# *N*-Fluorenyl Tryptamines as a Useful Platform for Catalytic Enantioselective Pictet–Spengler Reactions

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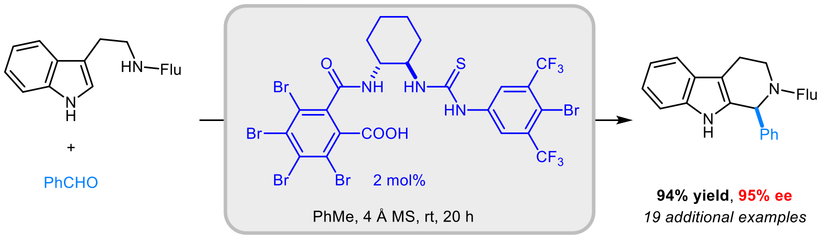

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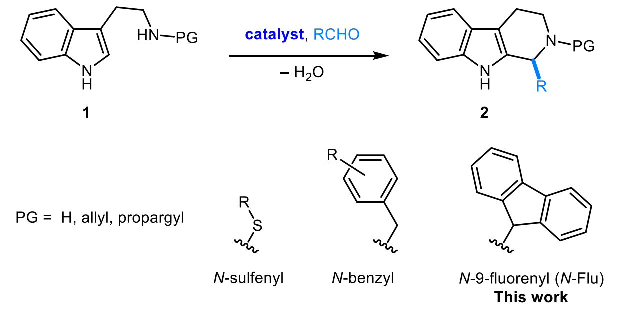
**Abstract** In the presence of a thiourea-carboxylic acid catalyst, *N*-9-fluorenyl tryptamines undergo highly enantioselective Pictet–Spengler reactions with a range of aldehydes. The reaction works particularly well with aromatic aldehydes, tolerating electronically diverse substituents in all ring positions. Electron-deficient tryptamines are viable substrates. Removal of the fluorenyl protecting group is readily accomplished without deterioration of product ee.

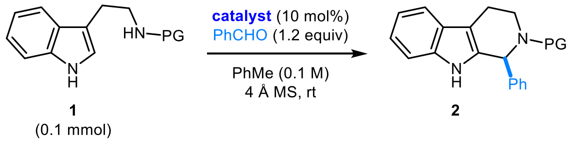
Key words: Pictet–Spengler reaction, asymmetric catalysis, Brønsted acid catalysis, heterocycles, ion-pairing

First discovered in 1911,[1] the Pictet–Spengler reaction remains one of the most powerful transformations to access chiral tetrahydroisoquinolines, tetrahydro-β-carbolines, and a broad range of related heterocycles.[2] A significant number of catalytic enantioselective variants have been reported,[2,3] the majority of which utilize chiral Brønsted acid catalysts.[4] Catalytic enantioselective Pictet–Spengler reactions of tryptamine derivatives have drawn particular attention, a fact that is not surprising, given that tetrahydro-β-carbolines are core structures of numerous alkaloids and other biologically active compounds.[2] Pictet–Spengler cyclizations of unmodified tryptamines (**1**, PG = H) with anything other than highly electron-deficient aldehydes/ketones pose a considerable challenge, as the immediate products are more basic than tryptamine itself, resulting in reduced catalyst turnover due to significant product inhibition (Scheme 1).[3q] While other solutions to this challenge have been devised (i.e., activation of tryptamine-derived imines by in situ acylation),[3a,3d] the use of *N*-substituted tryptamines has been applied most widely. *N*-allyl and *N*-propargyl tryptamines have been employed in instances where these activating groups are subsequently used as handles for further functionalization. *N*-sulfenyl tryptamines have been used in asymmetric Pictet–Spengler cyclizations, facilitating the formation of enantioenriched tetrahydro-β-carbolines with up to 87% ee.[3c] While the *N*-sulfenyl group is relatively easy to remove, it is rather expensive to install. Benzyl-type protecting/activating groups are the most common and have enabled the preparation of tetrahydro-β-carbolines in excellent enantioselectivities. However, *N*-benzyl-type substituents can be challenging to remove while maintaining the integrity of the newly formed stereogenic center, particularly for products derived from aromatic aldehydes. Here we introduce the *N*-9-fluorenyl group[5] as an improved protecting/activating group for tryptamines, enabling highly enantioselective Pictet–Spengler cyclizations.



**Scheme 1** Examples of Common Substrates for Catalytic Enantioselective Pictet–Spengler Reactions of Tryptamines.

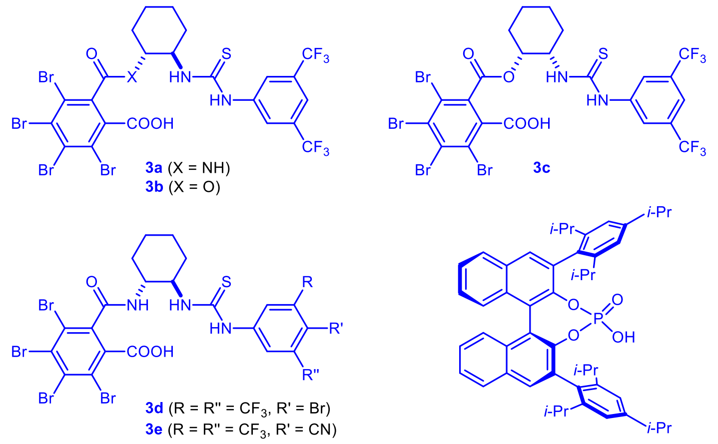
Our group previously introduced thiourea-carboxylic acids (e.g., **3**) as effective catalysts for a range of asymmetric transformations.[3q,3v,6] These catalysts derive their high levels of acidity ($pK_a$ (MeCN) = 11.8–13.6)[6d,6e] primarily from conjugate-base-stabilization via (internal) anion-binding.[7] The bowl-shaped catalyst anion is believed to form a tight ion pair[8] with a substrate-derived cation, and enantiocontrol is achieved via a combination of multiple noncovalent interactions.[3v]



1
(0.1 mmol)

2

| entry | catalyst | PG | product | time [h] | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | Bn | **2a** | 24 | 95 | 38 |
| 2 | **3a** | $CHPh_2$ | **2b** | 12 | 95 | 50 |
| 3 | **3a** | Flu | **2c** | 6 | 95 | 95 |
| 4 | **3a** | $CPh_3$ | **2d** | 24 | - | - |
| 5 | **3b** | Flu | **2c** | 4 | 95 | 48 |
| 6 | **3c** | Flu | **2c** | 8 | 95 | 26 |
| 7 | **3d** | Flu | **2c** | 2.5 | 95 | 96 |
| 8 | **3e** | Flu | **2c** | 2.5 | 95 | 95 |
| 9 | **3f** | Flu | **2c** | 2 | 95 | 95 |
| 10 | **(*S*)-TRIP** | Flu | **2c** | 12 | 30 | 80 |



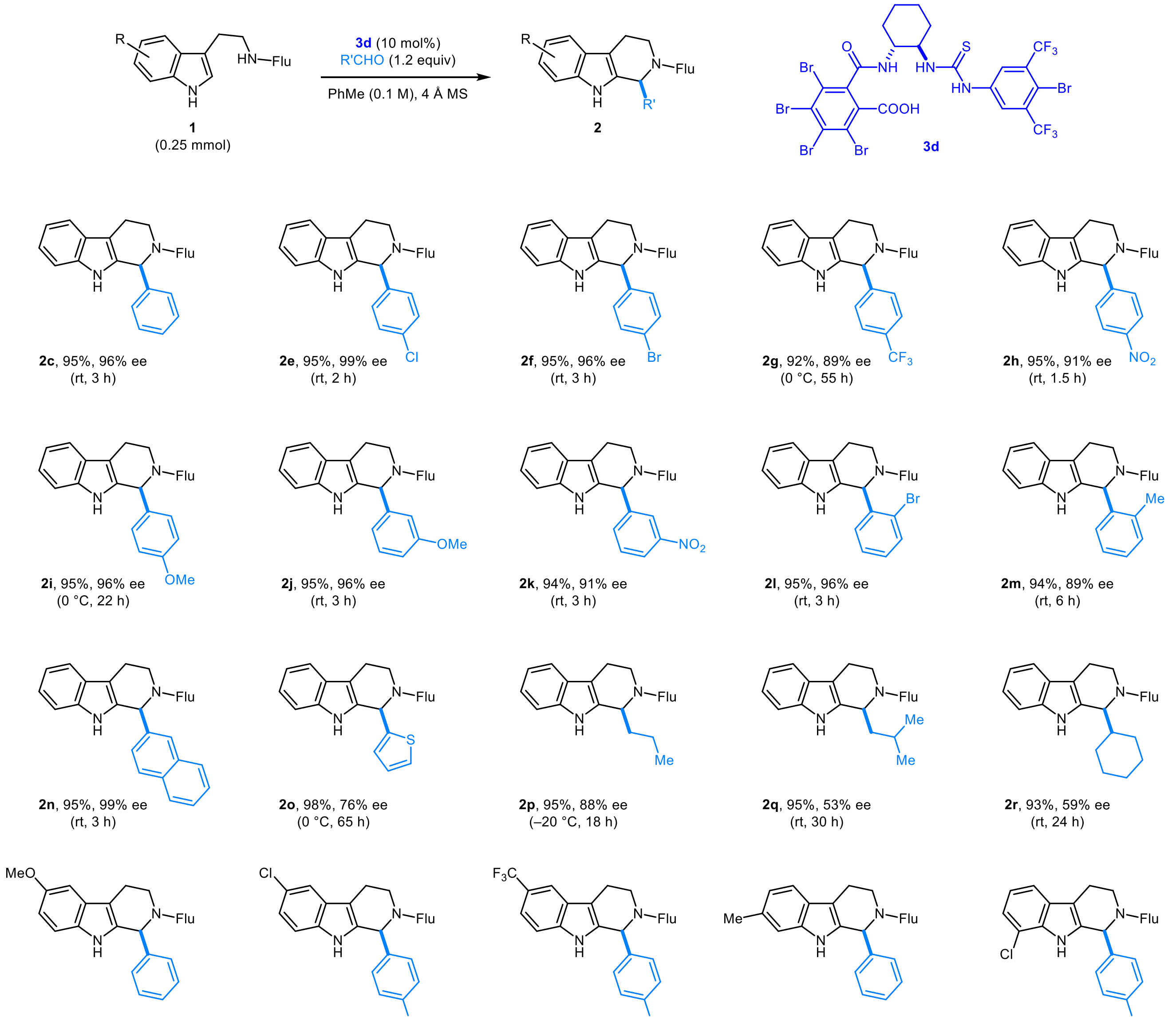
**3a** (X = NH)
**3b** (X = O)

**3c**

**3d** (R = R'' = $CF_3$, R' = Br)
**3e** (R = R'' = $CF_3$, R' = CN)
**3f** (R = H, R' = $NO_2$, R'' = $CF_3$)

**(*S*)-TRIP**

Scheme 2 Optimization of the Reaction Conditions.



1
(0.25 mmol)

2

**2c**, 95%, 96% ee
(rt, 3 h)

**2e**, 95%, 99% ee
(rt, 2 h)

**2f**, 95%, 96% ee
(rt, 3 h)

**2g**, 92%, 89% ee
(0 °C, 55 h)

**2h**, 95%, 91% ee
(rt, 1.5 h)

**2i**, 95%, 96% ee
(0 °C, 22 h)

**2j**, 95%, 96% ee
(rt, 3 h)

**2k**, 94%, 91% ee
(rt, 3 h)

**2l**, 95%, 96% ee
(rt, 3 h)

**2m**, 94%, 89% ee
(rt, 6 h)

**2n**, 95%, 99% ee
(rt, 3 h)

**2o**, 98%, 76% ee
(0 °C, 65 h)

**2p**, 95%, 88% ee
(–20 °C, 18 h)

**2q**, 95%, 53% ee
(rt, 30 h)

**2r**, 93%, 59% ee
(rt, 24 h)

**2s**, 95%, 93% ee
(rt, 4 h)

**2t**, 94%, 93% ee
(rt, 6 h)

**2u**, 84%, 62% ee
(rt, 40 h)

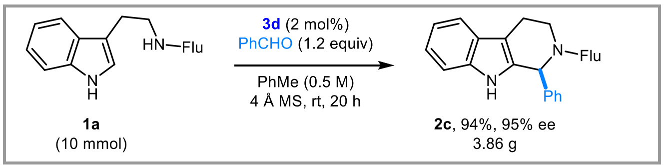
**2v**, 91%, 90% ee
(0 °C, 17 h)

**2w**, 93%, 95% ee
(rt, 12 h)

Scheme 3 Scope of the Reaction.

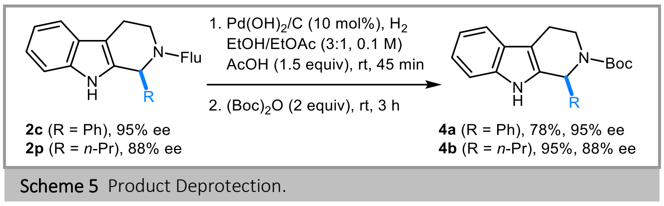
Utilizing catalyst **3a**, we previously reported catalytic enantioselective Pictet–Spengler reactions of unmodified tryptamine.[3q] The aforementioned challenge of product inhibition was addressed by using a stoichiometric amount of an achiral acid as an additive, which facilitated catalyst turnover. Alternatively, catalyst turnover could be achieved by in situ Boc-protection of the products. However, the reaction suffered from important limitations, such as the inability to accommodate aliphatic aldehydes. Also, the catalyst performance was strongly dependent on the electronic nature of the substrate, with electron-rich benzaldehydes (e.g., *p*-methoxy or *p*-methyl benzaldehyde) providing low reaction rates and dramatically reduced enantioselectivities. We thus decided to investigate the performance of our thiourea-carboxylic acid catalysts with *N*-substituted tryptamines (Scheme 2). With *N*-benzyl tryptamine and benzaldehyde as the substrates, catalyst **3a** displayed good reactivity, providing product **2a** in excellent yield but low enantioselectivity (entry 1). A significant improvement in reactivity and enantioselectivity was observed with *N*-benzhydryl tryptamine (entry 2). Gratifyingly, the use of *N*-9-fluorenyl tryptamine enabled a further increase in reactivity, resulting in the formation of **2a** in excellent yield and ee (entry 3). Interestingly, *N*-trityl tryptamine proved to be entirely unreactive under otherwise identical conditions (entry 4). Evaluation of a number of other catalysts led to the identification of thiourea-carboxylic acid **3d** as the most active and selective catalyst (entry 7). **(*S*)-TRIP**,[9] one of the most widely used chiral phosphoric acid catalysts ($pK_a$ (MeCN) = 13.6),[10] provided a promising level of enantioselectivity but relatively low activity.

The scope of the transformation was evaluated with catalyst **3d** (Scheme 3). *N*-9-fluorenyl tryptamine underwent highly enantioselective Pictet–Spengler cyclizations with a broad range of benzaldehydes, tolerating both electron-donating and electron-withdrawing substituents in all ring positions (products **2c**–**2n**). Lower selectivity was achieved with thiophene-2-carbaldehyde (product **2o**). *n*-Butyraldehyde was found to be highly reactive, providing product **2p** in good yield and ee when the reaction was conducted at –20 °C.[11] Unexpectedly, valeraldehyde and cyclohexanecarboxaldehyde were significantly less reactive and provided the corresponding products **2q** and **2r** with reduced enantioselectivities. High enantioselectivities can be achieved with ring-substituted *N*-9-fluorenyl tryptamines, tolerating substitution at different positions (products **2s**–**2w**). Notably, highly enantioselective Pictet–Spengler cyclizations with electron-deficient tryptamines have not previously been reported.

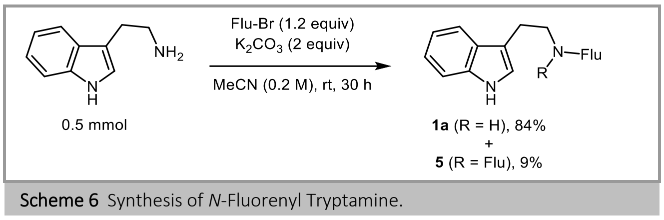


Scheme 4 Scale-up Experiment.

To illustrate the overall practicality of the method, a scale-up experiment was conducted at a 10 mmol scale (Scheme 4). The outcome of the reaction was nearly identical to the smaller scale experiments, with product **2c** being isolated in excellent yield and ee. By keeping the concentration of the catalyst identical to the optimized conditions, a 5-fold reduction in both solvent and catalyst loading was achieved.



Scheme 5 Product Deprotection.



Scheme 6 Synthesis of *N*-Fluorenyl Tryptamine.

Removal of the *N*-9-fluorenyl substituent was readily achieved via hydrogenolysis as illustrated with *N*-9-fluorenyl tetrahydro-β-carbolines **2c** and **2p** (Scheme 5). In situ Boc-protection was conducted for ease of product isolation and ee determination. Products **4a** and **4b** both were obtained in good yields. In the case of **2c**, some amount of over-reduced byproduct was obtained (see Experimental Section). Importantly, no reduction in ee was observed for either product.

As a final point, it is worth commenting on the synthesis of the *N*-9-fluorenyl tryptamine starting materials (Scheme 6). While substrate **1a** can be prepared from tryptamine and 9-fluorenone via the corresponding imine, we found it advantageous to access **1a** via alkylation of tryptamine with 9-bromofluorene. While bis-fluorenylation of tryptamine was found to be surprisingly facile, undesired side product **5** was easily separated from **1a** via column chromatography.

In summary, we have achieved highly enantioselective Pictet–Spengler cyclizations with *N*-9-fluorenyl tryptamines and a range of aldehydes. Among the favorable characteristics of the *N*-9-fluorenyl group are its ability to impart enhanced electrophilicity to the intermediate iminium ions, in addition to ease of installation and ease of removal.

The experimental section has no title; please leave this line here.

Starting materials and reagents were purchased from commercial sources and used as received unless stated otherwise. All liquid aldehydes were freshly distilled, and solid aldehydes were recrystallized prior to use. Toluene was dried using a JC-Meyer solvent purification system. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 $F_{254}$ plates. Visualization was accomplished with UV light and Dragendorff-Munier stain, followed by heating. Proton nuclear magnetic resonance spectra ($^{1}$H-NMR) were recorded on Varian VNMRS-500 MHz and Bruker 400 MHz instruments and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}$C-NMR) were recorded on Varian VNMRS-500 MHz and Bruker 400 MHz instruments and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.16 ppm). High resolution mass spectra (HRMS) were obtained from the Mass

Spectrometry Core Laboratory of the University of Florida (Agilent 6200 ESI-TOF coupled to an IonSense DART ET-100 ionization source for DART-TOF analysis). HPLC analysis was carried out on an Agilent 1100 series instrument with autosampler and multiple wavelength detectors. Supercritical fluid chromatography (SFC) analysis was carried out on an Agilent 1260 Infinity II series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and 22 °C.

**Procedures**

**General Procedure A** - To a flame dried round bottom flask was added the tryptamine **1** (1.0 equiv), 9-bromofluorene (1.2 equiv), $K_2CO_3$ (2 equiv), and dry acetonitrile (0.2 M). The mixture was stirred at room temperature under inert atmosphere until the tryptamine was completely consumed. The crude reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with water, brine, and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (using a gradient eluent from EtOAc/hexanes 10:90 v/v to EtOAc/hexanes 20:80 v/v to EtOAc).

***N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1a) and *N*-(2-(1H-indol-3-yl)ethyl)-N-(9H-fluoren-9-yl)-9H-fluoren-9-amine (5)**

Following general procedure A, compound **1a** and **5** were obtained from tryptamine **1** (80 mg, 0.5 mmol), 9-bromofluorene (147 mg, 0.6 mmol, 1.2 equiv), and $K_2CO_3$ (139 mg, 1 mmol, 2 equiv) as white solids in 84% yield (136 mg) and 9% yield (14 mg) respectively.

**$R_f$ =** 0.52 in 100 % EtOAc.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.71–7.65 (comp, 4H), 7.43–7.36 (comp, 3H), 7.33–7.22 (comp, 3H), 7.17 (app t, *J* = 7.6 Hz, 1H), 7.05 (app t, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 5.08 (s, 1H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.76 (t, *J* = 7.1 Hz, 2H).

**$^{13}$C-NMR** (151 MHz, $CDCl_3$): δ = 145.0, 140.8, 136.4, 128.1, 127.4, 127.3, 124.9, 122., 122, 119.9, 119.3, 119, 113.7, 111.1, 63.3, 44.1, 26.1.

**HRMS (ESI-TOF)**: Calculated for $C_{23}H_{20}N_2$ [M + H]$^+$: 325.1705, found 325.1722.

**m.p.**: 157.8–160.2 °C

Characterization data for **5**:

**$R_f$ =** 0.6 in hexanes/EtOAc 90:10 v/v.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.70–7.69 (comp, 4H), 7.44–7.43 (comp, 4H), 7.39–7.36 (comp, 4H), 7.31–7.25 (comp, 5H), 7.14 (ddd, *J* = 8.2, 6.5, 1.6 Hz, 1H), 7.02–6.93 (comp, 2H), 6.85 (s, 1H), 5.01 (s, 2H), 3.06 (t, *J* = 6.1 Hz, 2H), 2.89 (t, 6.2 Hz, 2H).

**$^{13}$C-NMR** (151 MHz, $CDCl_3$): δ = 145.8, 140.8, 136.1, 128.0, 127.5, 127.1, 126.4, 121.7, 121.5, 119.8, 119.1, 118.8, 114.3, 110.9, 64.9. 48.9, 25.4.

**HRMS (ESI-TOF)**: Calculated for $C_{36}H_{28}N_2$ [M + H]$^+$: 489.2331, found 489.2243.

**m.p.**: 183–186 °C

***N*-(2-(5-methoxy-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1b)**

Following general procedure A, compound **1b** was obtained from 5-methoxytryptamine (191 mg, 1.0 mmol), 9-bromofluorene (294 mg, 1.2 mmol, 1.2 equiv), and $K_2CO_3$ (276 mg, 2.0 mmol, 2 equiv) as a white solid in 80% yield (283 mg).

**$R_f$** = 0.38 in 100% EtOAc.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.61–7.59 (comp, 2H), 7.44–7.43 (comp, 2H), 7.30–7.26 (comp, 2H), 7.21–7.16 (comp, 3H), 6.79 (app d, *J* = 2.2 Hz, 1H), 6.74 (app d, *J* = 2.2 Hz, 1H), 6.63 (app dd, *J* = 8.7, 2.3 Hz, 1H), 4.88 (s, 1H), 3.75 (s, 3H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 6.9 Hz, 2H).

**$^{13}$C-NMR** (151 MHz, $CDCl_3$): δ = 156.5, 140.8, 137.1, 128.1, 127.29, 124.9, 121.8, 120.8, 119.8, 119.6, 113.6, 109.3, 94.6, 63.2, 55.7, 43.9, 26.1.

**HRMS (ESI-TOF)**: Calculated for $C_{24}H_{22}N_2O$ [M + H]$^+$: 355.1811, found 355.1824

**m.p.**: 163.1–164.5 °C

***N*-(2-(5-chloro-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1c)**

Following general procedure A, compound **1c** was obtained from the hydrochloride salt of 5-chloro tryptamine (120 mg, 0.6 mmol), 9-bromofluorene (177 mg, 0.72 mmol, 1.2 equiv), and $K_2CO_3$ (250 mg, 1.8 mmol, 3 equiv) as a white solid in 73% yield (155 mg).

**$R_f$** = 0.45 in 100% EtOAc.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 7.72–7.70 (comp, 2H), 7.49–7.48 (comp, 2H), 7.40–7.37 (comp,3H), 7.30–7.24 (comp, 3H), 7.15–7.13 (m, 1H), 7.00 (s, 1H), 4.96 (s, 1H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.8 Hz, 2H).

**$^{13}$C-NMR** (151 MHz, $CDCl_3$): δ = 145.1, 140.8, 134.7, 128.5, 128.2, 127.3, 125.1, 124.8, 123.5, 122.3, 119.9, 118.6, 113.6, 112.1, 63.3, 43.8, 26.1.

**HRMS (ESI-TOF)**: Calculated for $C_{23}H_{19}N_2Cl$ [M + H]$^+$: 359.1316, found 359.1328.

**m.p.**: 126.8–131.4 °C

***N*-(2-(5-(trifluoromethyl)-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1d)**

Following general procedure A, compound **1d** was obtained from 5-trifluoromethyl tryptamine (200 mg, 0.8 mmol), 9-bromofluorene (258 mg, 1.05 mmol, 1.2 equiv), and $K_2CO_3$ (243 mg, 1.6 mmol, 2 equiv) as a yellow solid in 65% yield (224 mg).

**$R_f$** = 0.2 in 100 % EtOAc.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 7.62–7.54 (comp, 3H), 7.35–7.33 (comp, 2H), 7.30–7.17 (comp, 5H), 7.15–7.11 (comp, 2H), 6.86 (s, 1H), 4.84 (s, 1H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.1, 140.8, 137.7, 128.3, 127.4, 126.7, 124.7, 123.9, 124.1, 121.6 (q, $J_{C–F}$ = 31.5 Hz), 120.0, 118.75 (q, $J_{C–F}$ = 3.6 Hz), 116.74 (q, $J_{C–F}$ = 4.3 Hz). 114.6, 112.0, 63.3, 43.9, 26.1.

**$^{19}$F NMR** (377 MHz, $CDCl_3$): δ = -59.88.

**HRMS (ESI-TOF)**: Calculated for $C_{24}H_{19}N_2F_3$ [M + H]$^+$: 393.1500, found 393.1636.

**m.p.**: 163–165 °C

***N*-(2-(6-methyl-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1e)**

Following general procedure A, compound **1e** was obtained from the hydrochloride salt of 6-methyl tryptamine (105 mg, 0.6 mmol), 9-bromofluorene (177 mg, 0.72 mmol, 1.2 equiv), and $K_2CO_3$ (250 mg, 1.8 mmol, 3 equiv) as a white solid in 80% yield (160 mg).

**$R_f$** = 0.55 in 100% EtOAc.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ = 7.87 (s, 1H), 7.70–7.68 (comp,2H), 7.62–7.58 (comp, 2H), 7.39–7.34 (comp, 2H), 7.33–7.24 (comp, 3H), 7.10 (s, 1H), 6.92–6.83 (comp, 2H), 4.99 (s, 1H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.74 (t, *J* = 7.1 Hz, 2H), 2.44 (s, 3H).

**$^{13}$C-NMR** (151 MHz, $CDCl_3$): δ = 145.2, 140.8, 136.8, 131.8, 128.1, 127.2, 125.3, 124.9, 121.3, 121.0, 119.8, 118.6, 113.6, 111.0, 63.3, 44.2, 26.3, 21.7.

**HRMS (ESI-TOF)**: Calculated for $C_{24}H_{22}N_2$ [M + H]$^+$: 339.1862, found 339.1896.

**m.p.**: 152.3–155.8 °C

***N*-(2-(7-chloro-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine (1f)**

Following general procedure A, compound **1f** was obtained from the hydrochloride salt of 7-chloro tryptamine (347 mg, 1.5 mmol), 9-bromofluorene (441.21 mg, 1.80 mmol, 1.2 equiv), and $K_2CO_3$ (622 mg, 4.5 mmol, 3 equiv) as a white solid in 76% yield (409 mg).

**$R_f$** = 0.5 in 100 % EtOAc.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.63–7.60 (comp,2H), 7.40–7.38 (comp, 2H), 7.32–7.23 (comp, 3H), 7.21–7.14 (comp, 3H), 7.10 (app d, *J* = 7.6 Hz, 1H), 6.98 (app d, *J* = 2.3 Hz, 1H), 6.93–6.89 (m, 1H), 4.86 (s, 1H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.9 Hz, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.0, 140.8, 133.0, 128.9, 128.0, 127.3, 124.8, 122.6, 121.4, 120.1, 119.9, 117.7, 116.6, 114.9, 63.3, 43.9, 26.2.

**HRMS (ESI-TOF)**: Calculated for $C_{23}H_{19}N_2Cl$ [M + H]$^+$: 359.1316, found 359.1323.

**m.p.**: 156–159 °C

### *N*-benzhydryl-2-(1H-indol-3-yl)ethan-1-amine (1g)

To a solution of tryptamine **1** (1.6 g, 10 mmol) in dry toluene (50 mL) in a round bottom flask equipped with Dean-Stark apparatus were added benzophenone (2.16 g, 12 mmol, 1.2 equiv) and acetic acid (0.57 ml, 10 mmol, 1 equiv). The reaction mixture was heated under reflux for 8 hours. After cooling to room temperature, toluene was removed under vacuo, followed by the addition of methanol (50 mL). The flask was placed in an ice-water bath, followed by the addition of $NaBH_4$ (0.567 g, 15 mmol). The reaction mixture was allowed to stir for an additional hour before quenching with saturated $NH_4Cl$ aqueous solution. Methanol was removed under vacuo, and the aqueous layer was extracted with ethyl acetate (3×50ml). The combined organic layers were washed with water, brine, and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was directly purified by silica gel chromatography (using a gradient eluent from EtOAc/hexanes 10:90 v/v to EtOAc/hexanes 20:80 v/v to EtOAc). Compound **1g** was obtained as a white solid in 86% yield (2.8 g) after further purification by recrystallization from dichloromethane.

**$R_f$ =** 0.78 in 100% EtOAc.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H), 7.49 (app d, *J* = 7.9 Hz, 1H), 7.30–7.26 (comp, 4H), 7.26–7.22 (m, 1H), 7.18 (comp, 4H), 7.14–7.06 (comp, 3H), 7.01 (m, 1H), 6.89 (app d, *J* = 2.3 Hz, 1H), 4.76 (s, 1H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.4, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 144.3, 136.4, 128.5, 127.6, 127.3, 126.9, 122.0, 121.8, 119.3, 118.9, 114.2, 111.1, 67.4, 48.1, 25.9.

**HRMS (ESI-TOF)**: Calculated for $C_{23}H_{22}N_2$ [M + H]$^+$: 327.1862, found 327.1853.

**m.p.**: 117–119 °C

**General Procedure B** - To a flame dried vial were successively added the protected tryptamine substrate (1 equiv), the corresponding acid catalyst (10 mol%), 4 Å MS (100 mg) and dry toluene (0.1 M). The resulting mixture was stirred under nitrogen at room temperature or cooled to the indicated temperature over 15 minutes. The corresponding aldehyde (1.2 equiv) was then added, and the reaction mixture was stirred for the indicated time before being quenched with triethylamine (0.1 mL). The resulting mixture was directly purified by flash chromatography on silica gel topped with celite (using a gradient eluent from hexanes to EtOAc/hexanes 10:90 v/v).

### (*S*)-2-benzyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2a)

Following the general procedure B, compound **2a** was obtained from benzyl protected tryptamine (28 mg, 0.1 mmol), benzaldehyde (13 mg, 0.12 mmol, 1.2 equiv) and catalyst **3a** (8.5 mg, 0.01 mmol,10 mol%) as a white solid in 95% yield (32 mg).

**$R_f$** = 0.55 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +3.223 (c 0.5, $CHCl_3$, 38% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 1H), 7.51–7.45 (comp, 2H), 7.43–7.31 (comp, 7H), 7.31–7.24 (comp, 2H), 7.24–7.18 (m, 1H), 7.16–7.09(comp, 2H), 4.68 (s, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.40 (d, *J* = 13.8 Hz, 1H), 3.29–3.24 (m, 1H), 2.99–2.91 (m, 1H), 2.86–2.80 (m, 1H), 2.76–2.65 (m, 1H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 141.5, 139.6, 136.3, 134.9, 129.0, 128.8, 128.7, 128.2, 128.1, 127.2, 126.9, 121.5, 119.4, 118.3, 110.8, 109.0, 64.6, 58.4, 48.4, 21.2.

**MS (ESI-MS)**: Calculated for $C_{30}H_{26}N_2$ [M + H]$^+$: 339.1783, found 339.1924.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i-PrOH* = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 5.90 min (major) and $t_R$ = 6.78 min (minor).

**m.p.**: 160–163 °C

### (*S*)-2-benzhydryl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2b)

Following the general procedure B, compound **2b** was obtained *N*-benzhydryl-2-(1H-indol-3-yl)ethan-1-amine **1g** (33 mg, 0.1 mmol), benzaldehyde (13 mg, 0.12 mmol, 1.2 equiv) and catalyst **3a** (8.5 mg, 0.01 mmol, 10 mol%) as a white solid in 95% yield (39 mg).

**$R_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +4.30 (c 0.5, $CHCl_3$, 50% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.64–7.58 (comp, 3H), 7.47–7.20 (comp, 15H), 7.18–7.13 (comp, 2H), 5.01 (s, 1H), 4.92 (s, 1H), 3.29–3.19 (m, 1H), 2.96–2.72 (comp, 3H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 143.3, 141.9, 140.1, 136.2, 134.0, 129.4, 128.8, 128.6, 128.4, 128.3, 128.1, 127.7, 127.3, 127.3, 126.9, 121.5, 119.3, 118.29, 110.8, 109.1, 68.0, 58.7, 42.3, 19.5.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{26}N_2$ [M + H]$^+$: 415.2179, found 415.2184.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 5.09 min (major) and $t_R$ = 6.89 min (minor).

**m.p.**: 135–140 °C

### (*S*)-2-(9H-fluoren-9-yl)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2d)

Following the general procedure B, compound **2d** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol) benzaldehyde (32 mg, 0.3 mmol, 1.2 equiv), catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (98 mg).

**$R_f$** = 0.45 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +300.97 (c 0.5, $CHCl_3$, 96% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.87–7.67 (comp, 5H), 7.60–7.57 (m, 1H), 7.53–7.45 (comp, 3H), 7.43–7.38 (comp, 3H), 7.36–7.28 (comp, 3H), 7.24–7.20 (m, 1H), 7.16–7.08 (comp, 2H), 5.76 (s, 1H), 4.94 (s, 1H), 2.89–2.78(m, 1H), 2.75–2.69 (m, 1H), 2.61–2.56 (m, 1H), 2.49–2.42 (m,1H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.9, 144.5, 141.5, 141.4, 140.4, 136.4, 135.7, 129.5, 129.2, 128.6, 128.1, 128, 127.5, 127.3, 126.6, 126.1, 125.2, 121.6, 120.4, 119.4, 119.4, 118.4, 110.8, 109.4, 64.7, 63.9, 44.0, 22.2.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{25}N_2$ [M + H]$^+$: 413.2018, found 413.2048.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 5.92 min (major) and $t_R$ = 8.15 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

### (*S*)-1-(4-chlorophenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2e)

Following the general procedure B, compound **2e** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 4-chlorobenzaldehyde (45 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (106 mg).

**$R_f$ =** 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ **=** +68.45 (c 0.5, $CHCl_3$, 96% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.79–7.76 (comp, 2H), 7.71 (app d, *J* = 7.5 Hz, 1H), 7.69–7.62 (m, 2H), 7.58–7.48 (m, 2H), 7.48–7.38 (comp, 4H), 7.37–7.21 (comp, 4H), 7.14–7.10 (comp, 2H), 5.74 (s, 1H), 4.89 (s, 1H), 2.88–2.81 (m, 1H), 2.79–2.71 (m, 1H), 2.52–2.57 (m, 1H), 2.53–2.44 (m, 1H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.5, 144.2, 141.5, 140.4, 140.1, 136.4, 134.9, 134.3, 130.7, 129.3, 128.2, 128.0, 127.5, 127.2, 126.6, 125.9, 125.1, 121.8, 120.4, 119.5, 119.4, 118.4, 110.8, 109.7, 64.8, 63.0, 44.0, 22.2.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{24}N_2Cl$ [M + H]$^+$: 447.1708, found 447.1603.

**HPLC:** Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 6.31 min (major) and $t_R$ = 8.99 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-1-(4-bromophenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2f)**

Following the general procedure B, compound **2f** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 4-bromobenzaldehyde (56 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (116 mg).

$\mathbf{R_f}$ = 0.52 in hexanes/EtOAc 90:10 v/v.

$[\boldsymbol{\alpha}]_{\mathrm{D}}^{22}$ = +6.46 (c 0.5, $CHCl_3$, 96% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.67–7.60 (comp, 2H), 7.57 (app d, *J* = 7.5 Hz, 1H), 7.44–7.34 (comp, 2H), 7.30–7.24 (comp, 2H), 7.23–7.05 (comp, 7H), 7.04–6.96 (comp, 2H), 5.55 (s, 1H), 4.74 (s, 1H), 2.75–2.51 (comp, 2H), 2.50–2.32 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.5, 144.2, 141.5, 140.6, 140.4, 136.4, 134.9, 132.2, 131.1, 128.2, 128.0, 127.5, 127.2, 126.6, 125.8, 125.1, 122.4, 121.8, 120.4, 119.5, 119.4, 118.4, 110.8, 109.7, 64.8, 63.1, 44.0, 22.1.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{24}N_2Br$ $[M + H]^+$: 491.1198, found 491.1082.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 6.42 min (major) and $t_R$ = 10.60 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2g)**

Following the general procedure B (reaction performed at 0 °C for 55 h), compound **2g** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 4-(trifluoromethyl) benzaldehyde (52 mg, 0.3 equiv, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a yellow solid in 92% yield (111 mg).

$\mathbf{R_f}$ = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\boldsymbol{\alpha}]_{\mathrm{D}}^{22}$ = +10.85 (c 0.5, $CHCl_3$, 89% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.85–7.83 (comp, 2H), 7.76 (app t, *J* = 7.7 Hz, 2H), 7.71–7.69 (comp, 2H), 7.54 (app d, *J* = 7.4 Hz, 1H), 7.50 (app d, *J* = 7.6 Hz, 1H), 7.43–7.38 (comp, 2H), 7.35–7.28 (comp, 2H), 7.25–7.21 (comp, 2H), 7.13 (comp, 2H), 5.80 (s, 1H), 4.84 (s, 1H), 2.92–2.72 (comp, 2H), 2.66–2.49 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.8, 145.3, 144.1, 141.4, 140.4, 136.4, 134.5, 129.7, 128.2, 128.1, 127.5, 127.1, 126.7, 126.0, 125.9(q, $J_{C\text{–}F}$ = 30 Hz), 125.1, 121.8, 120.4, 119.5 (q, $J_{C\text{–}F}$ = 80 Hz), 110.8, 109.9, 65.1, 63.1, 44.1, 22.1.

**$^{19}$F NMR** (377 MHz, $CDCl_3$) δ = –62.31.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{24}F_3$ $[M + H]^+$: 481.1968, found 481.1461.

**SFC**: Daicel Chiralcel AD-H, column temperature = 40 °C, $CO_2$/MeOH = 90/10, Flow rate =2 mL/min, UV = 280 nm, $t_R$= 13.36 min (major) and $t_R$= 19.75 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2h)**

Following the general procedure B, compound **2h** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 4-nitrobenzaldehyde (45 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a yellow solid in 95% yield (109 mg).

$\mathbf{R_f}$ = 0.3 in hexanes/EtOAc 90:10 v/v.

$[\boldsymbol{\alpha}]_{\mathrm{D}}^{22}$ = +78.63 (c 0.5, $CHCl_3$, 91% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 8.18–8.00 (comp, 2H), 7.81–7.52 (comp, 5H), 7.49–7.25 (comp, 6H),7.20–6.99 (comp, 4H) 5.65 (s, 1H), 4.67 (s, 1H), 3.02–2.70 (comp, 2H), 2.68–2.40 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 149.5, 148.0, 144.8, 143.9, 141.3, 140.5, 136.6, 133.8, 130.2, 128.4, 128.2, 127.6, 127.0, 126.9, 125.9, 125.1, 124.2, 122.1, 120.4, 119.7, 119.6, 118.6, 111.0, 110.2, 65.6, 62.7, 44.4, 22.2.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{24}N_3O$ $[M + H]^+$: 458.1948, found 458.1857.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 12.76 min (minor) and $t_R$ = 15.29 min (major).

**m.p.**: product decomposition at 162–165 °C (conversion to black charred material)

**(*S*)-1-(4-methoxyphenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2i)**

Following the general procedure B (reaction performed at 0 °C for 22 h), compound **2i** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 4-methoxybenzaldehyde (41 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (107 mg).

$\mathbf{R_f}$ = 0.48 in hexanes/EtOAc 90:10 v/v.

$[\boldsymbol{\alpha}]_{\mathrm{D}}^{22}$ = +33.86 (c 0.5, $CHCl_3$, 96% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.69 (app d, *J* = 7.5 Hz, 1H), 7.66–7.60 (comp, 3H), 7.59–7.55 (m, 1H), 7.48–7.43 (m, 1H), 7.36–7.32 (comp, 2H), 7.31–7.14 (comp, 7H), 7.06 (s, 1H), 6.68–6.58 (comp, 2H), 5.60 (s, 1H), 4.80 (s, 1H), 3.69 (s, 3H), 2.77–2.51 (comp, 2H), 2.43–2.39 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 159.8, 146.0, 144.5, 141.5, 140.4, 136.3, 136.0, 133.1, 132.0, 130.5, 128.0, 127.8, 127.4, 127.3, 126.5, 126.0, 125.1, 121.4, 120.3, 119.3, 119.3, 118.3, 114.4, 114.3, 110.8, 109.3, 65.0, 62.5, 54.7, 44.9, 23.9.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{27}N_2O$ $[M + H]^+$: 443.2203, found 443.2185.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 11.88 min (minor) and $t_R$ = 16.41 min (major).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-1-(3-methoxyphenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2j)**

Following the general procedure B, compound **2j** was obtained was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 3-methoxybenzaldehyde (41 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (107 mg).

$\mathbf{R_f}$ = 0.46 in hexanes/EtOAc 90:10 v/v.

$[\boldsymbol{\alpha}]_{\mathrm{D}}^{22}$ = +27.58 (c 0.5, $CHCl_3$, 96% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.74–7.57 (comp, 3H), 7.51 (app d, *J* = 7.3 Hz, 1H), 7.38 (app d, *J* = 7.5 Hz, 1H), 7.31–7.15 (comp, 8H), 7.14–7.12 (m, 1H), 7.07–6.95 (comp, 2H), 6.83 (ddd, *J* = 8.1, 2.7, 1.3 Hz, 1H), 5.63 (s, 1H), 4.86 (s, 1H), 3.76 (s, 3H), 2.80–2.56 (comp, 2H), 2.48–2.30 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 160.4, 145.9, 144.4, 142.9, 141.5, 140.4, 136.3, 135.5, 130.1, 128.0, 127.9, 127.4, 127.3, 126.6, 126.0, 125.1, 121.65, 121.5, 120.3, 119.3, 118.3, 114.5, 114.1, 110.8, 109.2, 64.7, 63.8, 55.3, 43.8, 22.1.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{27}N_2O$ $[M + H]^+$: 443.2203, found 443.2099.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 6.52 min (major) and $t_R$ = 8.62 min (minor).

**m.p.**: product decomposition at 161–163 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2k)**

Following the general procedure B, compound **2k** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 3-nitrobenzaldehyde (45 mg, 0.3 mmol,1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a yellow solid in 94% yield (107 mg).

**R$_f$** = 0.30 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +26.73 (c 0.5, CHCl$_3$, 91% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 8.39 (S, 1H), 8.08 (app d, *J* = 7.7 Hz, 1H), 7.86 (app d, *J* = 7.6 Hz, 1H), 7.69–7.57 (comp, 4H), 7.46–7.40 (comp, 2H), 7.35–7.22 (comp, 4H), 7.16–7.11 (comp, 2H), 7.08–6.99 (comp, 2H), 5.69 (s, 1H), 4.75 (s, 1H), 2.92–2.81 (comp, 2H), 2.58–2.56 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 141.4, 140.4, 135.6, 134.5, 133.6, 130.7, 129.5, 129.4, 128.6, 128.3, 128.1, 127.5, 126.7, 125.9, 125.1, 121.2, 120.4, 120.3, 119.5, 117.0, 116.3, 110.9, 66.2, 62.9, 42.7, 22.6.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{24}N_3O$ [M + H]$^+$: 458.1948, found 458.1898.

**SFC**: Daicel Chiralcel AD-H, column temperature = 40 °C, CO$_2$/MeOH = 70/30, Flow rate =2 mL/min, UV = 280 nm, t$_R$= 13.15 min (major) and t$_R$= 16.87 min (minor).

**m.p.**: product decomposition at 163–165 °C (conversion to black charred material)

**(*S*)-1-(2-bromophenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2l)**

Following the general procedure B, compound **2l** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 2-bromobenzaldehyde (56 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (116 mg).

**R$_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +284.51 (c 0.5, CHCl$_3$, 96% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 8.18 (s, 1H), 7.95–7.84 (comp, 4H), 7.75–7.67 (m, 1H), 7.63–7.48 (comp, 4H), 7.43–7.30 (comp, 4H), 7.19–7.07 (comp, 3H), 5.93 (s, 1H), 4.97 (s, 1H), 2.94–2.73 (comp, 2H), 2.66–2.58 (m, 1H), 2.52–2.48 (m, 1H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 145.5, 144.2, 141.4, 140.6, 140.4, 136.4, 134.9, 132.2, 131.1, 128.2, 128.01, 127.5, 127.2, 126.6, 125.9, 125.1, 122.4, 121.75, 120.4, 119.5, 119.4, 118.4, 110.8, 109.7, 64.8, 63.1, 44.0, 22.1.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{24}N_2Br$ [M + H]$^+$: 491.1198, found 491.1093.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 5.64 min (major) and t$_R$ = 6.41 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-(o-tolyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2m)**

Following the general procedure B, compound **2m** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 2-methylbenzaldehyde (36 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%)as a white solid in 94% yield (101 mg).

**R$_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +106.30 (c 0.5, CHCl$_3$, 89% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 7.74 (app d, *J* = 7.5 Hz, 1H), 7.68–7.55 (comp, 3H), 7.46 (app d, *J* = 7.4 Hz, 1H), 7.37 (app d, *J* = 6.8, 1H), 7.33–7.20 (comp, 4H), 7.19–7.16 (comp, 4H), 7.15–7.06 (comp, 2H), 7.03–7.0 (comp, 2H), 5.87 (s, 1H), 4.78 (s, 1H), 2.79–2.51 (comp, 2H), 2.53–2.26 (comp, 5H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 146.1, 144.3, 141.5, 140.4, 138.1, 137.9, 136.2, 135.1, 131.7, 131.6, 128.4, 128.0, 127.9, 127.5, 127.2, 126.6, 126.0, 125.4, 121.4, 120.4, 119.4, 119.3, 118.3, 110.8, 109.5, 65.0, 53.0, 44.3, 22.0, 19.6.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{27}N_2$ [M + H]$^+$: 427.2254, found 427.2181.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 5.66 min (minor) and t$_R$ = 10.42 min (major).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-(naphthalen-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2n)**

Following the general procedure B, compound **2n** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 2-naphthaldehyde (47 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (110 mg).

**R$_f$ =** 0.43 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ **=** +71.36 (c 0.5, CHCl$_3$, 99% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 8.18 (s, 1H), 7.96–7.83 (comp, 4H), 7.71 (dd, *J* = 27.4, 7.5 Hz, 2H), 7.64–7.48 (comp, 4H), 7.43–7.28 (comp, 6H), 7.19–7.01 (comp, 3H), 5.93 (s, 1H), 4.97 (s, 1H), 2.94–2.71 (comp, 2H), 2.67–2.57 (m, 1H), 2.52–2.48 (m, 1H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 145.8, 144.4, 141.5, 140.4, 138.9, 136.4, 135.4, 133.7, 133.3, 129.4, 128.5, 128.0, 127.9, 127.9, 127.8, 127.5, 127.3, 126.6, 126.6, 126.5, 126.3, 126.0, 125.2, 121.6, 120.4, 119.4, 119.3, 118.4, 110.8, 109.6, 64.7, 64.0, 43.9, 22.2.

**HRMS (ESI-TOF):** Calculated for $C_{34}H_{26}N_2$ [M + H]$^+$: 463.2254, found 463.2254.

**HPLC:** Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 6.35 min (major) and t$_R$ = 10.17 min (minor).

**m.p.:** product decomposition at 162–165 °C (conversion to black charred material)

**(*R*)-2-(9H-fluoren-9-yl)-1-(thiophen-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2o)**

Following the general procedure B (reaction performed at 0 °C for 65 h), compound **2o** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), 2-thiophenecarboxaldehyde (34 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 98% yield (98 mg).

**R$_f$ =** 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ **=** –1.39 (c 0.5, CHCl$_3$, 76% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 7.69–7.56 (comp, 4H), 7.38–7.36 (comp, 2H), 7.31–7.28 (comp, 2H), 7.29–7.22 (comp, 2H), 7.22–7.11 (comp, 2H), 7.06–7.02(m, 1H), 7.02–6.93 (comp, 2H), 6.02 (s, 1H), 5.21 (s, 1H), 5.05 (s, 1H), 2.58–2.54 (comp, 1H), 2.48–2.34 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 146.1, 145.6, 144.2, 141.5, 140.4, 136.3, 134.7, 128.1, 128.0, 127.5, 127.3, 127.2, 127.0, 126.6, 126.3, 125.9, 125.5, 121.7, 120.4, 119.4, 119.3, 118.5, 110.9, 109.0, 64.8, 59.2, 43.9, 22.0.

**HRMS (ESI-TOF)**: Calculated for $C_{28}H_{22}N_2S$ [M + H]$^+$: 419.1661, found 419.1560.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 7.59 min (minor) and t$_R$ = 18.32 min (major).

**m.p.**: product decomposition at 150–153 °C (conversion to black charred material)

**(*S*)-2-(9H-fluoren-9-yl)-1-propyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2p)**

Following the general procedure B (reaction performed at –20 °C for 18 h), compound **2p** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), butyraldehyde (22 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (90 mg).

**R$_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +3.52 (c 0.5, CHCl$_3$, 88% ee).

**$^1$H-NMR** (400 MHz, CDCl$_3$): δ = 7.72 (s, 1H), 7.72–7.56 (comp, 3H), 7.53 (app d, *J* = 7.3 Hz, 1H), 7.39 (app d, *J* = 7.7 Hz, 1H), 7.33–7.29 (comp,2H), 7.27–7.21 (comp, 3H), 7.13–6.95 (comp, 3H), 5.12 (s, 1H), 4.57 (s, 1H), 2.56–2.41 (comp, 2H), 2.28–2.06 (comp, 2H), 1.86–1.61 (m, 2H), 1.30–1.13 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C-NMR** (101 MHz, CDCl$_3$): δ = 145.7, 145.3, 140.9, 140.6, 136.0, 135.7, 134.4, 128.0, 127.9, 127.4, 127.4, 126.7, 125.8, 125.4, 121.3, 120.0, 119.5, 119.2, 118.1, 111.1, 66.4, 56.7, 43.4, 35.5, 22.0, 17.5, 14.5.

**HRMS (ESI-TOF)**: Calculated for $C_{27}H_{27}N_2$ [M + H]$^+$: 379.2174, found 379.2181.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 8.69 min (major) and $t_R$ = 10.97 min (minor).

**m.p.**: product decomposition at 150–153 °C (conversion to black charred material)

### (*S*)-2-(9H-fluoren-9-yl)-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2q)

Following the general procedure B, compound **2q** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), isovaleraldehyde (26 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 92% (93 mg).

$\mathbf{R_f}$ = 0.56 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +10.68 (c 0.5, $CHCl_3$, 53% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.78–7.60 (comp, 2H), 7.49 (app d, *J* = 7.3 Hz, 1H), 7.43–7.15 (comp, 5H), 7.11–7.03 (m, 1H), 7.01–6.93 (comp, 2H), 5.04 (s, 1H), 4.39 (s, 1H), 2.77–2.55 (comp, 2H), 2.37–2.30 (m,1H), 2.17–2.09 (comp, 3H), 1.88–1.81 (m, 1H), 1.73–1.67 (m,1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.9, 145.4, 140.7, 140.5, 136.7, 135.9, 128.0, 127.8, 127.4, 127.3, 126.8, 125.6, 125.5, 121.3, 119.7, 119.4, 119.2, 118.1, 110.6, 109.9, 68.6, 55.6, 44.1, 42.2, 25.1, 23.5, 22.9, 21.5.

**HRMS (ESI-TOF)**: Calculated for $C_{28}H_{28}N_2$ [M + H]$^+$: 393.2410, found 393.2235.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 4.29 min (minor) and $t_R$ = 5.49 min (major).

**m.p.**: product decomposition at 150–153 °C (conversion to black charred material)

### (*S*)-1-cyclohexyl-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2r)

Following the general procedure B, compound **2r** was obtained from *N*-(2-(1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1a** (81 mg, 0.25 mmol), cyclohexanecarbaldehyde (34 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 93% yield (101 mg).

$\mathbf{R_f}$ = 0.52 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +27.90 (c 0.5, $CHCl_3$, 59% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.76–7.53 (comp, 4H), 7.42–7.31 (comp, 3H), 7.19–7.06 (comp,4H), 6.96–6.93(m, 1H), 5.08 (s, 1H), 4.26 (s, 1H), 2.89–2.61 (comp, 2H), 2.36–2.26 (comp, 2H), 2.12–1.99 (comp, 5H), 1.84–1.57 (comp, 7H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.3, 144.0, 141.4, 140.4, 139.4, 135.6, 134.5, 133.6, 130.7, 129.5, 129.4, 128.6, 128.3, 128.1, 127.5, 126.7, 125.9, 125.1, 121.2, 120.4, 120.3, 119.5, 117.0, 116.3, 110.9, 64.7, 62.9, 60.4, 43.9, 29.7, 22.2, 21.1, 14.2.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{30}N_2$ [M + H]$^+$: 419.2567, found 419.2497.

**SFC**: Daicel Chiralcel AD-H, column temperature = 40 °C, $CO_2$/MeOH = 80/20, Flow rate =2 mL/min, UV = 280 nm, $t_R$= 12.92 min (minor) and $t_R$= 14.23 min (major).

**m.p.**: product decomposition at 150–153 °C (conversion to black charred material)

### (*S*)-2-(9H-fluoren-9-yl)-5-methoxy-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2s)

Following the general procedure B, compound **2s** was obtained from *N*-(2-(5-methoxy-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1b** (89 mg, 0.25 mmol), benzaldehyde (30 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 95% yield (105 mg).

$\mathbf{R_f}$ = 0.45 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +214.40 (c 0.5, $CHCl_3$, 93% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.71 (app d, *J* = 7.5 Hz, 1H), 7.66–7.63 (comp, 2H), 7.59 (app d, *J* = 7.4 Hz, 1H), 7.47 (app d, *J* = 7.4 Hz, 1H), 7.37–7.18 (comp, 8H), 7.08 (s, 1H), 6.67–6.65 (comp, 2H), 5.63 (s, 1H), 4.81 (s, 1H), 3.72 (s, 3H), 2.75–2.54 (comp, 2H), 2.47–2.27 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 156.2, 145.9, 144.5, 141.5, 141.5, 140.4, 137.1, 134.4, 129.4, 129.1, 128.5, 128.00, 127.9, 127.4, 126.6, 126.0, 125.9, 121.7, 120.3, 119.3, 118.9, 109.2, 108.8, 95.0, 64.6, 63.8, 55.7, 43.8, 22.2.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{27}N_2O$ [M + H]$^+$: 443.2203, found 443.2129.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 4.71 min (major) and $t_R$ = 5.62 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

### (*S*)-5-chloro-1-(4-chlorophenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2t)

Following the general procedure B, compound **2t** was obtained from *N*-(2-(5-chloro-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1c** (90 mg, 0.25 mmol), 4-chlorobenzaldehyde (45 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 94% yield (105 mg).

$\mathbf{R_f}$ = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +206.32 (c 0.5, $CHCl_3$, 93% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.72–7.56 (comp, 5H), 7.46 (app d, *J* = 7.3 Hz, 1H), 7.41–7.25 (comp, 6H), 7.21 –7.17 (comp, 3H), 7.03–6.93 (comp, 2H), 5.62 (s, 1H), 4.80 (s, 1H), 2.7–2.52 (comp, 2H), 2.45–2.29 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 149.5, 148.0, 144.8, 143.9, 141.3, 140.5, 136.6, 133.8, 130.2, 128.5, 128.2, 127.6, 127.0, 126.8, 125.9, 125.1, 124.2, 122.1, 120.4, 119.7, 119.6, 118.6, 111.0, 110.2, 67.0, 64.2, 46.4, 22.2.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{23}N_2Cl_2$ [M + H]$^+$: 481.1838, found 481.1810.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 16.18 min (major) and $t_R$ = 18.53 min (minor).

**m.p.**: product decomposition at 162–165 °C (conversion to black charred material)

### (*S*)-1-(4-chlorophenyl)-2-(9H-fluoren-9-yl)-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2u)

Following the general procedure B, compound **2u** was obtained from *N*-(2-(5-(trifluoromethyl)-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1d** (98 mg, 0.25 mmol), 4-chlorobenzaldehyde (45 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 83% yield (107 mg).

$\mathbf{R_f}$ = 0.28 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +8.92 (c 0.5, $CHCl_3$, 62% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.68–7.51 (comp, 5H), 7.42 (app d, *J* = 7.0 Hz, 1H), 7.35–7.28 (comp, 5H), 7.24–7.16 (comp, 2H), 7.04 (app d, *J* = 7.5 Hz, 1H), 6.95–6.91 (m, 1H), 5.61 (s, 1H), 4.77 (s, 1H), 2.79–2.55 (comp, 2H), 2.54–2.31 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 145.9, 145.2, 144.1, 141.4, 139.8, 138.6, 136.5, 134.9, 130.1, 129.7, 128.2, 128.1, 127.5, 127.1, 126.7, 126.0(q, $J_{C-F}$ = 41 Hz), 125.8, 125.1, 122.4, 120.4, 119.6, 119.5, 118.4, 110.8, 109.1, 66.3, 64.5, 62.8, 25.4, 22.1.

**$^{19}$F NMR** (377 MHz, $CDCl_3$): δ = –61.38

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{22}N_2ClF_3$ [M + H]$^+$: 515.1424, found 515.1321.

**HPLC**: Daicel Chiralpak OJ-H, n-hexane/*i*-PrOH = 95/05, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 6.06 min (major) and $t_R$ = 7.20 min (minor).

**m.p.**: product decomposition at 178–180 °C (conversion to black charred material)

### (*S*)-2-(9H-fluoren-9-yl)-7-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2v)

Following the general procedure B (reaction performed at 0 °C for 17 h), compound **2v** was obtained from *N*-(2-(6-methyl-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1e** (90 mg, 0.25 mmol) , benzaldehyde (30 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 91% yield (95 mg).

**R$_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +98.46 (c 0.5, $CHCl_3$, 90% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.72 (app d, *J* = 7.6 Hz, 1H), 7.65–7.57 (comp, 4H), 7.46 (app d, *J* = 7.4 Hz, 1H), 7.39–7.13 (comp, 8H), 7.03 (s, 1H), 6.89 (s, 1H), 6.82 (app d, *J* = 8.0, 1H), 5.62 (s, 1H), 4.82 (s, 1H), 2.69–2.57 (comp, 2H), 2.46–2.42 (m, 1H), 2.35–2.32 (comp, 4H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 146.0, 145.4, 144.5, 143.8, 141.5, 141.5, 140.7, 140.4, 139.7, 139.4, 136.8, 136.1, 135.0, 134.8, 134.5, 131.3, 131.1, 129.4, 129.1, 128.5, 128.0, 127.9, 127.4, 126.6, 126.0, 125.2, 121.0, 120.3, 119.3, 118.0, 110.9, 109.2, 64.7, 63.8, 43.9, 22.3, 21.8.

**HRMS (ESI-TOF)**: Calculated for $C_{31}H_{27}N_2$ [M + H]$^+$: 427.2254, found 427.1274.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 9.88 min (major) and $t_R$ = 13.89 min (minor).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**(*S*)-8-chloro-1-(4-chlorophenyl)-2-(9H-fluoren-9-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2w)**

Following the general procedure B, compound **2w** was obtained *N*-(2-(7-chloro-1H-indol-3-yl)ethyl)-9H-fluoren-9-amine **1f** (90 mg, 0.25 mmol), 4-chlorobenzaldehyde (45 mg, 0.3 mmol, 1.2 equiv) and catalyst **3d** (23.2 mg, 0.025 mmol, 10 mol%) as a white solid in 93% yield (105 mg).

**R$_f$** = 0.5 in hexanes/EtOAc 90:10 v/v.

$[\alpha]_D^{22}$ = +163.68 (c 0.5, $CHCl_3$, 95% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.67–7.63 (comp, 2H), 7.60 (app d, *J* = 7.5 Hz, 1H), 7.39–7.36 (comp, 3H), 7.32–7.13 (comp, 6H), 7.08–6.93 (comp, 3H), 6.03 (s, 1H), 5.06 (s, 1H), 2.78–2.51 (comp, 2H), 2.45–2.41 (comp, 2H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 141.4, 140.5, 134.7, 134.5, 131.0, 130.7, 129.4, 128.3, 128.2, 127.6, 126.7, 125.9, 125.2, 121.9, 121.2, 120.4, 119.5, 118.0, 111.8, 109.5, 64.8, 62.9, 29.7, 21.9.

**HRMS (ESI-TOF)**: Calculated for $C_{30}H_{23}N_2Cl_2$ [M + H]$^+$: 481.1838, found 481.1218.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 3.87 min (minor) and $t_R$ = 5.16 min (major).

**m.p.**: product decomposition at 160–165 °C (conversion to black charred material)

**General Procedure C** - In a flame dried vial, $Pd(OH)_2$ on carbon (10 mol%) was added , followed by addition of **2d** or **2p** (1.0 equiv), solvent (0.1 M) and acetic acid (AcOH) (1.5 equiv). The reaction mixture was purged with $H_2$ balloon for 10 minutes and allowed to react for additional 45 minutes. After complete consumption of starting material, triethyl amine (2.00 equiv) and $(Boc)_2O$ (2.00 equiv) were added to the reaction mixture. Stirring was then continued for 3 hours. The resulting mixture was passed through a short pad of celite, and the solvent was removed under reduced pressure. The residue was directly purified by flash chromatography on silica gel (using a gradient eluent from hexanes to EtOAc/hexanes 10:90 to EtOAc/hexanes 20:80).

***t*-butyl (*S*)-1-phenyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (4a) and *t*-butyl (2-(2-benzyl-1H-indol-3-yl)ethyl)carbamate (4a')**

Following general procedure C, compound **4a** and **4a**′ were obtained from (*S*)-2-(9H-fluoren-9-yl)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole **2d** (200 mg, 0.5 mmol), $Pd(OH)_2$ (35 mg, 0.05 mmol, 10 mol%), triethyl amine ($Et_3N$) (0.20 mL, 1 mmol, 2 equiv), and $(Boc)_2O$ (211 mg, 1 mmol, 2 equiv) as a white solid in 78% yield (130 mg) and as a yellow solid in 20% yield (31 mg) respectively.

**R$_f$ =** 0.23 in hexanes/EtOAc 80:20 v/v.

$[\alpha]_D^{25}$ = +148.37 (c 0.45, $CH_2Cl_2$, 95% ee).

The absolute configuration was assigned by comparing the sign of the optical rotation with the reported literature value of this product $[\alpha]_D^{25}$ = +130.8 (c 0.45, $CH_2Cl_2$, 87% ee).[3q]

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.58 (app d, 1.8 Hz, 1H), 7.37–7.32 (comp, 2H), 7.30–7.27 (comp, 2H), 7.26–7.23 (comp, 2H), 7.19–7.09 (comp, 2H), 4.14 (s, 1H), 3.55–3.30 (comp, 2H), 3.03–2.95 (comp, 2H), 1.44 (s, 9H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 154.6, 140.5, 136.2, 131.8, 128.7, 128.5, 128.3, 128.0, 126.8, 122.0, 119.6, 118.3, 110.9, 110.7, 80.3, 54.6, 53.7, 38.1, 29.6, 28.5, 21.4.

**HRMS (ESI-TOF)**: Calculated for $C_{22}H_{24}N_2O_2$ [M + H]$^+$: 349.1917, found 349.1929.

**SFC**: Daicel Chiralcel AD-H, column temperature = 40 °C, $CO_2$/MeOH = 80/20, Flow rate =2 mL/min, UV = 280 nm, $t_R$= 5.14 min (minor) and $t_R$= 8.90 min (major).

**m.p.**: 215–220 °C

Characterization data for **4a'**:

**R$_f$ =** 0.1 in hexanes/EtOAc 80:20 v/v.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.58 (app d, *J* = 7.1, 1.8 Hz, 1H), 7.34 (app d, *J* = 1.7 Hz, 1H), 7.31–7.19 (comp, 5H), 7.18–7.09 (comp, 2H), 4.14 (s, 2H), 3.47–3.38 (m, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 1.44 (s, 9H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 156.0, 138.6, 135.6, 134.4, 128.9, 128.7, 128.5, 128.4, 126.8, 121.5, 119.4, 118.4, 110.6, 109.4, 79.2, 53.6, 32.3, 28.6, 28.4, 24.8.

**HRMS (ESI-TOF):** Calculated for $C_{30}H_{26}N_2$ [M + Na]$^+$: 373.1994, found 373.1917.

**m.p.**: 146–148 °C

***t*-butyl (*S*)-1-propyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (4b)**

Following general procedure C, compound **4b** was obtained from (*S*)-2-(9H-fluoren-9-yl)-1-propyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole **2p** (0.5 mmol), $Pd(OH)_2$ (35 mg, 0.05 mmol, 10 mol%), triethyl amine ($Et_3N$) (0.20 mL, 1 mmol, 2 equiv), and $(Boc)_2O$ (211 mg, 1 mmol, 2 equiv) as a colorless liquid in 95% yield (150 mg).

**R$_f$ =** 0.34 in hexanes/EtOAc 80:20 v/v.

$[\alpha]_D^{25}$ = + 213.73 (c 0.45, $CH_2Cl_2$, 88% ee).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ = 8.30–8.06 (m, 1H), 7.52–7.50 (m, 1H), 7.34–7.28 (app d, *J* = 7.8 Hz, 1H), 7.20–7.11 (comp, 2H), 5.39–5.19 (m, 1H), 4.56–4.31 (m, 1H), 3.26–3.10 (m, 1H), 2.92–2.69 (comp, 2H), 1.85–1.70 (comp, 2H), 1.55–1.30 (comp, 11H), 1.08–0.93 (comp, 3H).

**$^{13}$C-NMR** (101 MHz, $CDCl_3$): δ = 155.2, 138.9, 128.6, 121.8, 121.5, 120.0, 119.3, 118.2, 117.9, 112.2, 80.8, 51.4, 49.7, 38.3, 36.4, 27.8, 18.7, 10.6.

**MS (ESI-MS)**: Calculated for $C_{19}H_{26}N_2O_2$ [M – Boc + 2H]$^+$: 215.14, found 215.10.

**HPLC**: Daicel Chiralpak AD-H, n-hexane/*i*-PrOH = 97/03, Flow rate = 1 mL/min, UV = 230 nm, $t_R$ = 9.81 min (minor) and $t_R$ = 11.60 min (major).

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## Supporting Information

YES (this text will be updated with links prior to publication)

## Primary Data

NO.

## Conflict of Interest

The authors declare no conflict of interest.

## References

(1) Pictet, A.; Spengler, T., *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

(2) Selected reviews on Pictet–Spengler and related reactions: (a) Stöckigt, J.; Antonchick, A. P.; Wu, F. R.; Waldmann, H., *Angew. Chem. Int. Ed.* **2011**, *50*, 8538; (b) Ingallina, C.; D'Acquarica, I.; Delle Monache, G.; Ghirga, F.; Quaglio, D.; Ghirga, P.; Berardozzi, S.; Markovic, V.; Botta, B., *Curr. Pharm. Design* **2016**, *22*, 1808; (c) Glinsky-Olivier, N.; Guinchard, X., *Synthesis* **2017**, *49*, 2605; (d) M. Heravi, M.; Zadsirjan, V.; Malmir, M., *Molecules* **2018**, *23*, 943; (e) Gholamzadeh, P., In *Adv. Heterocycl. Chem.*ed., Vol. 127; Scriven, E. F. V.; Ramsden, C. A., Eds.; Academic Press, **2019**, pp 153; (f) Zhu, Z.; Adili, A.; Zhao, C.; Seidel, D., *SynOpen* **2019**, *03*, 77; (g) Calcaterra, A.; Mangiardi, L.; Delle Monache, G.; Quaglio, D.; Balducci, S.; Berardozzi, S.; Iazzetti, A.; Franzini, R.; Botta, B.; Ghirga, F., *Molecules* **2020**, *25*, 414; (h) Zheng, C.; You, S.-L., *Acc. Chem. Res.* **2020**, *53*, 974.

(3) Examples of catalytic enantioselective Pictet–Spengler reactions: (a) Taylor, M. S.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2004**, *126*, 10558; (b) Seayad, J.; Seayad, A. M.; List, B., *J. Am. Chem. Soc.* **2006**, *128*, 1086; (c) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H., *Angew. Chem. Int. Ed.* **2007**, *46*, 7485; (d) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2007**, *129*, 13404; (e) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N., *Org. Lett.* **2008**, *10*, 1577; (f) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H., *J. Org. Chem.* **2008**, *73*, 6405; (g) Klausen, R. S.; Jacobsen, E. N., *Org. Lett.* **2009**, *11*, 887; (h) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J., *J. Am. Chem. Soc.* **2009**, *131*, 10796; (i) Holloway, C. A.; Muratore, M. E.; Storer, R. l.; Dixon, D. J., *Org. Lett.* **2010**, *12*, 4720; (j) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K., *ACS Comb. Sci.* **2012**, *14*, 285; (k) Huang, D.; Xu, F. X.; Lin, X. F.; Wang, Y. G., *Chem. Eur. J.* **2012**, *18*, 3148; (l) Cai, Q.; Liang, X. W.; Wang, S. G.; Zhang, J. W.; Zhang, X.; You, S. L., *Org. Lett.* **2012**, *14*, 5022; (m) Kerschgens, I. P.; Claveau, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H., *Chem. Commun.* **2012**, *48*, 12243; (n) Aillaud, I.; Barber, D. M.; Thompson, A. L.; Dixon, D. J., *Org. Lett.* **2013**, *15*, 2946; (o) Toda, Y.; Terada, M., *Synlett* **2013**, *24*, 752; (p) Cai, Q.; Liang, X. W.; Wang, S. G.; You, S. L., *Org. Biomol. Chem.* **2013**, *11*, 1602; (q) Mittal, N.; Sun, D. X.; Seidel, D., *Org. Lett.* **2014**, *16*, 1012; (r) Ruiz-Olalla, A.; Würdemann, M. A.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H., *J. Org. Chem.* **2015**, *80*, 5125; (s) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2017**, *139*, 12299; (t) Ahmad, S.; Shukla, L.; Szawkało, J.; Roszkowski, P.; Maurin, J. K.; Czarnocki, Z., *Catal. Commun.* **2017**, *89*, 44; (u) Wang, S.-G.; Xia, Z.-L.; Xu, R.-Q.; Liu, X.-J.; Zheng, C.; You, S.-L., *Angew. Chem. Int. Ed.* **2017**, *56*, 7440; (v) Odagi, M.; Araki, H.; Min, C.; Yamamoto, E.; Emge, T. J.; Yamanaka, M.; Seidel, D., *Eur. J. Org. Chem.* **2019**, *2019*, 486; (w) Glinsky-Olivier, N.; Yang, S.; Retailleau, P.; Gandon, V.; Guinchard, X., *Org. Lett.* **2019**, *21*, 9446; (x) Andres, R.; Wang, Q.; Zhu, J., *J. Am. Chem. Soc.* **2020**, *142*, 14276; (y) Retini, M.; Bartoccini, F.; Zappia, G.; Piersanti, G., *Eur. J. Org. Chem.* **2021**, *2021*, 825; (z) Lynch-Colameta, T.; Greta, S.; Snyder, S. A., *Chem. Sci.* **2021**, *12*, 6181; (aa) Kim, A.; Kim, A.; Park, S.; Kim, S.; Jo, H.; Ok, K. M.; Lee, S. K.; Song, J.; Kwon, Y., *Angew. Chem. Int. Ed.* **2021**, *60*, 12279; (ab) Chan, Y.-C.; Sak, M. H.; Frank, S. A.; Miller, S. J., *Angew. Chem. Int. Ed.* **2021**, *60*, 24573; (ac) Nakamura, S.; Matsuda, Y.; Takehara, T.; Suzuki, T., *Org. Lett.* **2022**, *24*, 1072; (ad) Andres, R.; Wang, Q.; Zhu, J., *Angew. Chem. Int. Ed.* **2022**, *61*, e202201788.

(4) Selected reviews on asymmetric Brønsted acid catalysis: (a) Yamamoto, H.; Futatsugi, K., *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; (b) Akiyama, T., *Chem. Rev.* **2007**, *107*, 5744; (c) Terada, M., *Synthesis* **2010**, 1929; (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M., *Chem. Rev.* **2014**, *114*, 9047; (e) Akiyama, T.; Mori, K., *Chem. Rev.* **2015**, *115*, 9277; (f) Rueping, M.; Parmar, D.; Sugiono, E., Wiley-VCH: Weinheim, **2015**; (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M., *Chem. Rev.* **2017**, *117*, 10608; (h) Min, C.; Seidel, D., *Chem. Soc. Rev.* **2017**, *46*, 5889; (i) Mitra, R.; Niemeyer, J., *ChemCatChem* **2018**, *10*, 1221; (j) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G., *Chem. Eur. J.* **2018**, *24*, 3925; (k) Schreyer, L.; Properzi, R.; List, B., *Angew. Chem. Int. Ed.* **2019**, *58*, 12761; (l) Benda, M. C.; France, S., *Org. Biomol. Chem.* **2020**, *18*, 7485; (m) Caballero-García, G.; Goodman, J. M., *Org. Biomol. Chem.* **2021**, *19*, 9565.

(5) The use of *N*-9-fluorenyl imines in asymmetric catalysis is known. Examples: (a) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M., *Angew. Chem. Int. Ed.* **2000**, *39*, 1650; (b) Zhu, Y.; Buchwald, S. L., *J. Am. Chem. Soc.* **2014**, *136*, 4500.

(6) (a) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D., *Angew. Chem. Int. Ed.* **2013**, *52*, 14084; (b) Zhao, C.; Seidel, D., *J. Am. Chem. Soc.* **2015**, *137*, 4650; (c) Min, C.; Lin, C.-T.; Seidel, D., *Angew. Chem. Int. Ed.* **2015**, *54*, 6608; (d) Zhu, Z.; Odagi, M.; Zhao, C.; Abboud, K. A.; Kirm, H. U.; Saame, J.; Lõkov, M.; Leito, I.; Seidel, D., *Angew. Chem. Int. Ed.* **2020**, *59*, 2028; (e) Zhu, Z.; Odagi, M.; Supantanapong, N.; Xu, W.; Saame, J.; Kirm, H.-U.; Abboud, K. A.; Leito, I.; Seidel, D., *J. Am. Chem. Soc.* **2020**, *142*, 15252.

(7) Selected reviews on catalysis with chiral anions and anion-binding catalysis: (a) Lacour, J.; Hebbe-Viton, V., *Chem. Soc. Rev.* **2003**, *32*, 373; (b) Lacour, J.; Moraleda, D., *Chem. Commun.* **2009**, 7073; (c) Zhang, Z.; Schreiner, P. R., *Chem. Soc. Rev.* **2009**, *38*, 1187; (d) Beckendorf, S.; Asmus, S.; Mancheño, O. G., *ChemCatChem* **2012**, *4*, 926; (e) Avila, E. P.; Amarante, G. W., *ChemCatChem* **2012**, *4*, 1713; (f) Phipps, R. J.; Hamilton, G. L.; Toste, F. D., *Nat. Chem.* **2012**, *4*, 603; (g) Woods, P. A.; Smith, A. D., *Supramolecular Chemistry: From Molecules to Nanomaterials* **2012**, *4*, 1383; (h) Mahlau, M.; List, B., *Angew. Chem. Int. Ed.* **2013**, *52*, 518; (i) Brak, K.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2013**, *52*, 534; (j) Seidel, D., *Synlett* **2014**, *25*, 783; (k) Busschaert, N.; Caltagirone, C.; Van Rossom, W.; Gale, P. A., *Chem. Rev.* **2015**, *115*, 8038; (l) Visco, M. D.; Attard, J.; Guan, Y.; Mattson, A. E., *Tetrahedron Lett.* **2017**, *58*, 2623; (m) Schifferer, L.; Stinglhamer, M.; Kaur, K.; Macheño, O. G., *Beilstein J. Org. Chem.* **2021**, *17*, 2270; (n) Entgelmeier, L.-M.; Mancheño, O. G., *Synthesis* **2022**, DOI: 10.1055/a.

(8) Selected reviews on asymmetric ion pairing and cooperative catalysis: (a) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M., *Angew. Chem., Int. Ed.* **2011**, *50*, 6216; (b) Allen, A. E.; MacMillan, D. W. C., *Chem. Sci.* **2012**, *3*, 633; (c) Brière, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V., *Chem. Soc. Rev.* **2012**, *41*, 1696; (d) Peters, R., ed., Vol.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2015**, p 427; (e) Gimeno, M. C.; Herrera, R. P., *Eur. J. Org. Chem.* **2020**, *2020*, 1057.

(9) (a) Hoffmann, S.; Seayad, A. M.; List, B., *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; (b) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B., *Synlett* **2010**, *2010*, 2189.

(10) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I., *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

(11) The synthesis of **2p** at room temperature was complete within 30 min, providing the product in 95% yield and with 80% ee.