Isothiourea-Catalyzed Formal Enantioselective Conjugate Addition of Benzophenone Imine Derivatives to β-Fluorinated α,β-Unsaturated Esters

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Supporting Information

1. General Experimental.................................................................2
2. General Procedures......................................................................4
3. Preparation of Starting Materials..................................................6
   3.1 Data for α,β-Unsaturated Aryl Esters.......................................6
   3.2 Data for Benzophenone Derivatives..........................................9
   3.3 Data for Benzophenone Imine Derivatives..............................10
4. Products.....................................................................................18
5. Gram Scale Synthesis.................................................................101
6. Hydrolysis of Product 5...............................................................102
7. Absolute Configuration: Hydrolysis of Product 25.........................107
8. References...............................................................................108
1. GENERAL EXPERIMENTAL

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N₂) using standard vacuum line techniques. Anhydrous solvents (CH₂Cl₂) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 °C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

Room temperature (rt) refers to 20–25 °C.

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 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 ILMVAC vacuum controller, or IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL Recirculating Coolers filled with ethylene glycol and set to −6 °C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm). 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.

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

Optical rotations 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-20A₅ 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-20A₅R degassing unit, LC-20AD liquid chromatography pypmp, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALPAK AD-H column using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.
Infrared spectra 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 wavenumber ($\nu_{\text{max}}$) reported in cm$^{-1}$.

$^1$H and $^{13}$C($^1$H) NMR spectra were acquired on either a Bruker AV300 with a BBFO probe ($^1$H 300 MHz; $^{13}$C($^1$H) 75 MHz), a Bruker AV400 with a BBFO probe ($^1$H 400 MHz; $^{13}$C($^1$H) 101 MHz), a Bruker AVII 400 with a BBFO probe ($^1$H 400 MHz; $^{13}$C($^1$H) 101 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe ($^1$H 500 MHz, $^{13}$C($^1$H) 126 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe ($^1$H 500 MHz, $^{13}$C($^1$H) 126 MHz), or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe ($^1$H 700 MHz, $^{13}$C($^1$H) 176 MHz) in the deuterated solvent stated. All chemicals 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 of 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 nuclear Overhauser effect spectroscopy (NOESY), 2D $^1$H–$^{13}$C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D $^1$H–$^{13}$C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry ($m$/z) data were acquired by nanospray ionisation (NSI) at the University of St Andrews Mass Spectrometry Facility ([A] quoted).
2. GENERAL PROCEDURES

General Procedure A1: Synthesis of α,β-Unsaturated Aryl Esters

The appropriate amount of α,β-unsaturated acid (1.0 equiv.) was charged in to a flame-dried flask with the appropriate amount of alcohol (1.5 equiv.), EDCI (2.0 equiv.), and DMAP (0.1 equiv.), in CH$_2$Cl$_2$ (0.15 M) at room temperature. The resulting solution was stirred for 16 h at room temperature and then concentrated in vacuo. The resulting oil was dissolved in EtOAc (100 mL) and washed with aqueous citric acid (10% w/v, 3 × 50 mL), dried over anhydrous MgSO$_4$, and concentrated in vacuo. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure A2:

The appropriate amount of carboxylic acid (1.0 equiv.) was dissolved in CH$_2$Cl$_2$ (0.33 M) and added with oxalyl chloride (1.0 equiv) and a few drops of DMF were added. The mixture was then stirred for 1 hour at room temperature. Diisopropylethylamine (2.0 equiv.) and the requisite aryl alcohol (1.0 equiv.) were then added and stirred overnight at room temperature. The mixture was then concentrated in vacuo and the residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure A3:

The appropriate amount of the corresponding carboxylic acid (1.0 equiv.) in CH$_2$Cl$_2$ (0.1 M) was added with the appropriate aryl alcohol (1.1 equiv.), DCC (1.1 equiv.), and DMAP (0.2 equiv.) at 0 ºC. The mixture was then stirred for 12 hours at room temperature. The mixture was then filtered and concentrated under vacuo. The residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure B: Synthesis of 2-Hydroxybenzophenone compounds

The appropriate amount of carbonic acid 4 was added with the appropriate aryl alcohol (1.1 equiv.), DCC (1.1 equiv.), and DMAP (0.2 equiv.) at 0 ºC. The mixture was then stirred for 12 hours at room temperature. The mixture was then filtered and concentrated under vacuo. The residue was purified by column chromatography under the conditions specified to afford the final product.
The appropriate amount of 2-hydroxybenzaldehyde derivative (1.0 equiv.), PdCl$_2$ (0.05 equiv.), LiCl (0.2 equiv.), Na$_2$CO$_3$ (2.0 equiv.) and DMF (0.12 M) were charged into a round-bottom flask under N$_2$ atmosphere. The reaction mixture was then heated to 120 °C, the requisite iodobenzene derivative (2.0 equiv.) was added and the reaction was stirred for 16 h – 20 h. The reaction mixture was added to EtOAc (20 mL), extracted with brine (3 × 20 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

**General Procedure C: Synthesis of 2-Hydroxybenzophenone Imines**

![Chemical structure of 2-Hydroxybenzophenone Imines]

The appropriate amount of 2-hydroxybenzophenone derivative (1.0 equiv.) was charged with NH$_3$ (7 N in MeOH) (5.0 equiv.) and the reaction mixture stirred for 6 h – 20 h at room temperature then concentrated in vacuo. The residue was purified by flash silica column chromatography under the conditions specified to afford the final product.

**General Procedure D: Synthesis of β-Amino Substituted Amides**

![Chemical structures of β-Amino Substituted Amides]

The requisite α,β-Unsaturated aryl ester (1.0 equiv.), 2-hydroxybenzophenone imine (2.0 equiv.), and isothiourea catalyst (20 mol%) were reacted in toluene (0.1 M) were stirred for 30 h at room temperature. The appropriate nucleophile (1.5 equiv.) was added, and the reaction stirred for 16 h at room temperature. The mixture was then concentrated in vacuo to give the crude material, which was purified by flash column chromatography under the conditions specified to afford the final product.
3. PREPARATION OF STARTING MATERIALS

3.1 Data for α,β-Unsaturated Aryl Esters

4-Nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (4)

Following General Procedure A1, (E)-4,4,4-trifluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH₂Cl₂ (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the titled compound (477 mg, 32%) as a colourless crystalline solid. mp 86 – 88 ºC (Lit. mp 93 – 95ºC); IR ν max (ATR) 3091 (Ar-H), 1739 (C=O), 1132 (C-F); ¹H-NMR (400 MHz, CDCl₃), δH: 6.75 (1H, dq, ³JHH = 15.8, ⁴JHF = 1.9, CH=CCH₂COOPNP), 7.05 (1H, dq, ³JHH = 15.8, ³JHF = 6.4, CF₃C=CH), 7.39 (2H, m, C(2, 6)ArH), 8.35 (2H, m, C(3, 5)ArH); ¹⁹F{¹H} NMR (376 MHz, CDCl₃), δF: -65.7. Spectroscopic data in agreement with the literature.¹

4-Nitrophenyl (E)-4,4-difluorobut-2-enoate

Following General Procedure A1, (E)-4,4-difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH₂Cl₂ (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colourless crystalline solid. mp 74 – 76 ºC (Lit. mp 74 – 76 ºC); IR ν max (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); ¹H-NMR (400 MHz, CDCl₃), δH: 6.36 (1H, tdd, ²JHF = 54.5, ³JHH = 3.8, ⁴JHH = 1.1, -CF₂H), 6.55 (1H, dtd, ³JHH = 15.9, ⁴JHF = 5.9, ⁴JHH = 1.1, CF₂HCH=CH), 7.08 (1H, dtd, ³JHH = 15.9, ³JHF = 10.3, ³JHH = 3.8, CF₂HCH=CH), 7.38 (2H, m, C(2, 6)ArH), 8.33 (2H, m, C(3, 5)ArH); ¹⁹F{¹H} NMR (376 MHz, CDCl₃), δF: -116.9. Spectroscopic data in agreement with the literature.¹

4-Nitrophenyl (E)-3-chloro-4,4-difluorobut-2-enoate

Following General Procedure A1, (E)-3-chloro-4,4-difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH₂Cl₂ (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colourless crystalline solid. mp 74 – 76 ºC (Lit. mp 74 – 76 ºC); IR ν max (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); ¹H-NMR (400 MHz, CDCl₃), δH: 6.36 (1H, tdd, ²JHF = 54.5, ³JHH = 3.8, ⁴JHH = 1.1, -CF₂H), 6.55 (1H, dtd, ³JHH = 15.9, ⁴JHF = 5.9, ⁴JHH = 1.1, CF₂HCH=CH), 7.08 (1H, dtd, ³JHH = 15.9, ³JHF = 10.3, ³JHH = 3.8, CF₂HCH=CH), 7.38 (2H, m, C(2, 6)ArH), 8.33 (2H, m, C(3, 5)ArH); ¹⁹F{¹H} NMR (376 MHz, CDCl₃), δF: -116.9. Spectroscopic data in agreement with the literature.¹
Following **General Procedure A1**, (E)-4-chloro-4,4-difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH$_2$Cl$_2$ (40 mL) was stirred at rt for 16 h, purified by flash chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colorless crystal solid. **mp 74 – 76 °C** (*Lit. mp 74 – 76 °C)*; **IR** $\nu_{\text{max}}$ (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **$^{1}$H-NMR** (400 MHz, CDCl$_3$), $\delta_{H}$: 6.63 (1H, dt, $^{3}J_{HH} = 15.5$, $^{4}J_{HF} = 1.8$, CH=CHCF$_2$Cl), 7.19 (1H, dt, $^{3}J_{HH} = 15.6$, $^{3}J_{HF} = 9.0$, CF$_2$ClCH=CH), 7.39 (2H, m, C(2,6)ArH), 8.35 (2H, m, C(3,5)ArH); **$^{19}$F{$^{1}$H} NMR** (376 MHz, CDCl$_3$), $\delta_{F}$: -54.5. Spectroscopic data in agreement with the literature.$^1$

**4-Nitrophenyl (E)-3-chloro-4,4-difluorobut-2-enoate**

Following **General Procedure A2**, (E)-4-bromo-4,4-difluorobut-2-enoic acid (523 mg, 2.6 mmol), oxalyl chloride (223 µL, 2.6 mmol), and few drops of DMF in CH$_2$Cl$_2$ (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (362 mg, 2.6 mmol), $i$Pr$_2$NEt (905 µL, 5.2 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography (5:1 Petrol:EtOAc) to give the title compound (432 mg, 52%) as a white crystalline solid. **mp 78 – 80 °C** (*Lit. mp 79 – 80 °C)*. **IR** $\nu_{\text{max}}$ (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **$^{1}$H-NMR** (400 MHz, CDCl$_3$), $\delta_{H}$: 6.54 (1H, dt, $^{3}J_{HH} = 15.6$, $^{4}J_{HF} = 1.8$, CH=CHCF$_2$Cl), 7.23 (1H, m, CF$_2$BrCH=CH), 7.39 (2H, m, C(2,6)ArH), 8.35 (2H, m, C(3,5)ArH). **$^{19}$F{$^{1}$H} NMR** (376 MHz, CDCl$_3$), $\delta_{F}$: -50.6. Spectroscopic data in agreement with the literature.$^1$

**4-Nitrophenyl (E)-4,4,5,5,5-pentafluoropent-2-enoate**

Following **General Procedure A2**, (E)-4,4,5,5,5-pentafluoropent-2-enoic acid (610 mg, 3.2 mmol), oxalyl chloride (275 µL, 3.2 mmol), and few drops of DMF in CH$_2$Cl$_2$ (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (446 mg, 3.2 mmol), $i$Pr$_2$NEt (1.12 mL, 6.4 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography (2:1 Petrol:EtOAc) to give the title compound (800 mg, 80%) as a yellow oil. **IR** $\nu_{\text{max}}$ (ATR) 3118 (Ar-H), 1735 (C=O), 1487 – 1531 (C=C), 1342 (C-F); **$^{1}$H-NMR** (400 MHz, CDCl$_3$), $\delta_{H}$: 6.81 (1H, d, $^{3}J_{HH} = 15.8$ CH=CHCF$_2$F$_5$), 7.05 (1H, m, C$_2$F$_5$CH=CH), 7.39 (2H, m, C(2,6)ArH), 8.35 (2H, m, C(3,5)ArH). **$^{19}$F{$^{1}$H} NMR** (376 MHz, CDCl$_3$), $\delta_{F}$: -50.6. Spectroscopic data in agreement with the literature.$^1$
Ethyl (4-nitrophenyl) fumarate

Following General Procedure A1, (E)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10 mmol), 4-nitrophenol (2.08 g, 15 mmol), EDCI (3.83 g, 20 mmol), DMAP (122 mg, 1 mmol), and 80 mL CH₂Cl₂ was stirred at rt for 16 h and gave the titled compound (889 mg, 34%) as a white solid. mp 68 – 69 ºC (Lit. mp 67 – 68 ºC); IR νmax (ATR) 3072 (Ar-H), 1716 (C=O), 1514 (N-O), 1489 (C=C); ¹H NMR (400 MHz, CDCl₃), δH: 1.35 (3H, t, JHH = 7.1, OCH₂C₃H₃), 4.32 (2H, q, JHH = 7.1, OC₃H₂CH₃), 7.05 (2H, m, CH=C), 7.36 (2H, m, C(2,6)ArH), 8.31 (2H, m, C(3,5)ArH). Spectroscopic data in agreement with the literature.

Benzyl (4-nitrophenyl)fumarate

Following General Procedure A3, (E)-4-(benzyloxy)-4-oxobut-2-enoic acid (645 mg, 3.13 mmol), 4-nitrophenol (440 mg, 3.16 mmol), DCC (0.710 g, 3.44 mmol), DMAP (76 mg, 0.63 mmol), and 3 mL CH₂Cl₂ was stirred at rt for 12 h and gave the titled compound (0.607 g, 59%) as a white solid. mp 74 – 75 ºC (Lit. mp 74 – 76 ºC); IR νmax (ATR) 3078 (Ar-H), 1716 – 1737 (C=O), 1517 (N-O), 1490 (C=C); ¹H NMR (400 MHz, CDCl₃), δH: 5.29 (2H, s, CO₂-C₆H₅-C₆H₅), 7.22 (2H, m, CH=CH), 7.35 (2H, m, C(2,6)ArH-NO₂), 7.41 (5H, m, CO₂-C₆H₅-ArH), 8.30 (2H, m, C(3,5)ArH-NO₂). Spectroscopic data in agreement with the literature.

4-Nitrophenyl (E)-4-oxo-4-phenylbut-2-enoate

Following General Procedure A2, (E)-4-oxo-4-phenylbut-2-enoic acid (0.44 g, 2.5 mmol), oxalyl chloride (0.21 mL, 2.5 mmol), and few drops of DMF in CH₂Cl₂ (0.33 M) was stirred for 1 hour. Then, 4-nitrophenol (0.34 g, 2.5 mmol), iPr₂NEt (0.87 mL, 5.0 mmol) was added and stirred at rt for 16 h and gave the titled product as a yellow solid (0.15 g, 20%). mp 127 - 129 ºC (Lit. mp 128 – 129 ºC); IR νmax (ATR) 3080 (Ar-H), 1747 (C=O), 1521 (N-O), 1489 (C=C);
$^1$H NMR (400 MHz, CDCl$_3$), $\delta_H$: 7.10 (1H, d, $^3J_{HH} = 16.6$, CH=CH-CO-Ph), 7.40 (2H, m, C(2,6)ArH-NO$_2$), 7.56 (2H, m, C(3,5)ArH), 7.67 (1H, m, C(4)ArH), 8.05 (2H, m, C(2,6)ArH), 8.13 (1H, d, $^3J_{HH} = 16.6$ CH=CH-CO-Ph), 8.33 (2H, m, C(3,5)ArH-NO$_2$). Spectroscopic data in agreement with the literature.$^3$

**4-Nitrophenyl (E)-4-(dibenzylamino)-4-oxobut-2-enoate**

Following **General Procedure A3**, (E)-4-(dibenzylamino)-4-oxobut-2-enoic acid (2.08 g, 7.04 mmol), 4-nitrophenol (1.0 g, 7.18 mmol), DCC (1.74 g, 8.44 mmol), DMAP (172 mg, 0.141 mmol), and 7 mL CH$_2$Cl$_2$ was stirred at rt for 12 h and gave the titled compound (2.20 g, 75%) as an orange solid. *mp 62 – 65 ºC (Lit. *mp 62 – 64ºC)$^1$; IR $\nu_{max}$ (ATR) 3030 (Ar-H), 1741 (C=O), 1587 (N-O), 1440 (C=C); $^1$H NMR (400 MHz, CDCl$_3$), $\delta_H$: 5.29 (2H, s, CO$_2$-C$_6$H$_5$-C$_6$H$_5$), 7.22 (2H, m, C$_6$H$_5$=C$_6$H$_5$), 7.35 (2H, m, C(2,6)ArH-NO$_2$), 7.41 (5H, m, CO$_2$-C$_6$H$_5$-ArH), 8.30 (2H, m, C(3,5)ArH-NO$_2$). Spectroscopic data in agreement with the literature.$^1$

**3.2 Data for Benzophenone Derivatives**

**(4-Bromo-2-hydroxyphenyl)(phenyl)methanone**

Following **General Procedure B**, 4-bromo-2-hydroxybenzaldehyde (289.4 mg, 1.2 mmol), Iodobenzene (266 µL, 2.4 mmol), PdCl$_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na$_2$CO$_3$ (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 ºC for 16 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc) to give the title compound (269.5 mg, 72%) as a pale yellow liquid. IR $\nu_{max}$ (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$: 7.02 (1H, dd, $^3J_{HH} = 8.5$, $^4J_{HH} = 1.9$, C(5)ArOH-Br), 7.28 (1H, d, $^4J_{HH} = 1.9$, C(3)ArOH-Br), 7.46 (1H, d, $^3J_{HH} = 8.6$, C(6)ArOH-Br), 7.52 (2H, t, $^3J_{HH} = 7.5$, C(3,5)ArH), 7.60 (1H, m, C(4)ArH), 7.66 (2H, m, C(2,6)ArH), 12.1 (1H, s, OH). Spectroscopic data in agreement with literature.$^4$

**(2-Hydroxy-4-nitrophenyl)(phenyl)methanone**
Following **General Procedure B**, 2-hydroxy-4-nitrobenzaldehyde (200.6 mg, 1.2 mmol), iodobenzene (266 µL, 2.4 mmol), PdCl₂ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na₂CO₃ (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 °C for 6 hours, then purified by flash column chromatography (20:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (66.3 mg, 23%) as a pale yellow solid.

**1H NMR** (400 MHz, CDCl₃) δ ℎ: 7.59 (2H, dd, ³/J_HH = 8.3, ⁴/J_HH = 6.9 Hz, C(3,5)Ar), 7.68 (1H, m, C(4)Ar), 7.73 (3H, m, C(1,2)ArH and C(5)ArHOH-NO₂), 7.83 (1H, d, ³/J_HH = 2.2, C(3)ArHOH-NO₂), 7.94 (1H, d, ⁴/J_HH = 2.6 Hz, C(3)ArH), 12.01 (1H, s, OH). Spectroscopic data in agreement with the literature.

**(2-Hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone**

Following **General Procedure B**, 2-hydroxy-4-methoxybenzaldehyde (182.6 mg, 1.2 mmol), 1-iodo-4-methoxybenzene (561.7 µL, 2.4 mmol), PdCl₂ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na₂CO₃ (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 °C for 6 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (223.8 mg, 72%) as a pale yellow solid. mp 108 – 110 °C (Lit. mp 110–112 °C)⁵ ; IR \( \nu_{\text{max}} \) (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), 1270 (C-O-CH₃) ; **1H NMR** (400 MHz, CDCl₃) δ ℎ: 3.87 (3H, s, ArH-OC₃H₃), 3.89 (3H, s, ArHOH-OC₃H₃), 6.42 (1H, dd, ³/J_HH = 8.9 Hz, ⁴/J_HH = 2.6 Hz, C(5)ArHOH-OCH₃), 6.52 (1H, d, ³/J_HH = 2.6 Hz, C(3)ArHOH-OCH₃), 6.99 (2H, m, C(3,5)ArH-OCH₃), 7.56 (1H, d, ³/J_HH = 8.9 Hz, C(6)ArHOH-OCH₃), 7.66 (2H, m, C(2,6)ArH-OCH₃), 12.69 (1H, s, OH). Spectroscopic data in agreement with the literature.⁵,⁶

### 3.3 Data for Benzophenone Imine Derivatives

**2-(Imino(phenyl)methyl)-5-methoxyphenol (3)**

Following **General Procedure C**, (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (685 mg, 3 mmol), and 7N NH₃ in MeOH (2.14 mL, 15 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (0.31 g, 45%) as a yellow solid. mp 123 – 126 °C; IR \( \nu_{\text{max}} \) (ATR): 2932 (N-H), 1608 (C=N), 1423 – 1447
(C=C), 1277 (C-O); \textbf{\textit{1H NMR}} (400 MHz, CDCl$_3$) $\delta$: 3.84 (3H, s, OCH$_3$), 6.23 (1H, m, C(4)ArHOH-OCH$_3$), 6.45 (1H, s, C(6)ArHOH-OCH$_3$), 7.06 (1H, d, $^3J_{HH} = 9.1$ Hz, C(3)ArHOH-OCH$_3$), 7.49 (5H, m, ArH), 8.18 (1H, s, NH), 15.07 (1H, s, OH). Spectroscopic data in agreement with the literature.$^7$

\textbf{2-(Imino(phenyl)methyl)-5-methylphenol}

Following \textbf{General Procedure C}, (2-hydroxy-4-methylphenyl)(phenyl)methanone (318.4 mg, 1.5 mmol), and 7N NH$_3$ in MeOH (1.07 mL, 7.5 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (237.1 mg, 75%) as a yellow solid. \textbf{mp} 66 – 70 °C (Lit. \textbf{mp} 69 °C)$^8$; \textbf{IR} $\nu_{\text{max}}$ (ATR): 2845 (N-H), 1616 (C=N), 1429 – 1493 (C=C), 1083 (Ar-CH$_3$); \textbf{\textit{1H NMR}} (400 MHz, CDCl$_3$) $\delta$: 2.36 (3H, s, CH$_3$), 6.57 (1H, d, $^3J_{HH} = 8.0$ Hz, C(5)ArHOH-CH$_3$), 6.88 (1H, s, C(3)ArHOH-CH$_3$), 7.09 (1H, d, $^3J_{HH} = 8.0$ Hz, C(6)ArHOH-CH$_3$), 7.42 (2H, d, $^3J_{HH} = 5.5$ Hz, C(2,6)ArH), 7.51 (3H, m, C(3,4,5)ArH), 9.14 (1H, s, NH), 14.74 (1H, s, OH). Spectroscopic data in agreement with the literature.$^8$

\textbf{2-(Imino(phenyl)methyl)phenol}

Following \textbf{General Procedure C}, (2-hydroxyphenyl)(phenyl)methanone (198 mg, 1 mmol), and 7N NH$_3$ in MeOH (717.7 µL, 5 mmol) stirred at rt for 16 hours gave the titled compound (153.4 mg, 78%) as a yellow solid. \textbf{mp} 82 – 84 °C (Lit. \textbf{mp} 94 – 97 °C)$^9$; \textbf{IR} $\nu_{\text{max}}$ (ATR): 2826 (N-H), 1589 (C=N), 1462-1508 (C=C); \textbf{\textit{1H NMR}} (400 MHz, CDCl$_3$) $\delta$: 6.79 (1H, dd, $^3J_{HH} = 8.2$, $^4J_{HH} = 1.2$, HN=CArH), 7.14 (1H, dd, $^3J_{HH} = 8.4$, $^4J_{HH} = 1.21$, C(5)ArHOH), 7.24 (1H, dd, $^3J_{HH} = 8.0$, $^4J_{HH} = 1.7$, C(4)ArHOH), 7.41 (1H, dd, $^3J_{HH} = 8.6$, $^4J_{HH} = 1.7$, C(6)ArHOH), 7.46 (2H, m, HN=CArH), 7.53 (3H, m, HN=CArH), 9.67 (1H, s, N-H), 14.26 (1H, bs, OH). Spectroscopic data in agreement with the literature.$^{7,8,9}$
5-Bromo-2-(imino(phenyl)methyl)phenol

Following General Procedure C, 2-(imino(phenyl)methyl)-5-methylphenol (260.3 mg, 0.8 mmol), and 7N NH₃ in MeOH (600 µL, 4.2 mmol) stirred at rt for 16 hours, purified by flash chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (169.7 mg, 65%) as a yellow solid. mp 115 – 117 °C; IR νmax (ATR): 3038 – 3057 (OH), 1587 (C=N), 1487 (C=C);

¹H NMR (400 MHz, CDCl₃) δH: 2.20 (3H, s, ArOH-Br), 6.98 (2H, m, C(3,6)ArOH-CH₃), 7.20 (1H, d, ³JHH = 8.5 Hz, C(4)ArOH-CH₃), 7.42 (2H, m, C(2,6)ArH), 7.51 (3H, m, C(3,4,5)ArH), 9.32 (1H, s, NH), 14.45 (1H, bs, OH). ¹³C{¹H} NMR (101 MHz, CDCl₃) δH: 116.7 (C(1)ArOH-Br), 120.7 (C(5)ArOH-Br), 122.2 (C(3)ArOH-Br), 127.3 (C(2,6)Ar), 128.4 (C(4)ArOH-Br), 128.9 (C(3,5)ArOH-Br), 130.4 (C(4)ArOH-Br), 128. (C(4)Ar), 133.1 (C(6)ArOH-Br), 138.1 (C(1)Ar), 165.9 (C(2)ArOH-Br), 180.3 (C=N); HRMS (NSI⁺) C₁₃H₁₀BrNO ([M+H⁺]) requires 276.0019, found 276.0012 (-2.5 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
2-(Imino(4-methoxyphenyl)methyl)-5-methoxyphenol

Following General Procedure C, (2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone (136.4 mg, 0.53 mmol), and 7N NH$_3$ in MeOH (0.38 mL, 2.65 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc then flushed with EtOAc) to give the titled compound (95.7 mg, 14%) as a yellow oil. IR $\nu_{\text{max}}$ (ATR): 2963 (Ar-H), 1608 (C=N), 1456 (C=C), 1219 – 1254 (C-O-CH$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$: 3.84 (3H, s, ArHOH-OCH$_3$), 3.90 (3H, s, ArH-OCH$_3$), 6.21 (1H, dd, $^3\text{J}_{HH} = 9.1$ Hz, $^4\text{J}_{HH} = 2.5$ Hz, C(5)ArHOH-OCH$_3$), 6.43 (1H, d, $^4\text{J}_{HH} = 2.5$ Hz, C(3)ArHOH-OCH$_3$), 7.02 (2H, d, $^3\text{J}_{HH} = 8.7$ Hz, C(3,5)ArH-OCH$_3$), 7.11 (1H, d, $^3\text{J}_{HH} = 9.1$, C(6)ArHOH-OCH$_3$), 7.42 (2H, d, $^3\text{J}_{HH} = 8.7$ Hz, C(2,6)ArH-OCH$_3$), 7.96 (1H, s, NH), 15.07 (1H, s, OH). $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) $\delta_C$: 55.4 (ArHOH-OCH$_3$), 55.5 (ArH-OCH$_3$), 102.4 (C(3)ArHOH-OCH$_3$), 106.7 (C(5)ArHOH-OCH$_3$), 110.6 (C(1)ArHOH-OCH$_3$), 114.2 (C(3,5)ArH-OCH$_3$), 129.5 (C(1,2,6)ArH-OCH$_3$), 133.6 (C(6)ArHOH-OCH$_3$), 161.3 (C(4)ArH-OCH$_3$), 165.5 (C(4)ArHOH-OCH$_3$), 173.3 (C(2)ArHOH-OCH$_3$), 176.6 (C=N); HRMS (NSI*) C$_{15}$H$_{15}$NO$_3$ ([M+H$^+$]) requires 258.1125, found 258.1117 (-3.1 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
4. PRODUCTS

(R)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (5)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) -BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.20) to give the titled compound (29.8 mg, 70%) as a yellow oil. [α]_D^20 +95.5 (c = 0.87, CHCl_3); Chiral HPLC analysis. Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(R): 19.1 min, t_R(S): 25.3 min, 95:5 er; IR ν_max (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH_3), 1261 (CF_3); ^1H NMR (400 MHz, CDCl_3) δ_H: 1.86 – 1.98 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.75 (1H, dd, 3_J_HH = 15.4, 4_J_HF = 3.0, COC(2)H_AH_B), 2.98 (1H, dd, 3_J_HH = 15.2, 4_J_HF = 10.0, COC(2)H_AH_B), 3.44 – 3.57 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 3.84 (3H, s, OC_3H_3), 5.54 (OCH_3), 58.7 (q, ^2_J_CF = 28.3, C=OCH_3H_BC(3)HCF_3), 101.2 (N=CC(3)ArOH-OCH_3), 106.6 (N=CC(5)ArOH-OCH_3), 114.28 (N=CC(1)ArOH-OCH_3), 118.4 (CF_3), 128.2 (N=CC(2,3,5,6)ArH), 129.5 (N=CC(4)Ar), 134.4 (N=CC(1)Ar), 164.4 (N=CC(2)ArOH-OCH_3), 165.5 (C=N), 166.3 (N=CC(4)ArOH-OCH_3), 178.9 (C=O). HRMS (NSI^+ ) C_{21}H_{23}F_{3}N_{2}O_{3}^- ([M+H]^+) requires 421.1734, found 421.1729 (-1.2 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for \([(R)-4,4,4\text{-trifluoro-3-}\text{((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino}-1\text{-}(pyrrolidin-1-yl)butan-1-one}\]: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C) \(t_{R}(R)\): 19.1 min, \(t_{R}(S)\): 25.3 min, 95:5 er.

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(R)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (9)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-Trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methylphenol (42.2 mg, 0.2 mmol), (R)-(+-)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) ($R_f$=0.53) to give the titled compound (49%, 19.8 mg) as a yellow oil. $[\alpha]^{20}_D$ +48.8 (c = 0.40, CHCl$_3$); Chiral HPLC analysis. Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin$^{-1}$, 254 nm, 30 °C) $t_R$(R): 12.7 min, $t_R$(S): 15.2 min, 96:4 er; IR $\nu$ max (ATR), 2976 (Ar-H), 1624 (C=O), 1595 (C=N), 1446 (C=C), 1261 (C-F); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.83 – 2.02 (4H, m, NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 2.30 (3H, s, CH$_3$), 2.74 (1H, dd, $^3$J$_{HH}$ = 15.5, $^4$J$_{HF}$ = 2.9, COC(2)H$_A$H$_B$), 2.95 (1H, dd, $^3$J$_{HH}$ = 15.5, $^4$J$_{HF}$ = 9.6, COC(2)H$_A$H$_B$), 3.41 – 3.52 (4H, m, N=C(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 4.53 (1H, m, COCH$_A$H$_B$C$_3$), 6.49 (1H, dd, $^3$J$_{HH}$ = 8.2, N=CC(5)ArOH-CH$_3$), 6.66 (1H, s, N=CC(6)ArOH-CH$_3$), 6.81 (1H, m, N=CC(2,3,5,6)Ar), 14.33 (1H, s, N=CC(2)ArOH); $^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$), $\delta$: -74.22 (-CF$_3$); $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) $\delta$: 21.7 (ArOH-CH$_3$), 24.4 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 26.1 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 35.4 (C=OCH$_A$H$_B$CF$_3$), 46.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 47.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 59.2 (q, $^2$J$_{CF}$ = 27.3, C=OCH$_A$H$_B$C(3)HCF$_3$), 118.1 (N=CC(3)ArOH-CH$_3$), 119.5 (N=CC(5)ArOH-CH$_3$), 121.60 (N=CC(1)ArOH-CH$_3$), 128.4 (N=CC(3,5)Ar), 129.0 (N=CC(4)Ar), 129.1 (CF$_3$), 129.5 (N=CC(2,6)Ar), 129.5 (N=CC(4)Ar), 131.5 (N=CC(1)Ar), 132.8 (N=CC(6)ArOH-CH$_3$), 162.5 (N=CC(2)ArOH-CH$_3$), 166.3 (C=O), 170.2 (C=N). HRMS (NSI$^+$) C$_{22}$H$_{23}$F$_3$N$_2$O$_2^+$ ([M+H]$^+$) requires 405.1785, found 405.1774 (-2.7 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C{\textsuperscript{1}H}, CDCl\textsubscript{3}, 101 MHz
$^1$H, CDCl$_3$, 376 MHz
HPLC Data for \((R)-4,4,4\text{-trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)}\)butan-1-one: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin\(^{-1}\), 254 nm, 30 °C) \(t_R(R): 12.7\) min, \(t_R(S): 15.2\) min, 96:4 er.

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(R)-3-(((4-Bromo-2-hydroxyphenyl)(phenyl)methylene)amino)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (10)

Following General Procedure C, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (Rf = 0.20) to give the titled compound (11.3 mg, 24%) as a yellow oil. $[\alpha]_D^{20}$ +33.2 (c = 0.37, CHCl$_3$); Chiral HPLC analysis. Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mLmin$^{-1}$, 254 nm, 30 °C) $t_r$(S): 20.7 min, 96:4 er; IR $\nu_{max}$ (ATR), 2974 (Ar-H), 1625 (C=O), 1595 (C=N), 1448 (C=C), 1288 (C-O-CH$_3$), 1259 (C-F); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H: 1.86 – 1.97 (4H, m, N=C(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 2.77 (1H, dd, N=C(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 3.44 – 3.52 (4H, m, N=C(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 2.98 (1H, dd, N=C(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 4.56 (1H, m, COCH$_3$), 6.65 (1H, d, N=CC(6)ArOH-Br), 6.82 (1H, dd, N=CC(5)ArOH-Br), 7.21 (1H, d, N=CC(3)ArOH-Br), 7.52 (5H, m, N=CC(2,3,5,6)Ar), 12.18 (1H, s, N=CC(2)ArOH-Br); $^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$), $\delta$F: -74.06 (-CF$_3$); $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) $\delta$C: 24.4 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 59.0 (q, $^{2}J_{CF}$ = 29.3, C=OCH$_3$H$_2$C(3)H$_2$C(5)H$_2$), 119.0 (C=OArOH-Br), 120.9 (C(3)ArOH-Br), 121.5 (C(5)ArOH-Br), 123.4 (CF$_3$), 127.8 (C(1)ArOH-Br), 128.5 (C(2,3,5,6)Ar), 129.7 (C(1)Ar), 132.4 (C(1)Ar), 133.8 (C(4)Ar), 163.1 (C(2)ArOH-Br), 166.19 (C=O), 179.4 (C=N). HRMS (NSI$^+$) C$_{21}$H$_{20}$BrF$_3$N$_2$O$_2$$^+$ ([M+H]$^+$) requires 469.0733, found 469.0727 (-1.3 ppm).
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for \((R)-3-(((4\text{-bromo-2-hydroxyphenyl})(phenyl)methylene)amino)-4,4,4\text{-trifluoro-1-(pyrrolidin-1-yl)}\text{butan-1-one}\): Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 254 nm, 30 °C) \(t_R(R): 15.0\) min, \(t_R(S): 20.7\) min, 96:4 er.

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(R)-4,4,4-Trifluoro-3-((2-hydroxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidine-1-yl)butan-1-one (11)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)phenol (39.4 mg, 0.2 mmol), (R)-(+) BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by Biotage® Isolera™ 4 [SNAP Ultra 10g, 75 mL min⁻¹, Petrol:EtOAc (100:0 2CV, 100:0 to 80:20 1 CV, 80:20 to 80:20 1 CV, 80:20 25 CV) to give the titled compound (14.0 mg, 36%) as a yellow oil. $[\alpha]_D^{20} +35.02$ (c 1.9, CHCl₃).

**Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tₚ(S): 11.9 min, tₚ(R): 17.2 min, 96:4 er; IR νmax (ATR), 2926 (Ar-H), 1647 (C=O), 1609 (C=N), 1447 (C-F); ¹H NMR (400 MHz, CDCl₃) δH: 1.87 – 1.95 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 2.79 (1H, dd, 3JHH = 15.4, 4JHF = 3.0, COC(2)H₁H₂); 2.98 (1H, dd, 3JHH = 15.4, 4JHF = 9.6, COC(2)H₁H₂), 3.44 – 3.53 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 4.57 (1H, dd, 3JHH = 15.4, 4JHF = 9.6, COC(2)H₁H₂), 3.44 – 3.53 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 6.70 (1H, dd, 3JHH = 15.4, 4JHF = 9.6, COC(2)H₁H₂), 3.44 – 3.53 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 6.70 (1H, dd, 3JHH = 8.1, 3JHH = 7.1, 4JHH = 1.2, N=CC(5)ArOH), 6.82 (1H, dd, 3JHH = 8.0, 4JHH = 1.7, N=CC(6)ArOH), 7.02 (1H, dd, 3JHH = 8.4, 4JHH = 1.2, N=CC(3)ArOH), 7.33 (1H, dd, 3JHH = 8.8, 4JHH = 7.2, 4JHH = 1.7, N=CC(4)ArOH), 7.52 (5H, m, N=CC(2,3,4,5,6)ArH), 14.47 (1H, s, N=CC(2)ArOH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δC: 24.4 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 26.0 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 35.5 (C=OCH₃H₂CF₃), 45.9 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 47.0 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 59.4 (q, 2JCF = 28.5, C=OCH₃H₂C(3)HCF₃), 117.7 (N=CC(3)ArOH), 118.1 (N=CC(5)ArOH), 120.2 (CF₃), 123.6 (N=CC(1)Ar), 128.4 (N=CC(3,5)Ar), 129.4 (N=CC(2,4,6)Ar), 132.8 (N=CC(6)ArOH), 132.9 (N=CC(1)ArOH), 133.4 (N=CC(4)ArOH), 162.4 (N=CC(2)ArOH), 166.4 (C=O), 179.8 (C=N).

**HRMS (NSI⁺)** C₂₁H₂₁F₃N₂O₂⁺ ([M+H⁺]⁺) requires 391.1628, found 391.1622 (1.6 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C{($^1$H)}, CDCl$_3$, 101 MHz
HPLC Data for \((R)-4,4,4\text{-trifluoro-3-}((2\text{-hydroxyphenyl})(\text{phenyl})\text{methylene})\text{amino}-1-(\text{pyrrolidine-1-yl})\text{butan-1-one}\): Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) \(t_R(S): 11.9\) min, \(t_R(R): 17.2\) min, 96:4 er.

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(R)-3-((Diphenylmethyleneamino)-4,4,4-trifluoro-1-(pyrrolidine-1-yl)butan-1-one (12)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), diphenylmethanimine (36.2 mg, 0.2 mmol), (R)-(+-)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (15 mg, 40%) as a yellow oil. [α]_D^{20} +35.0 (c = 1.9, CHCl_3); Chiral HPLC analysis. Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mL min^{-1}, 250 nm, 30 °C) t_{R}(S): 6.9 min, t_{R}(R): 13.6 min, 83:17 er; IR ν_{max} (ATR), 2976 (Ar-H), 1633 (C=O), 1598 (C=N), 1448 (C=C), 1276 (C-F); ^1H NMR (400 MHz, CDCl_3) δ_H: 1.83 – 1.90 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.69 (1H, dd, 3J_{HH} = 15.7, 4J_{HF} = 2.5, COC(2)H_2A), 2.93 (1H, dd, 3J_{HH} = 15.8, 4J_{HF} = 9.6, COC(2)H_2B), 3.41 – 3.52 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 3.80 (3H, s, CH_3O-ArOH), 3.86 (3H, s, CH_3O-Ar), 4.59 (1H, m, COCH_2A), 7.33 – 7.35 (3H, m, N=CC(1-3,4,5)Ar), 7.50 (3H, m, N=CC(1-3,4,5)Ar), 7.65 (2H, m, N=CC(2,6)Ar), 7.83 (2H, m, N=CC(2,6)Ar); ^19F{^1H} NMR (376 MHz, CDCl_3), δ_F: -74.1 (-CF_3); ^13C{^1H} NMR (101 MHz, CDCl_3) δ_C: 24.4 – 26.1 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 35.5 (C=OCH_3H_2C), 45.9 – 47.0 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 60.7 – 61.21 (q, 2J_{CF} = 28.0, C=OCH_3H_2C(3)HCF_3), 128.4 (1), 128.95 (1), 129.1 (1), 130.1 (1), 139.3 N=CC(1)Ar, 167.2 (C=O), 174.3 (C=N). HRMS (NSI*) C_{21}H_{21}F_3N_2O ([M+H]^+) requires 375.1679, found 375.1670 (-2.4 ppm).
$^1$H, CDCl$_3$, 400 MHz
$\text{^{13}C\{^1\text{H}\}}$, CDCl$_3$, 101 MHz
$^{19}\text{F}, \text{CDCl}_3, 376 \text{ MHz}$
HPLC Data for \((R)-3-((diphenylmethylene)amino)-4,4,4\text{-trifluoro-1-(pyrrolidine-1-yl)butan-1-one}\): Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mL\(\cdot\)min\(^{-1}\), 250 nm, 30 °C) \(t_R(S)\): 6.9 min, \(t_R(R)\): 13.6 min, 83:17 er.
Following General Procedure C, 4-nitrophenyl (E)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(4-methoxyphenyl)methyl)-5-methoxyphenol (51.5 mg, 0.2 mmol), (R)-(+) -BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine (12.5 µL, 0.15 mmol) and stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.21) to give the titled compound (18 mg, 41%) as a yellow oil. [α]_D^{20} +57.1 (c = 0.92, CHCl_3); Chiral HPLC analysis. Chiralpak IA [α]_20^D (95:5 Hexane:IPA, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_{R(S)}: 31.5 min, t_{R(R)}: 39.9 min, 95:5 er; IR ν_{max} (ATR), 2970 (Ar-H), 1621 (C=O), 1593 (C=N), 1442 (C=C), 1342 (C-O-CH_3), 1247 (C-F); ^1H NMR (400 MHz, CDCl_3) δ_H: 1.83 – 1.94 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.69 (1H, dd, ^3J_{HH} = 15.5, ^4J_{HF} = 2.9, COC(2)H_AH_B), 2.93 (1H, dd, ^3J_{HH} = 15.6, ^4J_{HF} = 9.7, COC(2)H_AH_B), 3.41 – 3.52 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 3.80 (3H, s, CH_3O-ArOH), 3.86 (1H, m, COCH_AH_BH_C), 6.22 (1H, d, ^3J_{HH} = 8.95, ^4J_{HH} = 2.43 N=CC(5)ArOH-OCH_3), 6.44 (1H, d, ^3J_{HH} = 2.58, N=CC(3)ArOH-OCH_3), 6.73 (1H, d, ^3J_{HH} = 9.00, N=CC(6)ArOH-OCH_3), 7.05 (2H, m, N=CC(2,6)Ar-OCH_3), 7.40 (2H, m, N=CC(3,4)ArH-OCH_3), 15.2 (1H, s, N=CC(2)ArOH-OCH_3); ^19F{^1H} NMR (376 MHz, CDCl_3), δ_F: -66.22, -74.11, -74.33 (-C_F_3); ^13C{^1H} NMR (101 MHz, CDCl_3) δ_C: 24.5 – 26.2 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 35.6 (C=OCH_AH_BH_C, 46.1 – 47.1 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 55.4 (CH_3O-ArOH), 55.5 (CH_3O-Ar), 58.3 – 59.1 (q, 2J_{CF} = 28.6, C=OCH_AH_BH_C, 101.36 (C(3)ArOH-OCH_3), 106.17 (C(5)ArOH-OCH_3), 113.9 (C(1)ArOH-OCH_3, C(2,6)Ar-OCH_3), 125.29 (C(1)Ar-OCH_3), 126.22 (CF_3), 129.6 – 129.9 (C(3,5)Ar-OCH_3), 134.3 (C(6)ArOH-OCH_3), 160.3 (C(4)Ar-OCH_3), 164.0 (C(4)ArOH-OCH_3), 165.6 (C(2)ArOH-OCH_3), 166.7 (C=O), 179.0 (C=N). HRMS (NSI^*) C_{23}H_{25}F_3N_2O_4^+ ([M+H]^+) requires 451.1839, found 451.1827 (-2.7ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C{($^1$H)}, CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for \((R,E)-4,4,4\text{-trifluoro-3-}((2\text{-hydroxy-4-methoxyphenyl})(4\text{-methoxyphenyl})\text{methylene}amino)\text{-1-(pyrrolidin-1-yl)}\text{butan-1-one}\): Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C) \(t_R\)(S): 31.5 min, \(t_R\)(R): 39.9 min, 95:5 er.

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![Chromatogram 2](image)
Following General Procedure D, 4-nitrophenyl (E)-4,4-difluorobut-2-enoate (24.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (1:1) ($R_f = 0.24$) to give the titled compound (16.0 mg, 40%) as a yellow oil. $[\alpha]_{D}^{20} +23.8 \; (c = 0.72, \text{CHCl}_3)$; Chiral HPLC analysis. Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mL min$^{-1}$, 220 nm, 30 °C) $t_{R}(S): 48.5$ min, $t_{R}(R): 52.1$ min, 97:3 er.; IR ν$_{max}$ (ATR), 2976 (Ar-H), 1622 (C=O), 1595 (C=N), 1444 (C=C), 1259 (C-F); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$: 1.86 – 1.96 (4H, m, NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 2.72 – 2.74 (2H, qd, $^3$J$_{HH} = 15.7$, $^4$J$_{HH} = 3.0$, COCH$_2$), 3.45 (4H, m, NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 3.82 (3H, s, ArOH-OC$_3$H), 4.24 (1H, m, COCH$_2$), 5.94 (1H, td, $^2$J$_{HF} = 55.8$, $^4$J$_{HF} = 3.0$, CF$_2$H), 6.23 (1H, dd, $^3$J$_{HH} = 9.0$, $^4$J$_{HH} = 2.5$, N=CC(5)ArOH-OCH$_3$), 6.52 (1H, s, N=CC(3)ArOH-OCH$_3$), 6.68 (1H, d, $^3$J$_{HH} = 9.0$, N=CC(6)ArOH-OCH$_3$), 7.45 (5H, m, N=CC(2,3,4,5,6)Ar), 15.3 (1H, s, N=CC(2)ArOH-OCH$_3$). $^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$), δ$_F$: -125.3 (d, $^2$J$_{FF} = 282.1$, -CF$_2$F$_2$H), -126.8 (d, $^2$J$_{FF} = 282.0$, -CF$_3$F$_2$H); $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) δ$_C$: 24.4 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 26.1 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 35.1 (C=OCH$_3$H$_8$CF$_3$), 45.9 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 55.0 (-OCH$_3$), 58.7 – 59.9 (q, $^2$J$_{CF} = 29.3$, C=OCH$_3$H$_8$CF$_3$), 101.4 (C(3)ArOH-OCH$_3$), 106.5 (C(5)ArOH-OCH$_3$), 113.3 (C(1)ArOH-OCH$_3$), 115.2 (–CF$_2$H), 127.8 (C(1,2,6)Ar), 128.6 (C(3,4,5)Ar), 133.99 (C(6)ArOH-OCH$_3$), 165.4 (C(2)ArOH-OCH$_3$), 166.1 (C(4)ArOH-OCH$_3$), 167.1 (C=O), 177.3 (C=O). HRMS (NSI$^+$) C$_{22}$H$_{25}$F$_2$N$_2$O$_3^+$ ([M+H]$^+$) requires 403.1828, found 403.1822 (-1.5 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz

![NMR Spectrum](image-url)
HPLC Data for \( R \)-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one: \( \) Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mL/min, 220 nm, 30 °C) \( t_R(S) \): 48.5 min, \( t_R(R) \): 52.1 min, 97:3 er.
(R)-4-Chloro-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (15)

Following General Procedure D, 4-nitrophenyl (E)-4-chloro-4,4-difluorobut-2-enoate (27.8 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (1:1) \((R_f = 0.16)\) to give the titled compound (31.9 mg, 73%) as a yellow oil. \([\alpha]_D^{20} +9.60 \ (c = 1.60, \ CHCl_3)\); Chiral HPLC analysis. Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin\(^{-1}\), 211 nm, 30 °C) \(t_R(S): 22.0 \) min, \(t_R(R): 29.0 \) min, 96:4 er; IR \(\nu_{max} \) (ATR), 2974 (Ar-H), 1635 (C=O), 1593 (C=N), 1444 (C=C), 1263 (C-F); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta H: 1.86 – 1.96 (4H, m, NC(2)H\_2C(3)H\_2C(4)H\_2C(5)H\_2), 2.82 (1H, dd, \(3J_{HH} = 15.1, 4J_{HH} = 3.2, COC(2)H\_A H\_B\)), 2.97 (1H, dd, \(3J_{HH} = 15.1, 4J_{HH} = 9.2, COC(2)H\_A H\_B\)), 3.50 (4H, m, NC(2)H\_2C(3)H\_2C(4)H\_2C(5)H\_2), 3.83 \(3J_{HH} = 9.0, 4J_{HH} = 2.5, N=CC(5)ArOH-OCH\_3\)), 6.26 (1H, dd, \(3J_{HH} = 9.0, 4J_{HH} = 2.3, N=CC(3)ArOH-OCH\_3\)), 6.51 (1H, d, \(4J_{HH} = 2.3, N=CC(3)ArOH-OCH\_3\)), 7.24 (1H, N=CC(4)ArH), 7.52 (4H, m, N=CC(2,3,5,6)ArH), 15.1 (1H, s, N=CC(2)ArHOCH\_3). \(^{19}F\{^1\}H\) NMR (376 MHz, CDCl\(_3\)), \(\delta F: -58.6 \ (d, 2J_{FF} = 164.8, -CF\_AFC\_B Cl), -59.8 \ (dd, 2J_{FF} = 164.8, 3J_{HF} = 2.8, CF\_AFC\_B Cl); ^{13}C\{^1\}H\) NMR (101 MHz, CDCl\(_3\)) \(\delta C: 24.4 \ (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 26.1 \ (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 36.8 \ (C=OCH\_3H\_6CF\_3), 46.0 \ (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 \ (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 55.45 \ (-OCH\_3), 63.5 – 63.9 \ (q, 2J_{CF} = 20.2, C=OCH\_3H\_6C(3)HCF\_2Cl), 101.3 \ (N=CC(3)ArOH-OCH\_3), 106.2 \ (N=CC(5)ArOH-OCH\_3), 128.1 \ (N=CC(4)Ar), 128.4 \ (N=CC(2,6)Ar), 129.3 \ (CF_2Cl), 129.4 \ (N=CC(3,5)Ar), 132.9 \ (N=CC(1)Ar), 134.2 \ (N=CC(6)ArOH-OCH\_3), 161.2 \ (N=CC(2)ArOH-OCH\_3), 164.0 \ (N=CC(1)ArOH-OCH\_3), 165.4 \ (N=CC(4)ArOH-OCH\_3), 166.4 \ (C=O), 178.4 \ (C=N). HRMS (NSI\(^+\)) C\(_{22}H_{29}ClF_2N_2O_3^+ \ ([M+H]^+) \) requires 437.1438, found 437.1429 (-2.1 ppm).
§H, CDCl₃, 400 MHz
$^{13}$C\({}^1\text{H}\), CDCl$_3$, 101 MHz
$^{19}\text{F, CDCl}_3$, 376 MHz
HPLC Data for (R)-4-chloro-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL/min, 211 nm, 30 °C) $t_{R}(S)$: 22.0 min, $t_{R}(R)$: 29.0 min, 96:4 er.

![Chemical structure](image)

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![Graph 2](image)
(R)-4-Bromo-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (16)

Following General Procedure C, 4-nitrophenyl (E)-4-Bromo-4,4-difluorobut-2-enoate (32.2 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+-)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (Rf = 0.24) to give the titled compound (34.6 mg, 72%) as a yellow oil. $[\alpha]_{D}^{20} +70.8$ (c = 0.67, CHCl3); Chiral HPLC analysis. Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mL/min, 211 nm, 30 °C), tR(R): 13.5 min, tR(S): 18.7 min, 96:4 er; IR νmax (ATR), 2970 (Ar-H), 1637 (C=O), 1591 (C=N), 1442 (C=C), 1261 (C-F); 1H NMR (400 MHz, CDCl3) δH: 1.84 – 1.95 (4H, m, NC(2)H2C(3)H2C(4)H2C(5)H2), 2.82 (1H, dd, 2JHH = 15.1, 3JHH = 3.2, COC(2)H), 2.95 (1H, dd, 2JHH = 15.1, 3JHH = 9.0, COC(2)H), 3.44 – 3.56 (4H, m, NC(2)H2C(3)H2C(4)H2C(5)H2), 3.82 (3H, s, ArOH-OC3), 4.46 (1H, 3JHH = 9.0, 3JHH = 3.3, COCH), 6.25 (1H, dd, 3JHH = 8.9, 4JHH = 2.6, N=C(5)ArOH-OCH3), 6.48 (1H, d, 4JHH = 2.6, N=C(3)ArOH-OCH3), 6.70 (1H, d, 3JHH = 9.0, N=C(6)ArOH-OCH3), 7.23 (1H, m, N=C(4)ArH), 7.50 (4H, m, N=C(2,3,5,6)ArH), 15.1 (1H, s, N=C(2)ArH), 18.7 (1H, m, N=C(2,3,5,6)ArH), 164.0 (N=C(4)ArOH-OCH3), 165.3 (N=C(2)ArOH-OCH3), 166.4 (C=O), 178.4 (C=N). HRMS (NSI+): C22H24BrF2N2O3+ ([M+H]+) requires 481.3378, found 481.0933 (-0.60 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
$^{19}\text{F}, \text{CDCl}_3, 376 \text{ MHz}$
HPLC Data for (R)-4-Bromo-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene) amino)-1-(pyrrolidin-1-yl)butan-1-one: Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C), tᵣ(R): 13.5 min, tᵣ(S): 18.7 min, 96:4 er.
Following General Procedure D, 4-nitrophenyl (E)-4,4,5,5,5-pentafluoropentan-2-enoate (31.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) -BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R = 0.20) to give the titled compound (38.1 mg, 81%) as a yellow oil. $[\alpha]_{D}^{20} +95.2$ ($c = 0.31$, CHCl$_3$); Chiral HPLC analysis. Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C) $t_R$(R): 13.9 min, $t_R$(S): 20.6 min, 97:3 er; IR $\nu_{\text{max}}$ (ATR), 2974 (Ar-H), 1622 (C=O), 1593 (C=N), 1445 – 1456 (C=C), 1207 (C$_5$F$_5$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$: 1.84 – 1.95 (4H, m, NNC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 2.82 (1H, dd, $^2$J$_{HH}$ = 15.1, $^3$J$_{HH}$ = 3.9, O=CC(2)H$_A$H$_B$), 2.90 (1H, dd, $^2$J$_{HH}$ = 15.1, $^3$J$_{HH}$ = 8.8, O=CC(2)H$_A$H$_B$), 3.43 – 3.54 (4H, m, NNC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 3.83 (3H, s, -OC$_3$H$_3$), 4.66 (1H, m, O=CCH$_A$H$_B$C(3)H), 6.27 (1H, dd, $^3$J$_{HH}$ = 8.9, $^4$J$_{HH}$ = 2.2, N=CC(5)ArOH-OCH$_3$), 6.50 (1H, d, $^4$J$_{HH}$ = 2.4, N=CC(3)ArOH-OCH$_3$), 6.69 (1H, d, $^3$J$_{HH}$ = 9.0, N=CC(6)ArOH-OCH$_3$), 7.18 (1H, m, N=CC(2)ArH), 7.52 (4H, m, N=CC(3,4,5,6)ArH), 14.9 (1H, s, -OH). $^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$) $\delta_F$: -80.9 (-CF$_A$F$_B$CF$_3$), -120.6 (d, $^2$J$_{FF}$ = 272.9, -CF$_A$F$_B$CF$_3$), -121.2 (d, $^2$J$_{FF}$ = 272.9, -CF$_A$F$_B$CF$_3$); $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) $\delta_C$: 24.4 – 26.1 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 35.2 (O=CC(2)H$_A$H$_B$), 46.0 – 47.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 55.4 (-OCH$_3$), 57.9 (t, $^2$J$_{CF}$ = 22.2, O=CCH$_A$H$_B$C(3)H), 101.2 (N=CC(3)ArOH-OCH$_3$), 106.22 (N=CC(5)ArOH-OCH$_3$), 113.7 (N=CC(1)ArOH-OCH$_3$), 126.2 (N=CC(1)Ar), 127.9 (N=CC(2,6)Ar), 129.5 (N=CC(3,4,5)Ar), 132.7 (-CF$_2$CF$_3$), 134.2 (N=CC(6)ArOH-OCH$_3$), 139.4 (-CF$_2$CF$_3$), 163.7 (N=CC(2)ArOH-OCH$_3$), 165.1 (N=CC(4)ArOH-OCH$_3$), 166.3 (C=O), 178.5 (C=N). HRMS (NSI$^+$) C$_{23}$H$_{23}$F$_5$N$_2$O$_3^{-}$. ([M+H]$^+$) requires 471.1702, found 471.1690 (-2.5 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}C\{^1H\}$, CDCl$_3$, 101 MHz
HPLC Data for \( (R)-4,4,4\text{-trifluoro-3-(((2\text{-hydroxy-4-methoxyphenyl})methylene)amino)-1-(piperidin-1-yl)butan-1\text{-one}} \): Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 211 nm, 30 °C) \( t_R(R) \): 13.9 min, \( t_R(S) \): 20.6 min, 97:3 er.

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Ethyl (R)-2-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (18)

Following General Procedure D, ethyl (4-nitrophenyl)fumarate (26.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) -BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at 40 °C for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH₂Cl₂ (Rf = 0.20) to give the titled compound (8.5 mg, 20%) as a yellow oil. +2.94 (c = 1.10, CHCl₃); Chiral HPLC analysis.

Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 270 nm, 30 °C) tᵣ(S): 34.5 min, tᵣ(R): 44.7 min, 96:4 er; ¹H NMR (400 MHz, CDCl₃) δH: 1.34 (3H, t, ³JHH = 7.1, CO₂CH₂CH₃), 1.93 – 2.04 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 2.82 (1H, dd, ²JHH = 15.7, ³JHH = 7.7, COC(2)HHB), 2.98 (1H, dd, ²JHH = 15.8, ³JHH = 5.6, COC(2)HHB) 3.57 – 3.64 (4H, m, NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 3.81 (3H, s, ArOH-OC₃H₃), 4.28 (2H, q, ³JHH = 7.1, CO₂CH₂CH₃), 4.62 (1H, dd, ³JHH = 7.6, ³JHH = 5.6, COCH₂H₂CH₃), 6.20 (1H, dd, ³JHH = 8.9, ⁴JHH = 2.6, N=CC(5)ArOH-OCH₃), 6.46 (1H, d, ⁴JHH = 2.6, N=CC(3)ArOH-OCH₃), 6.67 (1H, d, ³JHH = 9.0, N=CC(6)ArOH-OCH₃), 7.37 (1H, m, N=CC(4)ArH), 7.48 (4H, m, N=CC(2,3,5,6)ArH), 15.5 (1H, s, N=CC(2)ArOH-OCH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃) δC: 14.1 (CO₂CH₂CH₃), 24.4 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 26.1 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 38.3 (C=OCH₂H₂CHCO₂Et), 45.7 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 46.8 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 55.4 (-OCH₃), 59.8 (CH₂CO₂CH₂CH₃), 61.1 (CO₂CH₂CH₃), 101.4 (N=CC(3)ArOH-OCH₃), 105.8 (N=CC(5)ArOH-OCH₃), 113.7 (N=CC(1)ArOH-OCH₃), 128.4 (N=CC(2,6)Ar), 129.22 (N=CC(3,4,5)Ar), 133.5 (N=CC(6)ArOH-OCH₃), 134.5 (N=CC(1)Ar), 162.1 (N=CC(2)ArOH-OCH₃), 163.7 (N=CC(4)ArOH-OCH₃), 166.4 (C=OCH₂H₂CHCO₂Et), 167.1 (C=OCH₂H₂CHCO₂Et), 167.8 (C=N). HRMS (NSI⁺) C₂₄H₂₈N₂O₅⁺ ([M+H]⁺) requires 425.2071, found 425.2063 (-1.9 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C\{$^{1}$H}, CDCl$_3$, 101 MHz
HPLC Data for Ethyl (R)-2-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin⁻¹, 270 nm, 30 °C) tᵣ(S): 34.5 min, tᵣ(R): 44.7 min, 96:4 er.

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mAU
Benzyl (R)-2-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (19)

Following General Procedure D, Benzyl (4-nitrophenyl)fumarate (32.7 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+-)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH₂Cl₂ (R = 0.42) to give the titled compound (9.7 mg, 20%) as a yellow oil. [α]_D^20 +2.71 (c = 2.9, CHCl₃); Chiral HPLC analysis. Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) t_R (R): 35.0 min, t_R (S): 44.7 min, 87:13 er; IR νmax (ATR), 2970 (Ar-H), 1736 (CO₂Bn), 1639 (C=O), 1593 (C=N), 1443 (C=C); ¹H NMR (400 MHz, CDCl₃) δ_H: 1.80 – 1.98 (4H, m, N=C(2)H₂C(3)H₂C(4)H₂C(5)H₂), 2.84 (1H, dd, 2_J HH = 15.8, 3_J HH = 7.7, O=CC(2)H A H B), 3.01 (1H, dd, 2_J HH = 15.8, 3_J HH = 5.6, O=CC(2)H A H B), 3.40 – 3.64 (4H, m, N=C(2)H₂C(3)H₂C(4)H₂C(5)H₂), 3.82 (3H, s, -OC₃H₃), 4.67 (1H, dd, 3_J HH = 7.5, 3_J HH = 5.5, O=CCH₂H₂C(3)H), 5.17 (2H, m, CO₂CH₂Ph), 6.21 (1H, dd, 3_J HH = 8.9, 4_J HH = 2.6, N=C(3)ArOH-CH₂OCH₃), 6.66 (1H, d, 3_J HH = 8.9, N=C(6)ArOH-CH₂OCH₃), 7.30 – 7.46 (10H, m, N=C(2,3,4,5,6)ArH & CO₂CH₂C(2,3,4,5,6)ArH), 15.5 (1H, bs, -OCH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 24.4 – 26.0 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 38.3 (O=CC(2)H₂H₂B), 45.7 – 46.7 (NC(2)H₂C(3)H₂C(4)H₂C(5)H₂), 55.4 (-OCH₃), 59.9 (O=CCH₂H₂C(3)H), 67.1 (CO₂CH₂Ph), 101.4 (N=C(3)ArOH-CH₂OCH₃), 105.8 (N=C(5)ArOH-CH₂OCH₃), 113.7 (N=C(1)ArOH-CH₂OCH₃), 128.2 (N=C(2,6)Ar), 128.3 (N=C(1,3,5)Ar & CO₂CH₂C(1)Ar), 128.4 (N=C(4)Ar), 128.5 (CO₂CH₂C(3,5)Ar), 128.8 (CO₂CH₂C(4)Ar), 133.6 (N=C(6)ArOH-CH₂OCH₃), 163.7 (N=C(4)ArOH-CH₂OCH₃), 166.2 (N=C(2)ArOH-CH₂OCH₃), 167.7 (C=O-pyrrolidiny1), 170.8 (CO₂CH₂Ph), 176.2 (C=N). HRMS (NSI⁺) C₉₀H₇₀N₂O₅⁺ ([M+H]⁺) requires 487.2228, found 487.2222 (-1.2 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
HPLC Data for Benzyl (R)-2-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tᵣ(R): 35.0 min, tᵣ(S): 44.7 min, 87:13 er.
Methyl (R)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)butanoate (20)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Methanol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (R_f = 0.13) to give the titled compound (24.4 mg, 64%) as a yellow oil.

[a]_D^{20} +91.9 (c = 0.36, CHCl_3); Chiral HPLC analysis. Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R(R): 5.92 min, t_R(S): 9.13 min, 97: 3 er; IR ν_max (ATR), 2957 (Ar-H), 1743 (C=O), 1593 – 1605 (C=N), 1442 (C=C), 1261 (CF_3);

1H NMR (400 MHz, CDCl_3) δ_H: 2.84 – 2.86 (1H, dd, J_HH = 16.3, J_HH = 3.7, COC(2)H_B), 2.90 – 2.95 (1H, dd, J_HH = 16.3, J_HH = 9.2, COC(2)H_B), 3.68 (3H, s, COC(2)H), 3.84 (3H, s, ArOH-OCH_3), 4.36 (1H, m, COCH_AH_BCHCF_3), 6.26 – 6.28 (1H, dd, J_HH = 9.0, J_HH = 2.6, N=CC(5)ArHOH-OCH_3), 6.55 – 6.56 (1H, d, J_HH = 2.6, N=CC(3)ArHOH-OCH_3), 6.69 – 6.73 (1H, d, J_HH = 9.0, N=CC(6)ArHOH-OCH_3), 7.26 (1H, m, N=CC(2)ArH), 7.37 (1H, m, N=CC(6)ArH), 7.55 (3H, m, N=CC(3,4,5)ArH), 14.6 (1H, s, -OH); 19F{1H} NMR (376 MHz, CDCl_3): -74.58 (-CF_3); 13C{1H} NMR (101 MHz, CDCl_3) δ_C: 40.3 (COC(2)H_BCHCF_3), 55.9 (CO_2CH_3), 57.7 (ArOH-OCH_3), 58.0 (q, J_CF = 28.9, COCH_AH_BCHCF_3), 101.2 (N=CC(3)ArOH-OCH_3), 106.2 (N=CC(5)ArOH-OCH_3), 113.9 (N=CC(1)ArOH-OCH_3), 123.6 (N=CC(1)Ar), 125.8 (-CF_3), 127.6 (N=CC(2,6)Ar), 132.9 (N=CC(3,4,5)Ar), 134.9 (N=CC(6)ArOH-OCH_3), 163.9 (N=CC(2)ArOH-OCH_3), 165.1 (N=CC(4)ArOH-OCH_3), 172.1 (CO_2CH_3), 178.8 (C=O); HRMS (NSI⁺) C_{19}H_{18}F_3NO_4⁺ ([M+H]^+) requires 382.1261, found 382.1255 (-1.6 ppm).
$^{1}H$, CDCl$_3$, 400 MHz
$^{13}$C{($^1$H)}, CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for methyl \((R,E)-4,4,4\text{-trifluoro-3-}(((2\text{-hydroxy-4-methoxyphenyl})(phenyl)methylene)amino)\text{butanoate}\): Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin\(^{-1}\), 211 nm, 30 °C) \(t_R\): 5.92 min, \(t_S\): 9.13 min, 97:3 er.

![HPLC chromatogram](image1)

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![HPLC chromatogram](image2)

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![HPLC chromatogram](image3)
Benzyl (R)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)butanoate (21)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+) -BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzyl alcohol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (Rf 0.33) to give the titled compound (19.3 mg, 42%) as a yellow oil.

\[\alpha \]_D^20 +78.4 (c = 0.45, CHCl₃); Chiral HPLC analysis. Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) t_R(r): 8.13 min, t_S(s): 10.8 min, 96:4 er; IR ν₂₀₀₀ (ATR), 2933 (Ar-H), 1741 (C=O), 1593 – 1616 (C=N), 1444 (C=C), 1261 (CF₃); ¹H NMR (400 MHz, CDCl₃) δ: 2.86 – 2.91 (1H, dd, 2J_HH = 15.9, 3J_HH = 3.6, COC(2)H_AH_B), 2.96 – 3.03 (1H, dd, 2J_HH = 16.0, 3J_HH = 9.5, COC(2)H_AH_B), 3.86 (3H, s, ArOH-OC₃H), 4.36 (1H, m, COCH_AH_B C(3)H), 5.12 (2H, m, CO₂CH₂Ph), 6.28 (1H, dd, 3J_HH = 9.0, 4J_HH = 2.5, N=C(C(5)ArOH-OCH₃), 6.60 (1H, d, 4J_HH = 2.5, N=C(C(3)ArOH-OCH₃), 6.65 (1H, d, 3J_HH = 9.0, N=C(C(6)ArOH-OCH₃), 7.13 – 7.23 (2H, m, N=C(C(2,6)Ar)), 7.28 (5H, m, CO₂CH₂C(2,3,4,5,6)Ar), 7.49 (3H, m, N=C(C(3,4,5)ArH), 14.5 (1H, bs, -OH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ: 33.5 (COC(2)H_AH_B CHCF₃), 55.6 (-OC₃H), 58.5 (COCH₃H_B CHCF₃), 67.0 (CO₂CH₂Ph), 101.2 (N=C(C(3)ArOH-OCH₃), 106.7 (N=C(C(5)ArOH-OCH₃), 113.5 (N=C(C(1)ArOH-OCH₃), 123.1 (-CF₃), 127.9 (N=C(C(1)Ar), 128.2 (N=C(C(2,6)Ar), 128.3 (CO₂CH₂C(2,6)Ar), 128.4 – 128.5 (CO₂CH₂C(3,4,5)Ar), 128.6 (N=C(C(3,4,5)Ar), 134.3 (N=C(C(6)ArOH-OCH₃), 135.3 (CO₂CH₂C(1)Ar), 164.4 (N=C(C(2)ArOH-OCH₃), 165.2 (N=C(C(3)ArOH-OCH₃), 169.0 (C=O), 179.0 (C=N). HRMS (NSI⁺) C₂₅H₂₃F₃NO₄⁺ ([M+H]⁺) requires 458.1574, found 458.1563 (-2.4 ppm).
^1H, CDCl₃, 400 MHz
$^{13}$C($\text{H}$), CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for Benzyl (R)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)butanoate: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) tᵣ(R): 8.13 min, tᵣ(S): 10.8 min, 96:4 er.
(R)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(piperidin-1-yl)butan-1-one (22)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+)–BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Piperidine was added (14.8 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) ($R_f$ = 0.21) to give the titled compound (23.0 mg, 53%) as a yellow oil. $\Delta\delta^2_{D}$ +89.0 (c = 0.50, CHCl$_3$); Chiral HPLC analysis. Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin$^{-1}$, 220 nm, 30 °C) $t_R$(S): 12.2 min, $t_R$(R): 16.3 min, 96:4 er; IR $\nu_{max}$ (ATR), 2941 (Ar-H), 1620 (C=O), 1593 (C=N), 1445 (C=C), 1259 (CF$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H: 1.59 (6H, m, NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)H$_2$), 2.79 (1H, dd, $^2$J$_{HH} = 15.4$, $^3$J$_{HH} = 9.5$, O=CC(2)H$_A$H$_B$), 3.06 (1H, dd, $^2$J$_{HH} = 15.4$, $^3$J$_{HH} = 3.0$, O=CC(2)H$_A$H$_B$), 3.43 – 3.57 (4H, m, NC(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)H$_2$), 3.83 (3H, s, -OC$_3$H$_3$), 4.50 (1H, m, O=CCH$_A$H$_B$C(3)H), 6.27 (1H, dd, $^3$J$_{HH} = 9.0$, $^4$J$_{HH} = 2.6$, N=CC(5)ArOH-OCH$_3$), 6.51 (1H, d, $^4$J$_{HH} = 2.6$, N=CC(3)ArOH-OCH$_3$), 6.68 (1H, d, $^3$J$_{HH} = 9.0$, N=CC(6)ArOH-OCH$_3$), 7.23 (1H, s, N=CC(2)ArH), 7.50 (4H, m, N=CC(3,4,5,6)ArH), 14.9 (1H, s, -O-H). $^{19}$F($^1$H) NMR (376 MHz, CDCl$_3$), $\delta$F: -74.15 (-CF$_3$); $^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$) $\delta$C: 37.9 (O=CC(2)H$_A$H$_B$), 43.9 (NHCH$_2$Ph), 55.5 (-OCH$_3$), 58.8 – 59.4 (q, $^2$J$_{CF} = 23.3$ O=CCH$_A$H$_B$C(3)H), 101.3 (N=CC(3)ArOH-OCH$_3$), 106.4 (N=CC(5)ArOH-OCH$_3$), 113.8 (N=CC(1)ArOH-OCH$_3$), 125.8 (-CF$_3$), 127.4 (NHCH$_2$C(3,4,5)Ph), 127.6 (N=CC(2,6)ArH), 128.3 (NHCH$_2$C(2,6)Ph), 128.5 (N=CC(1)Ar), 129.4 (NHCH$_2$C(1)Ph), 164.2 (N=CC(2)ArOH-OCH$_3$), 165.3 (N=CC(4)ArOH-OCH$_3$), 167.8 (C=O), 179.2 (C=N). HRMS (NSI$^+$) C$_{23}$H$_{26}$F$_3$N$_2$O$_4^+$ ([M+H]$^+$) requires 435.1890, found 435.1878 (-2.8 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C($^1$H), CDCl$_3$, 101 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for \((R)-4,4,4\text{-trifluoro-3-\(((2\text{-hydroxy-4\text{-methoxyphenyl})\text{-methylene})\text{amino})-1\text{-\(\text{piperidin-1-yl}\)}\text{butan-1-one}}\):

Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C) \(t_R(R)\): 12.2 min, \(t_R(S)\): 16.3 min, 96:4 er.

**PDA Ch2 220nm**

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**PDA Ch2 220nm**

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Following General Procedure D, 4-nitrophenyl \((E)-4,4,4\text{-difluorobut-2-enoate}\) (26.1 mg, 0.1 mmol), \(2\text{-}(\text{imino} \text{(phenyl)})\text{methyl}\)-5-methoxyphenol (45.4 mg, 0.2 mmol), \((R)\text{-}(+)\text{-BTM}\) (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Morpholine was added (12.9 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) \((R_f = 0.19)\) to give the titled compound (22.6 mg, 52%) as a yellow oil. 

\[ [\alpha]_D^{20} +86.0 \quad (c = 0.45, \text{CHCl}_3) \]

Chiral HPLC analysis. Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C) \(t_R(R)\): 14.7 min, \(t_R(S)\): 20.1 min, 96:4 er; IR \(\nu_{\text{max}}\) (ATR), 2990 (Ar-H), 1645 (C=O), 1593 (C=N), 1444 (C=C), 1259 (CF\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H\): 2.74 (1H, dd, \(2J_{HH} = 15.4, \ 3J_{HH} = 2.9, \text{O}=\text{CC}(2)\text{H}_A\text{H}_B\)), 3.04 (1H, dd, \(2J_{HH} = 15.3, \ 3J_{HH} = 9.67, \text{O}=\text{CC}(2)\text{H}_A\text{H}_B\)), 3.48 – 3.66 (8H, m, \(\text{NC}(2)\text{H}_2\text{C}(3)\text{H}_2\text{C}(5)\text{H}_2\text{C}(6)\text{H}_2\text{O}\)), 3.84 (3H, s, -OC\(_3\)H\(_3\)), 4.49 (1H, m, COCH\(_A\text{H}_B\text{C}\)), 6.47 (1H, dd, \(3J_{HH} = 9.0, \ 4J_{HH} = 2.6, \text{N}=\text{CC}(5)\text{ArOH-OCH}_3\)), 6.55 (1H, d, \(4J_{HH} = 2.6, \text{N}=\text{CC}(3)\text{ArOH-OCH}_3\)), 6.70 (1H, d, \(3J_{HH} = 9.0, \text{N}=\text{CC}(6)\text{ArOH-OCH}_3\)), 7.23 (1H, m, \(\text{N}=\text{CC}(2)\text{ArH}\)), 7.46 – 7.52 (4H, m, \(\text{N}=\text{CC}(3,4,5,6)\text{ArH}\)), 14.75 (1H, s, -O\(_H\)). \(^{19}\)F\{\(^1\)H\} NMR (376 MHz, CDCl\(_3\)) \(\delta_F\): -74.21 (-CF\(_3\)); \(^{13}\)C\{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) \(\delta_C\): 33.5 (O=CC(2)H\(_A\)H\(_B\)), 42.2 – 46.3 (NC(2)H\(_2\)C(3)H\(_2\)C(5)H\(_2\)C(6)H\(_2\)O), 55.5 (-OCH\(_3\)), 58.8 (q, \(2J_{CF} = 22.9, \text{C}=\text{OCH}_3\text{H}_3\text{C}(3)\text{HCF}_3\)), 66.6 – 66.8 (NC(2)H\(_2\)C(3)H\(_2\)C(5)H\(_2\)C(6)H\(_2\)O), 101.3 (N=CC(3)ArOH-OCH\(_3\)), 106.6 (N=CC(5)ArOH-OCH\(_3\)), 113.6 (N=CC(1)ArOH-OCH\(_3\)), 126.0 (-CF\(_3\)), 128.2 (N=CC(1)Ar), 128.4 (N=CC(2,6)Ar), 129.5 (N=CC(3,4,5)Ar), 134.3 (N=CC(6)ArOH-OCH\(_3\)), 164.3 (N=CC(4)ArOH-OCH\(_3\)), 165.2 (N=CC(2)ArOH-OCH\(_3\)), 166.7 (C=O), 179.0 (C=N). HRMS (NSI\(^+\)) \(\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4^+\) ([M+H\(^+\)]\(^+\)) requires 437.1683, found 437.1673 (-2.3 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C$^1$(H), CDCl$_3$, 101 MHz
HPLC Data for (R)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-morpholinobutan-1-one: Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) $t_R(R)$: 14.7 min, $t_R(S)$: 20.1 min, 96:4 er.
(R)-N-Benzyl-4,4,4-trifluoro-3-((2-hydroxy-4-methoxyphenyl)methylene)amino) Butanamide (24)

Following General Procedure D, 4-nitrophenyl (E)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (R)-(+-)BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzylamine was added (16.4 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.18) to give the titled compound (23.8 mg, 52%) as a yellow oil. ([α]_D^{20} +108.8 (c = 0.51, CHCl_3); Chiral HPLC analysis. Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R (R): 13.0 min, t_R (S): 14.9 min, 97:3 er; IR ν max (ATR), 2956 (Ar-H), 1743 (O=CNHBn) 1604 (C=O), 1595 (C=N), 1442 (C=C), 1261 (CF_3); ¹H NMR (400 MHz, CDCl_3) δ_H: 2.72 – 2.76 (2H, m, O=CC(2)H_AH_B), 3.85 (3H, s, -OCH_3), 4.26 – 4.30 (1H, dd, 2_J_{HH} = 15.0, 3_J_{HH} = 5.3, O=CC(2)H_AH_B), 4.43 (1H, m, O=CCH_AH_BC(3)H), 4.52 – 4.56 (1H, dd, 2_J_{HH} = 15.0, 3_J_{HH} = 6.4, O=CCH_AH_BPh), 6.11 (1H, d, 3_J_{HH} = 6.4, O=CNH), 6.31 (1H, d, 3_J_{HH} = 9.0, 4_J_{HH} = 2.6, N=CC(5)ArOH-OCH_3), 6.49 (1H, d, 4_J_{HH} = 2.6, N=CC(3)ArOH-OCH_3), 6.67 (1H, d, 3_J_{HH} = 9.0, N=CC(6)ArOH-OCH_3), 7.07 – 7.10 (2H, m, NHCH_2C(2,6)ArH), 7.14 (3H, m, NHCH_2C(3,4,5)ArH), 7.21 (2H, m, N=CC(2,6)ArH), 7.49 (3H, m, N=CC(3,4,5)ArH), 14.9 (1H, s, -O). ¹⁹F{¹H} NMR (376 MHz, CDCl_3), δ_F: -74.49 (-CF_3); ¹³C{¹H} NMR (101 MHz, CDCl_3) δ_C: 37.9 (O=CC(2)H_AH_B), 43.9 (NHCH_2Ph), 55.5 (-OCH_3), 58.8 – 59.4 (q, 2_J_{CF} = 23.3 O=CCH_AH_B(C(3)H), 101.3 (N=CC(3)ArOH-OCH_3), 106.4 (N=CC(5)ArOH-OCH_3), 113.8 (N=CC(1)ArOH-OCH_3), 125.8 (-CF_3), 127.4 (NHCH_2C(3,4,5)Ph), 127.7 (N=CC(2,6)ArH), 128.3 (NHCH_2C(2,6)Ph), 128.6 (N=CC(1)Ar), 129.4 (N=CC(3,4,5)Ar), 134.2 (N=CC(6)ArOH-OCH_3), 137.6 (NHCH_2C(1)Ph), 164.2 (N=CC(2)ArOH-OCH_3), 165.3 (N=CC(4)ArOH-OCH_3), 167.8 (C=O), 179.2 (C=N). HRMS (NSI^+ ) C_{25}H_{23}F_{3}N_{2}O_{4}^{+} ([M+H]^+) requires 457.1734, found 457.1724 (-2.2 ppm).
$^1$H, CDCl$_3$, 400 MHz
$^{19}$F, CDCl$_3$, 376 MHz
HPLC Data for \((R)-N\text{-benzyl-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)butanamide}\): Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C) \(t_R(R): 13.0\) min, \(t_R(S): 14.9\) min, 97:3 er.
5. GRAM SCALE SYNTHESIS

\((R)-4,4,4\text{-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (5)}\)

Following General Procedure D, 4-nitrophenyl \((E)-4,4,4\text{-trifluorobut-2-enoate (1.436 g, 5.5 mmol)}, 2\text{-(imino(phenyl)methyl)-5-methoxyphenol (2.50 g, 11.0 mmol)}, (R)-(+)\text{-BTM (277.6 mg, 1.1 mmol)}, and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (678 µL, 8.25 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) \((R_f = 0.20)\) to give the titled compound (1.55 g, 67%) as a yellow oil. 

\([\alpha]_{D}^{20} +95.5 \quad \text{(c = 0.87, CHCl}_3\text{)}; \text{Chiral HPLC analysis. Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin}^{-1}, 211 \text{ nm, 30 °C} \text{) t_R(R): 19.1 min, t_R(S): 25.3 min, 95:5 er; IR } \nu_{\text{max}} \text{ (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH}_3\text{), 1261 (CF}_3\text{); } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta_H: 1.86 – 1.98 (4H, m, NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{), 2.75 (1H, dd, }^3J_{HH} = 15.4, ^4J_{HF} = 3.0, \text{COC(2)H}_A\text{H}_B\text{), 2.98 (1H, dd, }^3J_{HH} = 15.2, ^4J_{HF} = 10.0, \text{COC(2)H}_A\text{H}_B\text{), 3.44 – 3.57 (4H, m, NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{, 3.84 (3H, s, OCH}_3\text{), 4.54 (1H, m, COCH}_A\text{H}_B\text{CF}_3\text{), 6.28 (1H, dd, }^3J_{HH} = 9.0, \text{N=CC(5)ArOH-OCH}_3\text{), 6.58 (1H, s, N=CC(3)ArOH-OCH}_3\text{), 6.72 (1H, dd, }^3J_{HH} = 8.9, \text{N=CC(6)ArOH-OCH}_3\text{), 7.24 (1H, m, N=CC(4)ArH), 7.52 (4H, m, N=CC(2,3,5,6)ArH), 14.8 (1H, s, N=CC(2)ArOH-OCH}_3\text{); } ^{19}\text{F} \{^1\text{H} \} \text{NMR (376 MHz, CDCl}_3\text{)} \delta_F: -74.31 (-CF}_3\text{); } ^{13}\text{C} \{^1\text{H} \} \text{NMR (101 MHz, CDCl}_3\text{)} \delta_C: 24.4 \text{(NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{), 26.1 (NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{), 35.3 (C=OCH}_A\text{H}_B\text{CF}_3\text{), 45.9 (NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{), 47.0 (NC(2)H}_2\text{C(3)H}_2\text{C(4)H}_2\text{C(5)H}_2\text{, 55.54 (OCH}_3\text{), 58.7 (q, }^2J_{CF} = 28.3, \text{C=OCH}_A\text{H}_B\text{C(3)HCF}_3\text{, 101.2 (N=CC(3)ArOH-OCH}_3\text{), 106.6 (N=CC(5)ArOH-OCH}_3\text{), 114.28 (N=CC(1)ArOH-OCH}_3\text{), 118.4 (CF}_3\text{), 128.2 (N=CC(2,3,5,6)ArH), 129.5 (N=CC(4)Ar), 134.4 (N=CC(1)Ar), 164.4 (N=CC(2)ArOH-OCH}_3\text{), 165.5 (C=N), 166.3 (N=CC(4)ArOH-OCH}_3\text{), 178.9 (C=O). HRMS (NSI\textsuperscript{+}) C_{21}H_{23}F_3\text{N}_2\text{O}_3\text{+ ([M+H}\textsuperscript{+}) requires 421.1734, found 421.1729 (-1.2 ppm).}
6. HYDROLYSIS OF PRODUCT 5

(R)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (25)

Compound 5 (292 mg, 0.7 mmol), THF (0.05 M), and 10% HCl (1.1 mL, 3.45 mmol) was stirred at room temperature for 16 hrs. The crude mixture was purified by flash column chromatography MeOH to give the titled compound 25 (138 mg, 95% yield) as an off-white solid. \[^{[a]}_{D} +96.1\] (c = 0.84, CHCl\(_3\)); **Chiral HPLC analysis.** Chiralpak ADH (85:15 Hexane:IPA, flow rate 1 mLmin\(^{-1}\), 211 nm, 30 °C) \(t_{R}(S): 12.9\) min, \(t_{R}(R): 18.3\) min, 96:4 er; **IR** \(\nu_{\text{max}}\) (ATR), 3116 (NH\(_2\)), 2981 (Ar-H), 1715 (C=O), 1618 (Amide stretch), 1390 (C=C), 1296 (CF\(_3\)); **\(^{1}H\) NMR** (400 MHz, D\(_2\)O) \(\delta_H\): 1.90 – 1.98 (4H, m, NC(2)H(2)C(3)H(2)C(4)H(2)C(5)H(2)), 2.64 – 2.69 (1H, dd, \(^2J_{HH} = 16.8\), \(^3J_{HH} = 9.4\), COC(2)H(2)H(2)CHCF\(_3\)), 2.82 – 2.86 (1H, dd, \(^2J_{HH} = 15.9\), \(^3J_{HH} = 3.4\), COC(2)H(2)H(2)CHCF\(_3\)), 3.43 – 3.55 (4H, m, NC(2)H(2)C(3)H(2)C(4)H(2)C(5)H(2)), 3.90 (1H, s, COCH\(_A\)H(2)CHCF\(_3\)); **\(^{19}F\)\(^{\{1}H\)} NMR** (376 MHz, D\(_2\)O) \(\delta_F\): -77.47 (-CF\(_3\)); **\(^{13}C\)\(^{\{1}H\)} NMR** (101 MHz, D\(_2\)O) \(\delta_C\): 23.9 – 25.2 (NC(2)H(2)C(3)H(2)C(4)H(2)C(5)H(2)), 33.2 (COCH\(_A\)H(2)CHCF\(_3\)), 46.3 – 47.4 (NC(2)H(2)C(3)H(2)C(4)H(2)C(5)H(2)), 50.0 (q, \(^2J_{CF} = 33.0\), COCH\(_A\)H(2)CHCF\(_3\)), 128.5 (-CF\(_3\)), 170.3 (C=O). **HRMS** (NSI\(^{+}\)) C\(_8\)H\(_{14}\)F\(_3\)N\(_2\)O\(^+\) ([M+H]\(^+\)) requires 211.1053, found 211.1047 (-2.8 ppm).
$^1$H, D$_2$O, 400 MHz
$^{13}\text{C}'^{1\text{H}}$, D$_2$O, 101 MHz
$^{19}$F, D$_2$O, 376 MHz
HPLC Data for (R)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (25): Chiralpak ADH (85:15 Hexane:IPA, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tₘ(S): 12.9 min, tₘ(R): 18.3 min, 96:4 er.

![HPLC chart for (R)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (25)]
7. ABSOLUTE CONFIGURATION: HYDROLYSIS OF PRODUCT 25

(R)-3-amino-4,4,4-trifluorobutanoic acid

Compound 25 (41.3 mg, 0.2 mmol) was added with 6 N HCl (0.4 mL) stirred at 120 °C for 12 hrs. The crude mixture was then dried to obtain a crude beige solid. The crude solid was then added with dried EtOH (1.7 M) and propylene oxide (56 μL, 0.8 mmol) and the reaction mixture was stirred for 30 minutes. The mixture was then concentrated under vacuo and the crude solid was then washed with propanol to obtain the solid product (12.7 mg, 40% yield) as an off-white solid mp 173–175 °C; $\left[\alpha\right]_{D}^{25}$ +17.9 (c = 1.27, 6N HCl) (literature $\left[\alpha\right]_{D}^{25}$ +24.4 (c = 1.05, 6N HCl))$^{10}$; IR $\nu_{\text{max}}$ (ATR), 3387 (NH$_2$), 3045 (OH) 1615 (C=O), 1430 (CH$_2$ bend), 1296 (CF$_3$); $^1$H NMR (400 MHz, CD$_3$OD) δ$_{H}$: 2.50 (1H, m, COC(2)H$_{A}$H$_{B}$CHCF$_3$), 2.74 (1H, m, COC(2)H$_{A}$H$_{B}$CHCF$_3$), 3.94 (1H, m, COCH$_{A}$H$_{B}$CHCF$_3$). $^{19}$F{$^1$H} NMR (400 MHz, CD$_3$OD), δ$_{F}$: -77.9 (-CF$_3$). Data in agreement with literature.$^{10}$
8. REFERENCES


