dt, J 6.2, 1.2, C(6)H).

3-(Phenylsulfonfonyl)pyridine (S1)

Flame-dried 4 Å molecular sieves, benzenesulfinic acid, sodium salt (3.28 g, 20 mmol, 1.0 equiv), 3-pyridine boronic acid (3.69 g, 30 mmol, 1.5 equiv), copper(II) acetate monohydrate (1.25 g, 6.25 mmol, 1.25 equiv), triethylamine (12.5 mL, 90 mmol, 4.5 equiv), DMSO (100 mL, 0.2 M) and 1,4-dioxane were combined in a flame-dried 500 mL round bottom flask. The flask was sealed, and the reaction was stirred at 65 °C for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with brine (200 mL)
and NH$_4$OH (12 mL), and extracted with EtOAc:CHCl$_3$ (3:1, 3 × 200 mL). The organic layers were combined, wash with brine (100 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude purified by flash column chromatography (0-100% EtOAc in petrol; Rf 0.26 at 60% EtOAc in petrol then 0-8% EtO in CH$_2$Cl$_2$; Rf 0.4 at 10% EtO in CH$_2$Cl$_2$) to give the title compound (1.35 g, 31%) as a white solid with spectroscopic data in accordance with the literature.$^{[11]}$ mp 100-102 °C {Lit.$^{[11]}$ 120-122 °C}; $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$: 7.45 (1H, ddd, $J$ 8.1, 4.9, 0.8, C(5)H), 7.50–7.58 (2H, m, C(3',5')H), 7.58–7.69 (1H, m, C(4')H), 7.90–8.05 (2H, m, C(2',6')H), 8.22 (1H, ddd, $J$ 8.1, 2.3, 1.7, C(4)H), 8.79 (1H, dd, $J$ 4.9, 1.6, C(6)H), 9.15 (1H, d, $J$ 1.8, C(2)H).

1-Benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide (17)

Following general procedure B, using benzyl bromide (0.8 mL, 7.0 mmol, 1.5 equiv), 3-(phenylsulfonyl)pyridine S1 (1.03 g, 4.7 mmol, 1.0 equiv) and MeCN (29 mL, 0.16 M) for 18 h. Upon completion, the reaction mixture was concentrated in vacuo, diluted with Et$_2$O and filtered to give the title compound (1.64 g, 89%) as a peach solid. mp 172-174 °C; $\nu$$_{max}$ (solid): 2995 (C-H), 1489, 1450, 1333 (SO$_2$), 1315, 1176, 1146 (SO$_2$), 1122, 870, 596; $^1$H NMR (500 MHz, DMSO) δ$_H$: 5.99 (2H, s, C$_2$H), 7.40–7.51 (3H, m, C(3',5')H and C(4')H), 7.59 (2H, dd, $J$ 7.5, 1.9, C(2',6')H), 7.74 (2H, t, $J$ 7.8, C(3'',5'')H), 7.83 (1H, t, $J$ 7.5, C(4'')H), 8.14 (2H, dd, $J$ 8.1, 2.3, 1.7, C(4'H), 8.37 (1H, dd, $J$ 8.1, 6.2, C(5)H), 9.17 (1H, d, $J$ 8.6, C(4)H), 9.39 (1H, d, $J$ 6.1, C(6)H), 10.05 (1H, s, C(2)H); $^{13}$C{$^1$H} NMR (126 MHz, DMSO) δ$_C$: 63.9 (CH$_2$), 128.4 (C(2'',6'')H), 129.2 (C(2',6')H), 129.3 (C(3',5')H), 129.6 (C(4')H), 129.9 (C(5)H), 130.2 (C(3'',5'')H), 133.6 (C(1')), 135.4 (C(4'')H), 138.3 (C(1'')), 141.4 (C(3)), 144.5 (C(4)H or C(6)H), 144.6 (C(4)H or C(6)H), 149.0 (C(6)H); HRMS (ESI$^+$) C$_{18}$H$_{16}$NO$_2$S [M−Br]$^+$ found 310.0890, requires 310.0896 (−1.9 ppm).
1-(Naphthal-2'-ylmethyl)-3-(phenylsulfonfyl)pyridin-1-ium bromide (18)

Following general procedure B, using 2-(bromomethyl)naphthalene (332 mg, 1.5 mmol, 1.5 equiv), 3-(phenylsulfonfyl)pyridine S1 (219 mg, 1.0 mmol, 1.0 equiv) and MeCN (6.2 mL, 0.16 M) for 72 h gave, the title compound (346 mg, 78%) as a white solid. mp 142-144 °C; ν\textsubscript{max} (solid): 2986 (C-H), 2901 (C-H), 1634, 1474, 1329 (SO\textsubscript{2}), 1150 (SO\textsubscript{2}), 1126, 1080, 831, 766; \textsuperscript{1}H NMR (500 MHz, DMSO) δ\textsubscript{H}: 6.16 (2H, s, C\textsubscript{H\textsubscript{2}}), 7.51 – 7.62 (2H, m, C(6’\textprime)H and C(7’\textprime)H), 7.66 (1H, d, J 8.5, C(3’\textprime)H), 7.73 (2H, t, J 7.8, C(3’\textprime,5’\textprime)H), 7.83 (1H, t, J 7.4, C(4’\textprime)H), 7.88 – 7.98 (2H, m, C(5’\textprime)H and C(8’\textprime)H), 8.00 (1H, d, J 8.5, C(4)\textprime H), 8.09 – 8.25 (3H, m, C(1’\textprime)H and C(2’,6’\textprime)H), 8.36 (1H, dd, J 8.0, 6.3, C(5)\textprime H), 9.17 (1H, d, J 8.2, C(4)\textprime H), 9.43 (1H, d, J 6.1, C(6)\textprime H), 10.09 (1H, s, C(2)\textprime H); \textsuperscript{13}C{\textsuperscript{1}H} NMR (126 MHz, DMSO) δ\textsubscript{C}: 64.1 (C\textsubscript{H\textsubscript{2}}), 126.1 (C(3)\textprime H), 127.0 (ArCH), 127.3 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.4 (C(2’,6’\textprime)H), 129.0 (ArCH), 129.1 (ArCH), 129.9 (C(5)\textprime H), 130.2 (C(3’\textprime,5’\textprime)H), 130.9 (ArC), 132.7 (ArC), 133.0 (ArC), 135.4 (C(4’\textprime)H), 138.3 (C(1’\textprime)), 141.4 (C(3)), 144.5 (C(4)\textprime H), 144.7 (C(2)\textprime H), 149.1 (C(6)\textprime H); HRMS (ESI+) C\textsubscript{22}H\textsubscript{18}NO\textsubscript{2}S [M−Br]\textsuperscript{+} found 360.1042, requires 360.1053 (−3.0 ppm).

1-(4’-Methoxybenzyl)-3-(phenylsulfonfyl)pyridin-1-ium chloride (19)

Following general procedure B, using 4-methoxybenzyl chloride (0.20 mL, 1.5 mmol, 1.5 equiv), 3-(phenylsulfonfyl)pyridine S1 (219 mg, 1.0 mmol, 1.0 equiv) and MeCN (6.2 mL, 0.16 M) for 72 h gave, after recrystallisation from CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O, the title compound (273 mg, 65%) as a white solid. mp 136-138 °C; ν\textsubscript{max} (solid): 3051 (C-H), 2901 (C-H), 1628, 1610, 1516, 1447, 1337, 1252, 1175 (SO\textsubscript{2}), 1152, 1112, 1014, 868; \textsuperscript{1}H NMR (500 MHz, DMSO) δ\textsubscript{H}: 3.76 (3H, s, OCH\textsubscript{3}), 5.93 (2H, s, CH\textsubscript{2}), 7.00 (2H, d, J 8.6, C(3’\textprime,5’\textprime)H), 7.59 (2H, d, J 8.6, 7...
C(2',6')H), 7.73 (2H, t, J 7.8, C(3',5')H), 7.83 (1H, t, J 7.4, C(4')H), 8.15 (2H, d, J 7.5, C(2,6)H), 8.34 (1H, dd, J 7.9, 6.4, C(5)H), 9.13 (1H, d, J 8.2, C(4)H), 9.40 (1H, d, J 6.1, C(6)H), 10.04 (1H, s, C(2)H); $^{13}$C($^1$H) NMR (126 MHz, DMSO) δc: 55.3 (OCH3), 63.5 (CH2), 114.6 (C(3',5')H), 125.4 (C(1')), 128.4 (C(2',6')H), 129.8 (C(5)H), 130.2 (C(3',5')H), 131.2 (C(2',6')H), 135.4 (C(4')H), 138.3 (C(1'))), 141.3 (C(3)), 144.3 (C(2)H or C(4)H), 144.3 (C(2)H or C(4)H), 148.8 (C(6)H), 160.2 (C(4)); HRMS (ESI+) C19H18NO3S [M–Cl]$^+$ found 340.0991, requires 340.1002 (−3.2 ppm).

1-(3-fluorobenzyl)-3-(phenylsulfonyl)pyridin-1-ium bromide (20)

Following general procedure B, using 3-fluorobenzyl bromide (0.20 mL, 1.5 mmol, 1.5 equiv), 3-(phenylsulfonyl)pyridine S1 (219 mg, 1.0 mmol, 1.0 equiv) and MeCN (6.2 mL, 0.16 M) for 48 h gave, after filtration at room temperature and washing with Et2O, the title compound (280 mg, 67%) as a white solid. mp 158-160 °C; νmax (solid): 2995, 1630, 1582, 1487, 1450, 1427, 1333, 1317, 1244, 1184, 1153, 1121, 1111, 1084, 854, 797, 758; $^1$H NMR (500 MHz, DMSO) δt: 5.99 (2H, s, CH2), 7.29 (1H, app t, J 8.4, C(4')H), 7.44 (1H, d, J 7.6, C(6)H), 7.46 – 7.62 (2H, m, C(2')H and C(5')H), 7.74 (2H, app t, J 7.7, C(3',5')H), 7.83 (1H, app t, J 7.3, C(4')H), 8.14 (2H, d, J 7.8, C(2',6')H), 8.28 – 8.46 (1H, m, C(5)H), 9.17 (1H, d, J 8.2, C(4)H), 9.39 (1H, d, J 5.9, C(6)H), 10.04 (1H, s, C(2)H); $^{19}$F($^1$H) NMR (470 MHz, DMSO) δt: -111.9 (s); $^{13}$C($^1$H) NMR (126 MHz, DMSO) δc: 63.1 (CH2), 116.3 (d, $^2_\text{C-F}$ 22.6, (C(2')H), 116.6 (d, $^2_\text{C-F}$ 20.9, C(4')H), 125.5 (C(6)H), 128.4 (C(2',6')H), 130.0 (C(5)H), 130.3 (C(3',5')H), 131.4 (d, $^3_\text{C-F}$ 8.3, (C(5')H), 135.4 (C(4')H), 135.9 (d, $^3_\text{C-F}$ 8.0, C(1')), 138.4 (C(1'))), 141.5 (C(3)), 144.7 (C(4)H), 144.8 (C(2)H), 149.1 (C(6)H), 162.2 (d, $^1_\text{C-F}$ 244.9, C(3')); HRMS (ESI+) C18H15FNO3S [M–Br]$^+$ found 328.0792, requires 328.0802 (−3.0 ppm).
1-Benzylpyridin-1-ium bromide (21)

Benzyl bromide (2.2 mL, 18.3 mmol, 1.0 equiv) was slowly added to pyridine (1.5 mL, 18.7 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (3 mL, 6.1 M) and the reaction was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo to give the title compound (2.19 g, 48%) as a cream solid with spectroscopic data in accordance with the literature.$^{[12]}$ mp 66-70 °C [Lit.$^{[13]}$ 66-70 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ H: 6.34 (2H, s, C$_H^2$), 7.33 – 7.42 (3H, m, C(3',5')H and C(4')H), 7.63 – 7.72 (2H, m, C(2',6')H), 8.02 (2H, t, J 7.2, C(3,5)H), 8.41 (1H, tt, J 7.9, 1.3, C(4)H), 9.59 (2H, d, J 5.5, C(2,6)H).

1-Benzyl-3-chloropyridin-1-ium bromide (22)

Following general procedure B, using benzyl bromide (1.1 mL, 9 mmol, 1.5 equiv), 3-chloropyridine (0.6 mL, 6 mmol, 1.0 equiv) and MeCN (12 mL, 0.5 M) for 18 h gave, the title compound (1.48 g, 87%) as a beige solid. mp 126-130 °C; ν$_{max}$ (solid): 3003 (C-H), 2930 (C-H), 1620, 1491, 1452, 1206, 1187, 741, 714, 671; $^1$H NMR (400 MHz, CDCl$_3$) δ H: 6.44 (2H, s, CH$_2$), 7.29 – 7.42 (3H, m, C(3',5')H and C(4')H), 7.76 (2H, dd, J 6.7, 2.9, C(2',6')H), 8.09 (1H, dd, J 8.4, 6.1, C(5)H), 8.38 (1H, ddd, J 8.4, 1.8, 1.1, C(4)H), 9.58 – 9.92 (2H, m, C(2)H and C(6)H); $^{13}$C[$^1$H] NMR (101 MHz, CDCl$_3$) δc: 64.2 (CH$_2$), 129.0 (C(5)H), 129.8 (C(3',5')H), 130.0 (C(2',6')H), 130.3 (C(4')H), 132.6 (C(1')), 135.8 (C(3)), 143.9 (C(2)H or C(6)H), 144.0 (C(2)H or C(6)H), 145.2 (C(4)H); HRMS (ESI$^+$) C$_{12}$H$_{11}$ClN [M–Br]$^+$ found 204.0571, requires 204.0575 (−2.0 ppm).
1-Benzyl-3-carbamoylpyridin-1-ium bromide (23)

Following general procedure B, using benzyl bromide (1.8 mL, 15 mmol, 1.5 equiv), nicotinamide (1.22 g, 10 mmol, 1.0 equiv) and MeCN (20 mL, 0.5 M) for 18 h. The reaction mixture was filtered, washing with Et₂O, to give the title compound (2.7 g, 92%) as a white solid with spectroscopic data in accordance with the literature. [9] mp 215-217 °C [Lit.[9] 214-215 °C]; ¹H NMR (400 MHz, D₂O) δ H: 5.87 (2H, s, C₆H₂), 7.48 (5H, s, C(2',6')H, C(3',5')H and C(4')H), 8.16 (1H, dd, J 8.0, 6.3, C(5)H), 8.87 (1H, app dt, J 8.1, 1.4, C(4)H), 9.04 (1H, d, J 6.2, C(6)H), 9.33 (1H, s, C(2)H).

3-cyano-1-methylpyridin-1-ium iodide (24)

Following general procedure B, using methyl iodide (0.9 mL, 15.0 mmol, 1.5 equiv), 3-pyridinecarbonitrile (1.04 g, 10 mmol, 1.0 equiv) and MeCN (20 mL, 0.5 M) for 18 h gave the title compound (376 mg, 15%) as a yellow solid with spectroscopic data in accordance with the literature. [14] mp 196-198 °C (decomp.) [No Lit mp]; ¹H NMR (400 MHz, DMSO) δ H: 4.37 (3H, s, CH₃), 8.34 (1H, dd, J 8.0, 6.4, C(5)H), 9.07 (1H, d, J 8.2, C(4)H), 9.25 (1H, d, J 6.2, C(6)H), 9.74 (1H, s, C(2)H); ¹³C(¹H) NMR (101 MHz, DMSO) δ C: 48.6 (CH₃), 112.1 (C(3)), 113.9 (CN), 128.0 (C(5)H), 148.1 (C(4)H), 149.1 (C(6)H), 149.8 (C(2)H).
5. Synthesis of catalysis products

Optimisation tables 1 and 2 were carried out according to general procedure C.

Table 3 (probing the effect of the counterion) was carried out according to general procedure D.

N-Benzyl-2-(1'''-benzyl-3'''-cyano-1''',4'''-dihydropyridin-4'''-yl)-2-(p-tolyl)acetamide (6)

Following general procedure D, using 4-nitrophenyl 2-(p-tolyl)acetate 1 (81.4 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-cyanopyridin-1-ium bromide 2 (55 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.30 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave the crude product (65%, 90:10 dr). Purification by flash column chromatography (0 to 50% EtOAc in petrol; Rf 0.30 at 40% EtOAc in petrol then 100% Et₂O; Rf 0.70 at 100% Et₂O) gave the title compound (40 mg, 46%, single major diastereoisomer) as a yellow foam. \([\alpha]_D^{20} = -229.6\) (c 0.5, CHCl₃); HPLC: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) \(\tau_r\) (minor): 25.5 min, \(\tau_r\) (major): 31.7 min, 91.9 er; \(v_{\text{max}}\) (film, cm⁻¹) 3312 (C(O)N-H), 2920 (C-H), 2189 (C≡N), 1670 (C=C-N), 1649 (C=O), 1589, 1510, 1412, 1180, 1121, 1028, 729, 696; \(^1\)H NMR (500 MHz, CDCl₃) δH: 2.41 (3H, s, CH₃), 3.71 (1H, d, J 4.1, C(2)H), 4.06 (2H, s, N(1''')CH₂Ph), 4.33 – 4.46 (3H, m, C(4''')H and NHCH₂Ph), 4.99 (1H, dd, J 8.2, 4.2, C(5'''')H), 5.47 – 5.92 (2H, m, C(6'''')H and NH), 6.40 (1H, d, J 1.4, C(2''')H), 6.76 (2H, d, J 6.0, C(2''',6''')H), 7.15 (2H, d, J 7.8, C(3'',5''')H), 7.18 (2H, d, J 7.1, C(2',6')H), 7.21 – 7.33 (8H, m, ArCH); \(^{13}\)C\(^{1}\)H NMR (126 MHz, CDCl₃) δC: 21.4 (CH₃), 37.1 (C(4'')H), 43.8 (NHCH₂Ph), 57.2 (N(1'')CH₂Ph), 57.5 (C(2)H), 80.8 (C(3'')CN), 104.3 (C(5'')H), 121.2 (CN), 126.9 (C(2''')H), 127.5 (C(4')H), 127.8 (C(2')H), 128.0 (C(4''')H), 128.8 (C(3')H), 128.9 (C(3'''')H), 129.2 (C(3''')H), 129.5 (C(6''')H), 130.7 (C(2'')H),
133.0 (C(1’’)), 136.2 (C(1’’’)), 137.2 (C(4’’)), 138.3 (C(1’)), 144.1 (C(2’’’H)), 171.7 (C(1)); \textit{HRMS} (ESI−) \text{C}_{27}H_{27}N_{3}NaO [M+Na]^+ \text{ found 456.2040, requires 456.2046 (~1.3 ppm).}

Ethyl (R)-1-benzyl-4-((R)-2’-(benzamino)-2’-oxo-1’-phenylethyl)-1,4-dihydropyridine-3-carboxylate (25)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{O} \\
\text{N} & \quad \text{NH} \text{Bn} \\
\text{NHBn} & : 4’’’
\end{align*}
\]

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77.2 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(ethoxycarbonyl)pyridin-1-ium bromide 16 (64.4 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 m) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (61%, 90:10 dr). Purification by flash column chromatography (0 to 40% EtOAc in petrol; Rf 0.40 at 40% EtOAc in petrol) gave the title compound (30 mg, 32%, > 95:5 dr) as a yellow gum. \textit{HPLC}: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mL min\(^{-1}\), 211 nm, 30 °C) \text{tr:} 10.2 min and 18.0 min, 50:50 er; \nu_{\text{max}} (film, cm\(^{-1}\)) 3323 (N-H), 3028, 2926 (C-H), 1672 (C(=O)OR), 1651 (C(=O)NH), 1581, 1495, 1452, 1265, 1204, 1163, 1072, 1026, 731, 696; \textit{\textit{1}H NMR} (500 MHz, CDCl\(_3\)) \delta_{\text{H}}: 1.28 (3H, t, \text{J} 7.1, \text{CO}_2\text{CH}^\text{3}\text{H}^\text{3}\text{CH}_3), 3.96 (1H, d, \text{J} 3.6, \text{C}(1’’’H)), 4.06 (2H, s, NCH\text{Ph}), 4.15 – 4.26 (2H, m, CO\text{2}CH\text{3}H\text{3}CH\text{3}), 4.41 (2H, dd, \text{J} 5.7, 2.0, \text{CONHCH}^\text{3}\text{H}^\text{3}\text{Ph}), 4.49 (1H, app t, \text{J} 4.2, C(4’’’)), 5.19 (1H, dd, \text{J} 8.0, 4.8, C(5’’’)), 5.70 (1H, dd, \text{J} 8.2, 1.1, C(6’’’)), 5.77 (1H, t, \text{J} 5.4, NH), 6.69 (2H, dd, \text{J} 6.5, 2.9, C(2’’’),6’’’))H), 7.01 (1H, d, \text{J} 1.6, C(2’’’)), 7.17 – 7.22 (2H, m, C(2’’’),6’’’))H), 7.22 – 7.33 (11H, m, ArCH); \textit{\textit{1}C\text{\textsuperscript{13}H} NMR} (126 MHz, CDCl\(_3\)) \delta_{c}: 14.7 (CO\text{2}CH\text{3}H\text{3}CH\text{3}), 36.9 (C(4’’’)), 43.6 (CONHCH\text{3}H\text{3}Ph), 56.9 (C(1’’’)), 57.4 (NCH\text{Ph}), 59.7 (CO\text{2}CH\text{3}H\text{3}CH\text{3}), 98.5 (C(3’’’)), 105.9 (C(5’’’)), 126.9 (C(2’’’),6’’’))H), 127.1 (ArCH), 127.4 (ArCH), 127.7 (C(4’’’)), 127.8 (2 ArCH), 127.9 (2 ArCH), 128.7 (2 ArCH), 128.9 (2 ArCH), 129.5 (C(6’’’)), 130.9 (C(2’’’),6’’’))H), 136.8 (C(1’’’)), 137.2 (C(1’’’)), 138.6 (C(1’’’)), 143.0 (C(2’’’)),
168.2 (CO$_2$Et), 172.6 (CONH); HRMS (ESI$^+$) C$_{30}$H$_{20}$N$_2$O$_3$ [M−H]$^+$ found 465.2161, requires 465.2184 (−4.9 ppm).

(R)-N-Benzyl-2-((R)-1″-benzyl-3″-(phenylsulfonyl)-1″,4″-dihydropyridin-4″-yl)-2-phenylacetamide (26)

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 m) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (71%, 90:10 dr). Purification by flash column chromatography (0 to 5% EtO in CH$_2$Cl$_2$; R$_f$ 0.35 at 5% EtO in CH$_2$Cl$_2$) gave the title compound (62 mg, 58%, 95:5 dr) as a white foam. [α]$^0_{D}$ = +471 (c 1.0, CHCl$_3$); HPLC: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C) tr (major): 12.2 min, tr (minor): 14.6 min, 94:6 er; ν$_{max}$ (film, cm$^{-1}$) 3360 (N−H), 1666 (C=O), 1582, 1510 (C=C), 1495, 1281, 1136 (SO$_2$), 1086 (SO$_2$), 723, 688, 594; $^1$H NMR (500 MHz, CDCl$_3$) δH: 4.01 (2H, s, N(1″)CH$_2$Ph), 4.17 (1H, dd, J 5.0, 3.1, C(4′″)H), 4.29 – 4.49 (3H, m, C(2)H and NHCH$_2$Ph), 5.09 (1H, dd, J 7.9, 5.1, C(5′″)H), 5.56 – 5.76 (2H, m, NH and C(6′″)H), 6.64 (2H, dd, J 7.6, 1.6, C(2″′,6″′)H), 7.08 (1H, d, J 1.2, C(2″′)H), 7.17 (2H, d, J 6.9, C(2′,6′)H), 7.20 – 7.27 (4H, m, C(3″′,5″′)H and 2 ArCH), 7.26 – 7.30 (4H, m, C(3′,5′)H and 2 ArCH), 7.30 – 7.34 (1H, m, C(4″)H), 7.34 – 7.41 (2H, m, C(2″,6″)H), 7.52 (2H, t, J 7.5, C(3″′,5″′)H), 7.57 – 7.62 (1H, m, C(4″″)H), 7.85 – 7.94 (2H, m, C(2″″,6″″)H); $^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$) δC: 36.2 (C(4″)H), 43.6 (NHCH$_2$Ph), 57.2 (C(2)H), 57.5 (N(1″)CH$_2$Ph), 105.3 (C(5″)H), 105.5 (C(3″)), 127.0 (C(2″″,6″″)H), 127.4 (ArCH), 127.5 (ArCH), 127.5 (C(2″″,6″″)H), 127.7 (C(2′,6′)H), 127.9 (2 ArCH), 128.7 (2 ArCH), 128.9 (2 ArCH), 129.2 (C(3″″,5″″)H), 129.8 (C(6″″)H), 131.5 (C(2′,6′)H), 132.7 (C(4″″)H), 135.9 (C(1″″)), 136.2 (C(1″)), 138.4 (C(1″′)),
Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77.2 mg, 0.30 mmol, 1.5 equiv), 1-(naphthalen-2-ylmethyl)-3-(phenylsulfonyl)pyridin-1-ium bromide 18 (88.1 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 m) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (72%, 90:10 dr). Purification by flash column chromatography (0 to 5.5% EtO in CH2Cl2; Rf 0.32 at 5% EtO in CH2Cl2) gave the title compound (70 mg, 60%, 95:5 dr) as a yellow/white foam. [α]D 200 −417 (c 0.5, CHCl3); HPLC: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tr (major): 16.8 min, tr (minor): 20.8 min, 94:6 er; νmax (film, cm⁻¹): 3343 (C(O)N), 3055, 1664, 1584, 1508, 1414, 1279, 1134 (SO₂).

NMR (500 MHz, CDCl3) δH: 4.16 (2H, s, N(1″)CH4H3), 4.18 – 4.24 (1H, m, C(4″)H), 4.37 – 4.45 (3H, m, NCH4H3Ph and C(2)H), 5.12 (1H, dd, J 7.8, 5.2, C(5″)H), 5.65 – 5.86 (2H, m, C(6″)H and NH), 6.74 (1H, d, J 8.4, C(3″)H), 7.19 (3H, app d, J 8.7, C(2′,6′)H and C(2″)H), 7.22 – 7.34 (6H, m, C(3′,5′)H, C(4′)H, C(3″,5″)H and C(4″)H), 7.35 – 7.41 (3H, m, C(2″,6″)H and C(1″)H), 7.49 – 7.57 (4H, m, C(6″)H, C(7″)H and C(3″,5″,5‴)H), 7.61 (1H, t, J 7.3, C(4‴)H), 7.75 (1H, d, J 8.5, C(4″″)H), 7.76 – 7.80 (1H, m, C(8″″)H), 7.82 – 7.89 (1H, m, C(5″″)H), 7.94 (2H, d, J 7.7, C(2‴″,6‴″)H); 13C{1H} NMR (126 MHz, CDCl3) δC: 36.2 (C(4‴″)H), 43.5 (NCH4H3Ph), 57.2 (C(2)H), 57.7 (N(1″)CH4H3), 105.3 (C(5)H), 105.6 (C(3)), 125.0 (C(3‴″)H), 126.4 (ArCH), 126.5 (ArCH), 126.6 (ArCH), 127.4 (ArCH), 127.4 (ArCH), 127.5 (C(2‴″,6‴″)H), 127.6 (C(2′,6′)H), 127.8 (2 ArCH and ArCH), 127.9 (ArCH), 128.7
(C(3',5')H), 129.0 (C(4'')H), 129.2 (C(3''',5''')H), 129.7 (C(6'')H), 131.4 (C(2',6'')H), 132.7 (C(4''')H), 133.0 (C(4''')H), 143.2 (C(2''')H), 143.2 (C(2''')H), 136.1 (C(1''')), 138.3 (C(1'')), 141.0 (C(1'''')), 142.8 (C(2''')H), 172.5 (C(1)=O); HRMS (ESI) C_{37}H_{26}N_{2}NaO_{3}S [M+Na]^+ found 607.2012, requires 607.2026 (−2.3 ppm).

(R)-N-Benzyl-2-((R)-1''''-(4''''-methoxybenzyl)-3''''-(phenylsulfonyl)-1''''-4''''-dihydropyridin-4''''-yl)-2-phenylacetamide (28)

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77.2 mg, 0.30 mmol, 1.5 equiv), 1-(4-methoxybenzyl)-3-(phenylsulfonyl)pyridin-1-ium chloride 19 (84.1 mg, 0.20 mmol. 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (71%, 90:10 dr). Purification by flash column chromatography (0 to 7.5% EtO in CH_{2}Cl_{2}; Rf 0.33 at 7% EtO in CH_{2}Cl_{2}) gave the title compound (73 mg, 65%, 94:6 dr) as a yellow/white foam. [α]_{D}^{20} =423 (c 0.5, CHCl_{3}); HPLC: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) t_{R} (major): 14.8 min, t_{R} (minor): 17.4 min, 91:9 er; v_{max} (film, cm^{-1}) 3346 (C(O)N-H), 1664, 1582, 1510, 1414, 1281, 1246, 1134, 1086, 1026; ^{1}H NMR (400 MHz, CDCl_{3}) δH: 3.81 (3H, s, OCH_{3}), 3.93 (2H, s, N(1''')CH_{2}Ph), 4.16 (1H, dd, J 5.1, 3.1, C(4'')H), 4.33 – 4.43 (3H, m, C(2)H and CH{^3}HPh), 5.08 (1H, dd, J 7.9, 5.1, C(5'')H), 5.64 (1H, dd, J 7.9, 1.3, C(6'')H), 5.69 (1H, app t, J 5.7, NH), 6.58 (2H, d, J 8.7, C(2''',6''')H), 6.76 (2H, d, J 8.7, C(3''',5''')H), 7.06 (1H, d, J 1.1, C(2''')H), 7.11 – 7.19 (2H, m, C(2',6')H), 7.21 – 7.34 (6H, m, C(4')H, C(3',5')H and C(4')H), 7.34 – 7.40 (2H, m, C(2',6')H), 7.51 (2H, t, J 7.4, C(3''',5''')H), 7.54 – 7.61 (1H, m, C(4''')H), 7.84 – 7.94 (2H, m, C(2''',6''')H); ^{13}C{^{1}H} NMR (101 MHz, CDCl_{3}) δC: 36.3 (C(4''))H), 43.6 (CH{^3}HPh), 55.4 (OCH_{3}), 56.9 (N(1)CH_{2}Ph), 57.2 (C(2)H), 105.1 (C(5'')H), 105.2 (C(3'')), 127.3 (ArCH), 127.4 (ArCH), 127.4 (2 ArCH), 127.6
Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77.2 mg, 0.30 mmol, 1.5 equiv), 1-(3-fluorobenzyl)-3-(phenylsulfonyl)pyridin-1-ium bromide 20 (81.6 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5 equiv) for 24 h at 0 °C, gave crude product (57%, 90:10 dr). Purification by flash column chromatography (0 to 3.5% EtO in CH2Cl2; Rf 0.38 at 3% EtO in CH2Cl2 then 10 to 45% EtOAc in petrol; Rf 0.30 at 40% EtOAc in petrol) gave the title compound (34 mg, 31%, > 95:5 dr) as a pale yellow foam. [α]D20 +483 (c 0.5, CHCl3).

**HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tr (major): 14.5 min, tr (minor): 18.9 min, 93:7 er; νmax (film, cm⁻¹) 3350 (N-H), 3061, 2963, 1688 (C=O), 1587, 1533, 1447, 1412, 1287, 1211, 1140, 1088, 1043, 1022; ¹H NMR (500 MHz, CDCl3) δH: 4.00 (2H, s, N(1")CH2Ar), 4.16 (1H, dd, J 5.0, 3.1, C(4'")H), 4.33 – 4.51 (3H, m, NCH2Ph and C(2)H), 5.11 (1H, dd, J 7.9, 5.1, C(5'")H), 5.50 – 5.74 (2H, m, NH and C(6'")H), 6.36 – 6.47 (2H, m, C(2'")H and C(6'")H), 6.95 (1H, td, J 8.3, 2.1, C(4'")H), 7.06 (1H, d, J 1.3, C(2'")H), 7.15 – 7.19 (2H, m, C(2',6')H), 7.19 – 7.33 (7H, m, C(3',5')H, C(4')H, C(3',5')H, C(4')H and C(5'")H), 7.32 – 7.38 (2H, m, C(2',6')H), 7.53 (2H, app t, J 7.5, C(3'",5'"")H), 7.56 – 7.63 (1H, m, C(4'")H), 7.86 – 7.95 (2H, m, C(2'",6'"")H); ¹9F[¹H] NMR (470 MHz, CDCl3) δF: -111.9 (s); ¹3C[¹H] NMR (126 MHz, CDCl3) δC: 36.1 (C(4'")H), 43.6 (NCH2Ph),
57.0 (C(2)H and N(1")CH_{2}Ar), 105.5 (C(5")H), 106.1 (C(3")H), 114.1 (d, J_{CF} 21.7, C(2""')H),
115.1 (d, J_{CF} 21.2, C(4""')H), 122.7 (d, J_{CF} 2.8, C(6""')H), 127.5 (C(4')H), 127.5 (C(2""",6"""')H),
127.7 (C(2',6')H and C(4')H), 127.9 (C(3',5')H or C(3",5")H), 128.7 (C(3',5')H or C(3",5")H),
129.2 (C(3""",5"""')H), 129.7 (C(6")H), 130.6 (d, J_{CF} 8.3, C(5""')H), 131.5 (C(2',6")H), 132.8
(C(4""')H), 136.0 (C(1")H), 138.3 (d, J_{CF} 6.9, C(1""')H), 140.8 (C(1"""')H), 142.7
(C(2""')H), 163.0 (d, J_{CF} 247.4, C(3""')F), 172.5 (C(1)=O). \textbf{HRMS} (ESI+) C_{30}H_{29}FN_{2}NaO_{3}S
[M+Na]^+ found 575.1775, requires 575.1781 (-1.0 ppm).

(R)-N-Benzyl-2-((R)-1""'-benzyl-3""''-(phenylsulfonyl)-1""",4"""'-dihydropyridin-4""'"'-yl)-2-
(naphthalen-2""-yl)acetamide (30)

Following general procedure D, using 4-nitrophenyl 2-(naphthalen-2-yl)acetate 11 (92 mg,
0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg,
0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg,
0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL,
1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (71%, 95:5 dr). Purification by
flash column chromatography (0 to 4.5% Et{sub}2O in CH{sub}2Cl{sub}2; R{sub}f 0.31 at 4% Et{sub}2O in CH{sub}2Cl{sub}2)
gave the title compound (82 mg, 70%, > 95:5 dr) as a pale yellow solid. mp 70-74 °C; [α]{sub}D{sup}20
−457 (c 1.0, CHCl{sub}3); \textbf{HPLC}: Chiralpak AS-H, (80:20 hexane:IPA, flow rate 1.0 mLmin{−1},
211 nm, 30 °C) tr (minor): 22.4 min, tr (major): 40.7 min, 90:10 er; v_{max} (solid, cm{−1}) 3329 (N-
H), 3059, 1666, 1659, 1584, 1506, 1418, 1281, 1217, 1136 (SO{sub}2), 1085, 721, 688; \textbf{1H NMR}
(500 MHz, CDCl{sub}3) δ{sub}H: 3.91 (2H, s, N(1)CH{sub}2}Ph), 4.25 (1H, dd, J 5.0, 2.9, C(4")H), 4.33 – 4.50
(2H, m, NHCH{sub}2{sub}NHPh), 4.59 (1H, d, J 2.9, C(2)H), 5.20 (1H, dd, J 7.9, 5.1, C(5")H), 5.63 (1H,
dd, J 8.0, 1.3, C(6")H), 5.70 (1H, app t, J 5.8, NH), 6.29 (2H, d, J 7.3, C(2""",6"""')H), 6.74 (2H,
t, J 7.8, C(3""",5"""')H), 6.99 – 7.08 (2H, m, C(4""')H and C(2")H), 7.14 – 7.18 (2H, m, C(2',6')H),
7.20 – 7.29 (3H, m, C(3',5')H and C(4')H), 7.47 – 7.57 (5H, m, C(1")H, C(3")H, C(3""",5""""')H)
and 1 ArCH), 7.58 – 7.63 (1H, m, C(4'')H), 7.73 (1H, d, J 8.5, C(4'')H), 7.81 – 7.86 (2H, m, 2 ArCH), 7.88 (1H, d, J 7.7, 1 ArCH), 7.91 – 7.95 (2H, m, C(2'',6'')H); \(^{13}\)C(^{1}H) NMR (126 MHz, CDCl\(_{3}\)) δc: 36.3 (C(4'')H), 43.6 (NH\(^{1}\)H=Ph), 57.2 (C(2)H), 57.4 (N(1)CH=Ph), 105.4 (C(5'')H), 105.5 (C(3'')H), 126.1 (2 ArCH), 126.6 (C(2'',6'')H), 127.2 (C(4'')H), 127.5 (1 ArCH), 127.5 (C(2'',6'')H), 127.7 (2 ArCH), 127.7 (1 ArCH), 127.8 (1 ArCH), 128.4 (1 ArCH), 128.6 (C(3'',5'')H), 128.7 (2 ArCH), 129.2 (3 ArCH), 129.9 (C(6'')H), 130.7 (1 ArCH), 132.8 (C(4''')H), 132.8 (1 ArC), 133.2 (1 ArC), 133.9 (C(1'')), 135.5 (C(1''')), 138.3 (C(1'))), 140.9 (C(1''')), 142.9 (C(2')H), 172.6 (C(1)=O); HRMS (ESI) \(\text{C}_{27}\text{H}_{32}\text{N}_{2}\text{NaO}_{6}\text{S} [\text{M+Na}]^{+}\) found 607.2023, requires 607.2026 (−0.5 ppm).

(R)-N-Benzyl-2-((R)-1''-benzyl-3''-(phenylsulfonfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(4''-tolyl)acetamide (31)

Following general procedure D, using 4-nitrophenyl 2-(p-tolyl)acetate 1 (81.4 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (65%, 80:20 dr). Purification by flash column chromatography (0 to 5.5% EtO in CH\(_2\)Cl\(_2\); R\(_f\) 0.40 at 5% EtO in CH\(_2\)Cl\(_2\)) gave the title compound (59 mg, 54%, 95:5 dr) as a pale yellow solid. mp 160-162 °C; \([\alpha]^{20}_{D}\) −449 (c 1.0, CHCl\(_{3}\)); HPLC: Chiralpak IB, (85:15 hexane: IPA, flow rate 1.0 mLmin\(^{-1}\), 220 nm, 30 °C) \(t_\text{r}\) (major): 17.6 min, \(t_\text{r}\) (minor): 20.3 min, 98:2 er; \(\nu_{\text{max}}\) (solid, cm\(^{-1}\)) 3346 (CON-H), 2999 (C-H), 1661 (C=O), 1584, 1543, 1419, 1271, 1134 (SO\(_2\)), 1084, 723, 590; \(^{1}\)H NMR (500 MHz, CDCl\(_{3}\)) δ: 2.40 (3H, s, CH\(_{3}\)), 4.04 (2H, s, NCH=Ph), 4.16 (1H, dd, J 4.8, 3.2, C(4'')H), 4.34 – 4.43 (3H, m, C(2)H and CONHCH\(^{1}\)H=Ph), 5.07 (1H, dd, J 7.9, 5.1, C(5'')H), 5.60 – 5.73 (2H, m, NH and C(6'')H), 6.68 (2H, d, J 6.6, C(2'',6'''')H), 7.08 (1H, s, C(2'')H),
7.10 (2H, d, J 7.9, C(3',5')H), 7.17 (2H, d, J 7.1, C(2',6')H), 7.20 – 7.33 (8H, m, C(4')H, C(2',6')H, C(3',5')H C(4'')H and C(3',5')H), 7.52 (2H, t, J 7.6, C(3',5')H), 7.58 (1H, t, J 7.4, C(4'')H), 7.82 – 7.94 (2H, m, C(2'',6''))H); 1H NMR (126 MHz, CDCl3) δ: 21.5 (CH3), 36.1 (C(4'')H), 43.6 (CONHCH4HPh), 56.8 (C(2)H), 57.4 (NCH2Ph), 105.3 (C(5')H), 105.7 (C(3'')), 127.1 (C(2'',6'')H), 127.4 (C(4')H), 127.5 (C(2'',6'')H), 127.7 (C(2',6')H), 127.9 (C(4'')H), 128.7 (C(3',5'')H and 2 ArCH), 128.8 (2 ArCH), 129.2 (C(3''',5'''')H), 129.8 (C(6'')H), 131.4 (C(2',6')H), 132.7 (C(4''')H), 133.2 (C(1'')), 135.9 (C(1''')), 136.8 (C(4'')), 138.4 (C(1')), 141.0 (C(1''')), 142.8 (C(2'')H), 172.8 (C=O); HRMS (ESI+) C34H32N4NaO3S [M+Na]+ found 571.2019, requires 571.2026 (−1.2 ppm).

(R)-N-Benzyl-2-((R)-1''-benzyl-3''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(4'''-methoxyphenyl)acetamide (32)

Following general procedure D, using 4-nitrophenyl 2-(4-methoxyphenyl)acetate 12 (86.2 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 µL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (73%, 85:15 dr). Purification by flash column chromatography (0 to 5.5% EtO in CH2Cl2; Rf 0.36 at 6% EtO in CH2Cl2) gave the title compound (33 mg, 29%, > 95:5 dr) as a beige foam. \([\alpha]_D^{19} -200 (c 0.5, CHCl_3); \text{HPLC: Chiralpak IB, (90:10 hexane: IPA, flow rate 0.5 mLmin}^{-1}, 211 \text{nm, } 30 \text{ °C}) \text{ ts (major): 79.4 min, ts (minor): 87.9 min, 98.2 er; } \nu_{\text{max}} \text{ (film, cm}^{-1}) 3348 \text{ (CON-H), 2959, 2932, 1668, 1653, 1584, 1508, 1452, 1418, 1283, 1246, 1176, 1136 (SO_2), 1086, 1028;} \text{H NMR (500 MHz, CDCl}_3) \delta: 3.84 (3H, s, OCH_3), 4.06 (2H, s, N(1'')CH_2), 4.13 – 4.17 (1H, m, C(4'')H), 4.37 (1H, d, J 3.1, C(2)H), 4.39 (2H, d, J 5.8, NCH2Ph), 5.06 (1H, dd, J 7.9, 5.0, C(5'')H), 5.59 – 5.71 (2H, m, NH and C(6'')H), 6.60 – 6.68 (2H, m, C(2'',6''')H), 6.82
(2H, d, J 8.5, C(3',5')H), 7.09 (1H, s, C(2'')H), 7.17 (2H, d, J 7.4, C(2',6')H), 7.20 – 7.34 (8H, m, C(3',5')H, C(4')H, C(2'',6'')H, C(3''',5''')H and C(4'''')H), 7.52 (2H, t, J 7.6, C(3''',5''')H), 7.59 (1H, t, J 7.4, C(4'''')H), 7.90 (2H, d, J 7.7, C(2''',6''') H); 13C(1H) NMR (126 MHz, CDCl3) δ: 36.2 (C(4'')H), 43.6 (NCH2Ph), 55.3 (OCH3), 56.3 (C(2)H), 57.6 (N(1'')CH2Ph), 105.3 (C(5'')H), 105.6 (C(3'')H), 113.5 (C(3'',5'')H), 127.0 (C(2'',6''')H), 127.5 (C(4')H), 127.5 (2 ArCH), 127.7 (2 ArCH), 128.0 (C(4''')H), 128.2 (C(1'')), 128.7 (2 ArCH), 128.8 (2 ArCH), 129.2 (C(3''',5''''')H), 129.8 (C(6'')H), 132.6 (C(2'',6'')H), 132.8 (C(4''''')H), 136.0 (C(1''''')), 138.4 (C(1'')), 141.0 (C(1''''')), 142.9 (C(2''')H), 159.0 (C(4'')), 172.9 (C(1)=O); HRMS (ESI+) C33H32N2NaO4S [M+Na]+ found 587.1965, requires 587.1975 (~1.7 ppm).

(R)-N-Benzyl-2-((R)-1'''-benzyl-3''''-(phenylsulfonyl)-1''',4''''-dihydropyridin-4''''-yl)-2-(3'',4''''-dimethoxyphenyl)acetamide (33)

Following general procedure D, using 4-nitrophenyl 2-(3,4-dimethoxyphenyl)acetate 13 (95 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (65%, 90:10 dr). Purification by flash column chromatography (0 to 8.5% EtO in CH2Cl2; Rf 0.33 at 8% EtO in CH2Cl2) gave the title compound (65 mg, 55%, > 95:5 dr) as a white solid.

mp 122-124 °C; [α]D 0 -470 (c 1.0, CHCl3); HPLC: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tR (major): 31.2 min, tR (minor): 44.3 min, 96:4 er; νmax (solid, cm⁻¹) 3372 (C(O)N-H), 3063, 2924 (C-H), 1666 (C=O), 1582, 1516, 1454, 1422, 1273, 1260, 1234, 1155, 1132, 1086, 1022, 772; 1H NMR (500 MHz, CDCl3) δH: 3.68 (3H, s, C(3'')OCH3), 3.90 (3H, s, C(4''')OCH3), 4.08 (2H, s, N(1'')CH2Ph), 4.15 (1H, dd, J 4.9, 3.2,
C(4")H), 4.32 (1H, dd, J 14.9, 5.6, NCH\textsubscript{3}H\textsubscript{3}Ph), 4.38 (1H, d, J 3.1, C(2)H), 4.46 (1H, dd, J 14.9, 6.2, NCH\textsubscript{3}H\textsubscript{3}Ph), 5.10 (1H, dd, J 7.9, 5.0, C(5")H), 5.67 (1H, dd, J 8.0, 1.2, C(6")H), 5.77 (1H, app t, J 5.7, NH), 6.66 (2H, dd, J 6.5, 2.8, C(2",6")H), 6.78 (1H, d, J 8.2, C(5")H), 6.87 (1H, d, J 2.0, C(2")H), 6.95 (1H, dd, J 8.2, 2.0, C(6")H), 7.10 (1H, d, J 1.4, C(2")H), 7.13 – 7.20 (2H, m, C(2",6")H), 7.21 – 7.32 (6H, m, C(3",5")H, C(4")H, C(3",,5")H and C(4")H), 7.52 (2H, t, J 7.5, C(3",,5")H), 7.56 – 7.62 (1H, m, C(4")H), 7.80 – 7.93 (2H, m, C(2",6")H); \textsuperscript{13}C{[H]}

NMR (126 MHz, CDCl\textsubscript{3}) \textit{δ}: 36.2 (C(1")H), 43.5 (NCH\textsubscript{3}H\textsubscript{3}Ph), 55.8 (OCH\textsubscript{3}), 55.8 (OCH\textsubscript{3}), 56.7 (C(2)H), 57.6 (N(1")CH\textsubscript{2}Ph), 105.5 (C(5")H), 105.7 (C(3")H), 110.5 (C(5")H), 114.2 (C(2")H), 124.1 (C(6")H), 126.8 (C(2",6")H), 127.4 (C(2",6")H), 127.5 (C(4")H), 127.7 (C(2",6")H), 128.0 (C(4")H), 128.6 (C(1")H), 128.7 (C(3",5")H or C(3",,5")H), 128.9 (C(3",5")H or C(3",,5")H), 129.2 (C(3",,5")H), 129.7 (C(6")H), 132.7 (C(4")H), 135.9 (C(1")H), 138.5 (C(1")H), 140.9 (C(1")H), 142.9 (C(2")H), 148.1 (C(3")OCH\textsubscript{3}), 148.4 (C(4")OCH\textsubscript{3}), 172.7 (C(1)=O); HRMS (ESI\textsuperscript{+}) C\textsubscript{33}H\textsubscript{34}N\textsubscript{2}NaO\textsubscript{5}S [M+Na]\textsuperscript{+} found 617.2071, requires 617.2081 (-1.6 ppm).

(R)-N-Benzyl-2-((R)-1"-benzyl-3"-(phenylsulfonyl)-1",4"-dihydropyridin-4"-yl)-2-(thiophen-3"-yl)acetamide (34)

Following general procedure D, using 4-nitrophenyl 2-(thiophen-3-yl)acetate 14 (79 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzyamine (109 µL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (57%, 90:10 dr). Purification by flash column chromatography (0 to 5% Et\textsubscript{3}O in CH\textsubscript{2}Cl\textsubscript{2}; R\textsubscript{f} 0.35 at 5% Et\textsubscript{3}O in CH\textsubscript{2}Cl\textsubscript{2}) gave the title compound (54 mg, 50%, 93:7 dr) as a white foam. [\textalpha]\textsubscript{d}\textsubscript{20} = 399 (c 1.0, CHCl\textsubscript{3}); HPLC: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin\textsuperscript{−1}, 211 nm, 30 °C) t\textsubscript{R} (major):
15.4 min, tr (minor): 19.4 min, 89:11 er; v_max (film, cm⁻¹) 3362 (N-H), 1666 (C=O), 1585, 1526 (Ar=C=C), 1450, 1418, 1283, 1136 (SO₂); ¹H NMR (500 MHz, CDCl₃) δ: 3.93 – 4.21 (3H, m, N(1'')CH₂Ph and C(4'')H), 4.40 (2H, dd, J 5.8, 2.2, NHCH₃⁺Ph), 4.53 (1H, d, J 3.3, C(2)H), 5.01 (1H, dd, J 7.9, 5.0, C(5'')H), 5.72 (1H, dd, J 8.0, 1.3, C(6'')H), 5.83 (1H, app t, J 5.6, NH), 6.84 (2H, dd, J 7.1, 2.2, C(2'''',6'')H), 7.07 (1H, dd, J 4.9, 1.2, C(4')H), 7.12 (1H, d, J 1.4, C(2'')H), 7.15 – 7.21 (3H, m, C(2',6')H and C(5')H), 7.22 – 7.25 (1H, m, C(4')H), 7.27 – 7.35 (6H, m, C(3',5')H, C(2')H, C(3''',5''')H and C(4''')H), 7.52 (2H, t, J 7.6, C(3'''',5''')H), 7.55 – 7.62 (1H, m, C(4''')H), 7.85 – 7.91 (2H, m, C(2''''',6''''')H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 36.1 (C(4''')H), 43.6 (NHCH₃⁺Ph), 53.0 (C(2)H), 57.6 (N(1)CH₂Ph), 105.1 (C(5'')H), 106.0 (C(3''))), 124.7 (C(5')H), 125.8 (C(2')H), 127.2 (C(2''''',6''''')H), 127.5 (C(2''''',6''''')H), 127.6 (C(2',6')H), 128.1 (C(4')H), 128.8 (2 ArCH), 129.0 (2 ArCH), 129.2 (2 ArCH), 129.8 (C(4')H or C(6''')H), 129.8 (C(4')H or C(6''')H), 132.8 (C(4''')H), 136.0 (C(1''))), 136.4 (C(3'')), 138.4 (C(1')), 140.9 (C(1'''')), 142.6 (C(2')H), 171.9 (C(1)=O); HRMS (ESI⁺) C₅₁H₃₆N₁₃NaO₈S₂ [M+Na]⁺ found 563.1425, requires 563.1434 (−1.6 ppm).

(R)-N-Benzyl-2-((R)-1''''-benzyl-3''-(phenylsulfonfonyl)-1''''',4''''-dihydropyridin-4''''-yl)-2-(4''''-(trifluoromethyl)phenyl)acetamide (35)

Following general procedure D, using 4-nitrophenyl 2-(4-(trifluoromethyl)phenyl)acetate 15 (98 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 µL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (68%, 90:10 dr). Purification by flash column chromatography (0 to 3.5% Et₂O in CH₂Cl₂; Rf 0.32 at 3% Et₂O in CH₂Cl₂) gave the title compound (59 mg, 49%, > 95:5 dr) as a pale yellow solid. mp 62-64 (decomp) then 160-162 °C; HPLC: Chiralpak AS-H, (85:15 hexane: IPA, 0.5 mL/min, 254 nm, 10°C, 100% Et₂O, 5 min, 98.5:1.5 then 95:5 to 90:10 over 10 min, then 90:10 to 100% Et₂O over 5 min, then 100% Et₂O, 10 min, 30°C, 100% Et₂O, 15 min, 100% Et₂O, 15 ml).
flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (minor): 13.1 min, tᵣ (major): 30.0 min, 52:48 er; νmax (solid, cm⁻¹) 3343 (N-H), 1666 (C=O), 1582, 1531, 1418, 1323 (SO₂), 1136 (SO₂), 1111 (C-F), 1086, 1067, 723, 688, 590; ¹H NMR (500 MHz, CDCl₃) δH: 4.00 (2H, s, N(1)CH₂Ph), 4.13 (1H, dd, J 5.0, 3.0, C(4'')H), 4.31 – 4.44 (2H, m, NHCH₃H₂Ph), 4.45 (1H, d, J 3.0, C(2)H), 5.11 (1H, dd, J 7.9, 5.1, C(5'')H), 5.55 – 5.77 (2H, m, NH and C(6'')H), 6.69 (2H, dd, J 7.8, 1.5, C(2'',6''')H), 7.09 (1H, d, J 1.3, C(2'')H), 7.16 – 7.20 (2H, m, C(2',6')H), 7.22 – 7.34 (6H, m, C(3',5')H, C(4')H, C(3'',5''')H and C(4''')H), 7.47 – 7.57 (6H, m, C(2'',6'')H, C(3'',5'')H and C(3''',5''')H), 7.58 – 7.64 (1H, m, C(4''')H), 7.88 (2H, dd, J 8.3, 1.2, C(2''',6''''')H); ¹³F{¹H} NMR (471 MHz, CDCl₃) δF: -62.1; ¹³C{¹H} NMR (126 MHz, CDCl₃) δC: 36.7 (C(4'')H), 43.7 (NHCH₃H₂Ph), 56.9 (C(2)H), 57.5 (N(1)CH₂Ph), 104.8 (C(5'')H), 105.3 (C(3'')H), 124.4 (q, J₁C-F 272.1, CF₃), 124.7 (app d, J₁C-F 3.6, C(3'',5'')H), 127.2 (C(2''',6''''')H), 127.5 (C(2'''',6''''')H), 127.6 (C(4')H), 127.7 (C(2',6')H), 128.3 (C(4''')H), 128.8 (C(3',5')H or C(3'',5''')H), 129.0 (C(3',5')H or C(3'',5''')H), 129.3 (C(3'',5''')H), 129.5 (app d, J₁C-F 32.3, C(4'')), 129.9 (C(6''')H), 131.7 (C(2'',6'')H), 132.9 (C(4''''')H), 135.4 (C(1'')H), 138.1 (C(1'H)), 140.4 (C(1''H)), 140.7 (C(1''''')H), 142.8 (C(2''''')H), 171.7 (C(1)=O); HRMS (ESI⁺) C₃₉H₃₉F₃N₄O₃S [M+H]⁺ found 601.1787, requires 601.1778 (+1.4 ppm).

(R)-2-((S)-1''-[Benzy]-3''-(phenylsulfonyl)-1''''4''''-dihydropyridin-4''''-yl)-2-phenyl-1-(pyrrolidin-1'-yl)ethan-1-one (36)

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-iium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then pyrrolidine (84 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (67%, 90:10 dr). Purification by flash column chromatography (0 to 15% Et₂O in CH₂Cl₂; Rf 0.27 at 10% Et₂O in CH₂Cl₂)
gave the title compound (62 mg, 62%, 95:5 dr) as a white foam. \([\alpha]_D^{20} = -614 (c 1.0, \text{CHCl}_3)\).

**HPLC:** Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mL/min, 211 nm, 30 °C) \(t_R\) (minor): 11.1 min, \(t_S\) (major): 18.2 min, 93:7 er; \(\nu_{\text{max}}\) (film, cm\(^{-1}\)) 2872 (C-H), 1668, 1627, 1579, 1418, 1288, 1136 (SO\(_2\)), 1086, 1022, 876; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\text{H}:\) 1.59 – 1.73 (2H, m, C(3')H\(^\alpha\)H\(^\beta\) and C(4')H\(^\alpha\)H\(^\beta\)), 1.75 – 1.90 (2H, m, C(3')H\(^\alpha\)H\(^\beta\) and C(4')H\(^\alpha\)H\(^\beta\)), 2.72 – 2.80 (1H, m, C(2')H\(^\alpha\)H\(^\beta\)), 3.31 – 3.44 (2H, m, C(2')H\(^\alpha\)H\(^\beta\) and C(5')H\(^\alpha\)H\(^\beta\)), 3.47 – 3.55 (1H, m, C(5')H\(^\alpha\)H\(^\beta\)), 3.92 – 4.06 (3H, m, N(1''')CH\(_3\)Ph and C(4'')H), 4.45 (1H, d, \(J = 2.2\), C(2)H), 5.35 (1H, dd, \(J = 7.9, 5.2\), C(5'')H), 5.54 (1H, dd, \(J = 8.0, 1.3\), C(6'')H), 6.50 – 6.66 (2H, m, C(2'',6'')H), 7.14 (1H, d, \(J = 1.1\), C(2'')H), 7.18 – 7.25 (3H, m, C(3'',5'')H and C(4'')H), 7.25 – 7.33 (5H, m, C(2'',6'')H, C(3'',5'')H and C(4'')H), 7.51 (2H, t, \(J = 7.5\), C(3''',5''')H), 7.54 – 7.63 (1H, m, C(4''')H), 7.81 – 7.94 (2H, m, C(2''',6''')H); \(^{13}\)C\(^{1\text{H}}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\text{C}:\) 24.2 (C(3')H\(^\alpha\)H\(^\beta\) or C(4')H\(^\alpha\)H\(^\beta\)), 26.1 (C(3')H\(^\alpha\)H\(^\beta\) or C(4')H\(^\alpha\)H\(^\beta\)), 36.6 (C(4'')H), 45.9 (C(5')H\(^\alpha\)H\(^\beta\)), 46.7 (C(2')H\(^\alpha\)H\(^\beta\)), 56.2 (C(2)H), 57.4 (N(1'')CH\(_3\)Ph), 105.0 (C(3'')), 106.9 (C(5'')H), 126.9 (C(4'')H), 127.0 (C(2'',6'')H), 127.3 (C(2''',6''')H), 127.8 (C(3'',5'')H or C(3''',5''')H), 127.8 (C(4''')H), 128.9 (C(3'',5'')H or C(3''',5''')H), 129.1 (C(6'')H), 129.2 (C(3''',5''')H), 130.9 (C(2'',6'')H), 132.6 (C(4''')H), 135.9 (C(1'')), 136.0 (C(1''')), 141.5 (C(1''')), 143.3 (C(2)H), 171.8 (C(1)=O); HRMS (ESI\(^+\)) C\(_{30}\)H\(_{38}\)N\(_2\)NaO\(_3\)S [M+Na\(^+\)] found 521.1864, requires 521.1869 (−1.0 ppm).

(S)-2-(1''-Benzyl-5''-(phenylsulfonyl)-1'',2''-dihydropyridin-2''-yl)-2-phenyl-1-
(pyrrolidin-1'-yl)ethan-1-one (S2)

![](image)

The reaction for also gave product S2 (5%). Purification by flash column chromatography
(0 to 15% Et\(_2\)O in CH\(_2\)Cl\(_2\); \(R_t\) 0.27 at 10% Et\(_2\)O in CH\(_2\)Cl\(_2\)) gave the title compound (4 mg, 4%) as a pale yellow gum. \(\nu_{\text{max}}\) (film, cm\(^{-1}\)) 2957, 2918, 2851, 1628, 1556, 1431, 1298, 1180, 1134, 1090, 1063, 1028, 800, 752; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\text{H}:\) 1.69 – 1.80 (2H, m,
C(3')H^aH^b and C(4')H^aH^b), 1.80 – 1.94 (2H, m, C(3')H^aH^b and C(4')H^aH^b), 2.91 – 3.02 (1H, m, C(2')H^aH^b), 3.07 – 3.17 (1H, m, C(2')H^aH^b), 3.30 – 3.43 (1H, m, C(5')H^aH^b), 3.43 – 3.53 (1H, m, C(5')H^aH^b), 3.67 (1H, d, J 9.4, C(2)H), 4.38 – 4.52 (2H, m, C(3'')H and N(1'')CH^aH^bPh), 4.73 (1H, ddd, J 9.4, 5.9, 1.5, C(2'')H), 4.98 (1H, d, J 15.3, CH^aH^bPh), 6.23 (1H, dd, J 9.2, 1.1, C(4'')H), 7.07 – 7.13 (2H, m, C(2',6'')H), 7.17 (2H, d, J 6.4, C(2'','6''')H), 7.20 – 7.24 (3H, m, C(3',5'')H and C(4'')H), 7.27 – 7.32 (3H, m, C(3'','5''')H and C(4'')H), 7.35 (1H, s, C(6'')H), 7.43 – 7.57 (3H, m, C(3'','5''')H and C(4'')H), 7.78 – 7.90 (2H, m, C(2'','6''')H); \textsuperscript{13}C{^1}H NMR (126 MHz, CDCl\_3) \delta \textsuperscript{C}: 24.3 (C(3')H\_2 or C(4')H\_2), 26.1 (C(3')H\_2 or C(4')H\_2), 46.4 (C(2')H\_2 or C(5')H\_2), 46.4 (C(2')H\_2 or C(5')H\_2), 53.1 (C(2)H), 58.9 (C(2'')H), 59.7 (N(1'')CH\_2Ph), 110.4 (C(5'')), 111.4 (C(3'')H), 120.3 (C(4'')H), 126.5 (C(2'','6''')H), 127.3 (C(2'','6''')H), 127.7 (C(4')H or C(4'')H), 128.0 (C(4')H or C(4'')H), 128.6 (2 ArCH), 129.0 (2 ArCH), 129.1 (2 ArCH), 129.7 (C(2',6'')H), 132.0 (C(4'')H), 133.8 (C(1'')'), 137.6 (C(1'')), 143.2 (C(6'')H), 144.3 (C(1'')), 169.9 (C(1)=O); HRMS (ESI\^+) C\_30H\_30N\_2NaO\_6S [M+Na\textsuperscript{+}] \textsuperscript{+} found 521.1867, requires 521.1869 (0.4 ppm).

(R)-2-((S)-1'''-Benzy1-3'''- (phenylsulfonyl)-1'',4'''-dihydropyridin-4'''-yl)-1-morpho-lino-2-phenylethan-1-one (37)

![Chemical Structure](image)

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol, 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol\%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then morpholine (88 \mu L, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (62%, 95:5 dr). Purification by flash column chromatography (6 to 12% EtOAc in CH\_2Cl\_2; Rf 0.28 at 10% EtOAc in CH\_2Cl\_2 then 30 to 55% EtOAc in petrol; Rf 0.34 at 60% EtOAc in petrol) gave the title compound (58 mg, 56%, > 95:5 dr) as a pale yellow foam. [α]_D\textsuperscript{20} \text{b} = -346 (c 0.5, CHCl\_3); HPLC: Chiralpak
IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (major): 14.0 min, tᵣ (minor): 19.2 min, 94:6 er; νₓₜₕ (film, cm⁻¹) 1633, 1581, 1418, 1275, 1215, 1136, 1113, 1086; ¹H NMR (500 MHz, CDCl₃) δ: 2.90 – 3.00 (1H, m, C(3′)H₂⁺H¹b), 3.08 – 3.17 (1H, m, C(2′)H₄⁺H¹b), 3.22 – 3.31 (1H, m, C(2′)H₄⁺H¹b), 3.37 – 3.53 (3H, m, C(3′)H₄⁺H¹b, C(5′)H₄⁺H¹b and C(6′)H₄⁺H¹b), 3.62 – 3.69 (1H, m, C(5′)H₄⁺H¹b), 3.69 – 3.77 (1H, m, C(6′)H₄⁺H¹b), 3.94 – 4.05 (3H, m, NCH₃Ph and C(4′′)H), 4.54 (1H, d, J 2.3, C(2)H), 5.29 (1H, dd, J 8.0, 5.2, C(5′′)H), 5.53 (1H, dd, J 8.0, 1.5, C(6′′)H), 6.59 (2H, dd, J 7.7, 1.7, C(2′′′,6′′′)H), 7.17 (1H, d, J 1.1, C(2′′′)H), 7.19 – 7.25 (5H, m, C(2′′′,5′′′)H, C(4′′′)H and C(2′′′,6′′′)H), 7.27 – 7.34 (3H, m, C(3′′′,5′′′)H and C(4′′)H), 7.46 – 7.54 (2H, m, C(3′′′,5′′′)H), 7.56 – 7.61 (1H, m, C(4′′′)H), 7.85 – 7.93 (2H, m, C(2′′′,6′′′)H); ¹³C[¹H] NMR (126 MHz, CDCl₃) δ: 36.7 (C(4′′′)H), 42.2 (C(6′′)H), 46.5 (C(2′′)H), 54.3 (C(2)H), 57.4 (NCH₃Ph), 66.2 (C(3′′)H), 66.8 (C(5′′)H), 104.8 (C(3′′′)), 106.8 (C(5′′′)H), 127.0 (C(2′′′,6′′′)H), 127.2 (ArCH), 127.4 (C(2′′′,6′′′)H), 127.9 (ArCH), 128.0 (2 ArCH), 128.9 (2 ArCH), 129.2 (C(3′′′,5′′′)H), 129.3 (C(6′′′)H), 130.6 (C(2′′′,6′′′)H), 132.7 (C(4′′′)H), 135.9 (C(1′′′)), 143.3 (C(1′′″)), 143.3 (C(2′′′)H), 171.8 (C(1)=O); HRMS (ESI⁺) C₃₀H₃₀N₂NaO₃S [M⁺Na]⁺ found 537.1806, requires 537.1818 (–2.2 ppm).

**tert-Butyl-4-((R)-2′-((S)-1′′′-benzyl-3′′-((phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2′-phenylacetyl)piperazine-1-carboxylate (38)**

Following general procedure D, using 4-nitrophenyl 2-phenylacetate 10 (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78.0 mg, 0.20 mmol. 1.0 equiv), (R)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then 1-Boc-piperazine (186 mg, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (67%, 90:10 dr). Purification by flash column chromatography (25 to 50% EtOAc in petrol; Rᵣ 0.40 at 50% EtOAc in petrol then 6 to 10% Et₂O in CH₂Cl₂; Rᵣ 0.29 at 10% Et₂O in CH₂Cl₂) gave the title
compound (64 mg, 52%, > 95:5 dr) as a pale yellow foam. [α]_D^20 = -437 (c 1.0, CHCl₃); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tr (major): 12.1 min, tr (minor): 17.7 min, 93:7 er; νMax (film, cm⁻¹) 2970, 1691, 1668, 1638, 1581, 1416, 1367, 1284, 1187, 1086; **¹H NMR** (500 MHz, CD₃CN) δH: 1.38 (9H, s, C(CH₃)₃), 2.42 – 2.55 (1H, broad-m, C(2)H⁻H⁹), 2.96 – 3.10 (2H, m, C(6)H⁻H⁸ and C(3)H⁻H⁸), 3.10 – 3.16 (1H, m, C(3)H⁻H⁹), 3.16 – 3.22 (1H, m, C(2)H⁻H⁹), 3.24 – 3.34 (1H, m, C(5)H⁻H⁸), 3.37 – 3.46 (1H, m, C(6)H⁻H⁹), 3.58 – 3.69 (1H, m, C(5)H⁻H⁹), 3.88 (1H, dd, J 5.1, 2.3, C(4′′″)H), 4.09 (1H, d, J 15.7, NCH⁻H⁹Ph), 4.14 (1H, d, J 15.7, NCH⁻H⁹Ph), 4.31 (1H, d, J 2.3, C(2′)H), 5.12 (1H, dd, J 8.0, 5.1, C(5′′″)H), 5.61 (1H, dd, J 8.0, 1.3, C(6′′″)H), 6.67 (1H, dd, J 6.6, 2.9, C(2′′″,6′′″)H), 7.10 (2H, dd, J 8.1, 1.2, C(2″,6″)H), 7.20 (1H, d, J 1.1, C(2″)H), 7.22 – 7.30 (5H, m, C(3″,5″)H, C(3′′″,5′′″)H and C(4′′″)H), 7.30 – 7.35 (1H, m, C(4″)H), 7.61 (2H, tt, J 6.8, 1.6, C(3′′″,5′′″)H), 7.63 – 7.69 (1H, m, C(4′″″)H), 7.85 – 7.94 (2H, m, C(2′′″,6′′″)H); **¹³C{¹H} NMR** (126 MHz, CD₃CN) δC: 28.4 (C(CH₃)₃), 37.4 (C(4″)H), 42.2 (C(5)H₃), 43.3 (C(2)H₂ or C(5)H₂), 44.4 (C(2)H₂ or C(5)H₂), 46.2 (C(3)H₂), 54.9 (C(2′)H), 57.5 (NCH₃Ph), 80.2 (C(CH₃)₃), 105.8 (C(3″″)), 106.7 (C(5″″)H), 127.9 (C(2′″″,6′′″)H), 128.0 (C(4″)H), 128.0 (C(2′″″,6′′″)H), 128.4 (C(4′″″)H), 128.8 (2 ArCH), 129.6 (2 ArCH), 130.3 (C(3′″″,5′′″)H), 130.4 (C(6″)H), 131.2 (C(2″,6″)H), 133.7 (C(4′″″)H), 137.1 (C(1″″)), 137.8 (C(1′″″)), 142.9 (C(1″″″)), 144.1 (C(2″)H), 155.2 (C=Ocarbamate), 171.8 (C(1″)=O); **HRMS** (ESI⁺) C₃₅H₇₉N₇NaO₃S [M+Na]+ found 636.2491, requires 636.2503 (−1.9 ppm).
6. Control experiments

6.1. Control reaction of catalyst and pyridinium salt

6.2. Reaction of DABCO and pyridinium salt in PhMe

1-Benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78 mg, 0.2 mmol, 1.0 equiv) and DABCO (22.4 mg, 0.2 mmol, 1.5 equiv) were weighed into a 20 mL test tube. The test tube was sealed, purged, lowered into a cryostat bath at 0 °C. PhMe (1.3 mL, 0.15 M) was added and the reaction was stirred at 0 °C for 24 h. Upon completion, the reaction mixture was filtered and washed with PhMe (10 mL). The filtrate was concentrated under reduced pressure to give a mixture of DABCO : 1-benzyl-5-(phenylsulfonyl)-1,2-dihydropyridin-2-ol 39 (~1:1.3) as an orange solid (5 mg).
1-Benzyl-5-(phenylsulfonyl)-1,2-dihydropyridin-2-ol (39) characterised as mixture with DABCO (~1.3:1)

\[
\text{\( \nu_{\text{max}} \) (film, cm}^{-1}\text{) 3049, 2941, 2872, 2620, 1628, 1572, 1447, 1354, 1298, 1178, 1167, 1092, 1059, 1011, 997, 851, 777; \)}

\[
\text{\( ^1H \) NMR (500 MHz, DMSO)} \text{\( \delta_{\text{H}}: \) 4.74 (2H, s, N(1)CH\text{\_3}), 5.26 – 5.34 (2H, m, C(2)H and C(3)H), 6.32 (1H, dd, \text{\( J \) 9.5, 1.8, C(4)H), 6.40 (1H, broad d, \text{\( J \) 6.3, OH), 7.24 – 7.31 (2H, m, C(2',6')H), 7.31 – 7.34 (1H, m, C(4')H), 7.38 (2H, app t, \text{\( J \) 7.2, C(3',5')H), 7.53 – 7.64 (3H, m, C(3'',5'')H and C(4'')H), 7.65 – 7.70 (1H, m, C(6)H), 7.74 – 7.81 (2H, m, C(2'',6'')H); \)}

\[
\text{\( ^{13}C\{^{1H} \) NMR (126 MHz, DMSO)} \text{\( \delta_{\text{C}}: \) 55.0 (N(1)CH\text{\_3}), 75.3 (C(2)OH), 105.7 (C(5)), 113.5 (C(3)H), 119.8 (C(4)H), 126.0 (C(2'',6'')H), 127.9 (C(4')H), 128.0 (C(2',6')H), 128.7
\]
(C(3',5')H), 129.3 (C(3''5'')H), 132.2 (C(4')H), 136.6 (C(1'))), 142.5 (C(6)H), 143.9 (C(1''));
HRMS (ESI+) C_{18}H_{16}NO_2S [M] found 327.0908, requires 327.0924 (−4.9 ppm).

The presence of the alcohol peak (6.40 ppm) was confirmed by carrying out a D_2O shake, upon which it was not observable.

6.3. Subjecting product 39 to the catalysis conditions

1-Benzyl-3-(phenylsulfonyl)pyridin-1-iium bromide 17 (78 mg, 0.2 mmol, 1.0 equiv) and DABCO (22.4 mg, 0.2 mmol, 1.5 equiv) were weighed into a 20 mL test tube. The test tube was sealed, purged, lowered into a cryostat bath at 0 °C. PhMe (1.3 mL, 0.15 M) was added and the reaction was stirred at 0 °C for 24 h. Upon completion, the reaction mixture was filtered and washed with PhMe (10 mL). The previous carried out as a duplicate. The filtrates of the two reactions were concentrated almost to dryness, combined in a flame
dried 10 mL test tube and dissolved in anhydrous toluene (0.6 mL, 0.04 M). Based on the amount of hydroxydihydropyridine determined in experiment A, 4-Nitrophenyl 2-(naphthalen-2-yl)acetate (11) (12 mg, 0.04 mmol, 1.5 equiv) and (R)-BTM (1.3 mg, 5 μmol, 20 mol%) were added, the tube sealed, purged and lowered into a cryostat bath stirred at 0 °C for 24 h. Benzylamine (13 μL, 0.12 mmol, 5.0 equiv) and the reaction was stirred at 0 °C for a further 24 h. The reaction mixture was quenched with 1 M NaOH and extracted with CH₂Cl₂ (3 ×). The organic layer was washed successively with 1 M NaOH (2 ×) and brine (1 ×), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (4% Et₂O in CH₂Cl₂) to give (R)-N-Benzyl-2-((R)-1-benzyl-3-(phenylsulfonyl)-1,4-dihydropyridin-4-yl)-2-(naphthalen-2-yl)acetamide (30) as pale yellow glass (6 mg, 40% yield from filtrate, 6% yield from pyridinium salt).

6.4. Reaction of DABCO and pyridinium salt in CH₂Cl₂:

1-Benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide 17 (78 mg, 0.2 mmol, 1.0 equiv) and DABCO (22.4 mg, 0.2 mmol, 1.5 equiv) were weighed into a 20 mL test tube. The test tube was sealed, purged, lowered into a cryostat bath at 0 °C. CH₂Cl₂ (1.3 mL, 0.15 M) was added and the reaction was stirred at 0 °C for 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure. Quaternised DABCO with CH₂Cl₂ was observed with starting materials. Attempts to purify the mixture were unsuccessful.
7. Additional optimisation studies

Catalyst screen in toluene:

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<th>Entry</th>
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<th>Yield(^a) (%)</th>
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<th>er(^c)</th>
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<td>80:20</td>
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<td>80:20</td>
<td>52:48</td>
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[a] Combined yield of diastereoisomers. Determined by \(^1\)H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by \(^1\)H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Background reaction observed for trifluoromethylated ester:
## 8. X-Ray structure

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9. References


10. Appendix I: \(^1\text{H}\) and \(^{13}\text{C}\{^1\text{H}\}\) NMR spectra of novel compounds
$^1$H, DMSO, 500 MHz

$^{13}$C($^1$H), DMSO, 126 MHz
$^1$H, DMSO, 500 MHz

$^{13}$C($^1$H), DMSO, 126 MHz
$^1$H, DMSO, 500 MHz

$^{13}$C($^1$H), DMSO, 126 MHz
$^1$H, DMSO, 500 MHz

$^{13}$C($^1$H), DMSO, 126 MHz
$^1\text{H}$, DMSO, 500 MHz

$^{13}\text{C}(^1\text{H})$, DMSO, 126 MHz
$^1$H, DMSO, 500 MHz

$^{13}$C($^1$H), DMSO, 126 MHz
'H, DMSO, 500 MHz

$^{13}$C('H), DMSO, 126 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C($^1$H), CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 500 MHz

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$^{13}$C($^1$H), CDCl$_3$, 126 MHz
S2
$^1$H, CDCl$_3$, 500 MHz

S2
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$^1$H, CDCl$_3$, 500 MHz

$^{13}$C($^1$H), CDCl$_3$, 126 MHz
$^1$H, CD$_2$CN, 500 MHz

$^{13}$C($^1$H), CD$_2$CN, 128 MHz
11. Appendix II. HPLC traces

HPLC Data for 6: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (minor): 25.5 min, tᵣ (major): 31.7 min, 91:9 er
HPLC Data for 6 starting from chloride salt 7: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) tᵣ (minor): 25.5 min, tᵣ (major): 31.7 min, 91:9 er

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HPLC Data for 6 starting from PF₆ salt 8: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) tᵣ (minor): 25.5 min, tᵣ (major): 31.7 min, 83:17 er

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HPLC Data for 6 starting from BF₄ salt 9: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (minor): 25.5 min, tᵣ (major): 31.7 min, 84:16 er
HPLC Data for 25: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) t₁: 10.2 min and 18.0 min, 51:49 er

![Chemical Structure](image1)

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![Graph](image2)

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HPLC Data for 26: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (major): 12.2 min, tᵣ (minor): 14.6 min, 94:6 er

![Graph of HPLC data for compound 26](image)

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![Graph of HPLC data for compound 26](image)

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HPLC Data for **27**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) **tₚ** (major): 16.8 min, **tₚ** (minor): 20.8 min, 94:6 er
HPLC Data for 28: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C) t$_R$ (major): 14.8 min, t$_R$ (minor): 17.4 min, 91:9 er
HPLC Data for 29: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C) $t_R$ (major): 14.5 min, $t_R$ (minor): 18.9 min, 93:7 er
HPLC Data for **30**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) \( t_R \) (minor): 22.4 min, \( t_R \) (major): 40.7 min, 90:10 er
HPLC Data for 31: Chiralpak IB, (85:15 hexane: IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tᵣ (major): 17.6 min, tᵣ (minor): 20.3 min, 98:2 er

![Peak Table]

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![Peak Table]

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HPLC Data for 32: Chiralpak IB, (90:10 hexane: IPA, flow rate 0.5 mL/min, 211 nm, 30 °C) tR (major): 79.4 min, tR (minor): 87.9 min, 98:2 er
HPLC Data for 33: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tₘ (major): 31.2 min, tₑ (minor): 44.3 min, 96:4 er

![Chemical Structure of 33](image)

<Peak Table>

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HPLC Data for 34: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL/min, 211 nm, 30 °C) tR (major): 15.4 min, tR (minor): 19.4 min, 89:11 er

![HPLC chromatogram]

**<Peak Table>**

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![HPLC chromatogram]

**<Peak Table>**

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HPLC Data for 35: Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) \( t_R \) (minor): 13.1 min, \( t_R \) (major): 30.0 min, 52:48 er
HPLC Data for 36: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (minor): 11.1 min, tᵣ (major): 18.2 min, 93:7 er
HPLC Data for 37: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C) tᵣ (major): 14.0 min, tᵣ (major): 19.2 min, 94:6 er
HPLC Data for 38: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C) tᵣ (major): 12.1 min, tᵣ (major): 17.7 min, 93:7 er