Site-Selective Pd-Catalyzed C(sp$^3$)–H Arylation of Heteroaromatic Ketones

Anton Kudashev and Olivier Baudoin*
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1. General methods

Techniques:

All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm or 365 nm) or TLC stains (vanillin, KMnO₄ or anise). Chromatography was performed on Biotage® Isolera™ instrument using prepackaged Claricep™ (Agela Technologies) or Sfär™ Silica Duo 60 μm (Biotage) normal phase cartridges of varying size with indicated solvent systems in order of increasing polarity.

Chemicals:

Anhydrous solvents were purchased from Sigma-Aldrich, Acros Organics or Fluorochem. Solvents that were involved in C–H activation processes were additionally degassed by bubbling argon through (tert-amyl alcohol, DMF) or three cycles of freeze-pump-thaw (mesitylene) and were stored under the atmosphere of argon in Schlenk flasks. Solvents used for substrate synthesis were purchased from Avantor and used as received.

Palladium salts were purchased from Sigma-Aldrich and stored in an argon-filled glovebox at ambient temperature. Other chemicals were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Apollo Scientific, Fluorochem or Enamine and used as received unless specified otherwise.

Instrumentation:

GCMS analyses were performed with a Shimadzu QP2010SB GCMS apparatus on a Rtx®-5ms-Low-Bleed column lined with a mass (EI) detection system. HPLC analyses was performed using a Shimadzu Prominence system with SIL-20A auto sampler, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector.

Melting points were obtained on a Büchi melting point M-565, and are uncorrected.

IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm⁻¹).

Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ¹H δ 7.26 ppm, ¹³C δ 77.16 ppm) unless otherwise noted. ¹⁹F NMR spectra were referenced to internal trifluorotoluene. (δ -63.72 ppm). Both ¹³C and ¹⁹F NMR spectra are ¹H/(¹H) decoupled unless otherwise stated. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ddd = doublet of doublet of doublet and brs = broad singlet), coupling constant in Hz and integration.

High resolution mass spectra were recorded by Dr. M. Pfeffer (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer.
2. Synthesis of starting materials

- Representative procedure A – preparation of 1-(pyridin-2-yl)butan-1-one 1a

A vigorously stirred solution of picolinonitrile (20.8 g/19.3 mL, 0.2 mol) in diethyl ether (250 mL) was cooled to -20°C (30% aq. MeOH/dry ice) and solution of n-propylmagnesium chloride (1.1 eq, 0.22 mol, 110 mL of 2 mol/L solution in diethyl ether) was added dropwise. Upon completion, cooling bath was removed and a thick yellow slurry was stirred overnight. Reaction mixture was then cooled to 0°C (ice/water) and quenched by portionwise addition of 200 mL of 2M HCl (caution: vigorous and exothermic) and left stirring for 30 minutes. Reaction mixture is then basified (pH > 9) by addition of 2M NaOH. Ethyl acetate (200 mL) was then added and aqueous layer was separated. Aqueous layer was washed once with ethyl acetate and combined organic layer was washed with sat. NaHCO₃ solution and water. Organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then applied onto SNAP KP-Sil 340g cartridge and purified by column chromatography (10-20% EtOAc in cyclohexane) to yield 1-(pyridin-2-yl)butan-1-one (26.2 g) as a yellow liquid.

1-(pyridin-2-yl)butan-1-one (1a)

Prepared as stated above. The compound is described.¹

¹ Wu Q., Han S., Ren X., Lu H., Li J., Zou D., Wu D., Wu Y., Org. Lett. 2018, 20, 6345–6348

According to the procedure above, these compounds were synthesized:

2-methyl-1-(pyridin-2-yl)propan-1-one (1f)

Prepared from picolinonitrile (0.52 g) and isopropylmagnesium bromide (2.75 mL of 2M THF solution) to yield 0.4 g (54%) of titular compound as an orange oil. The compound is described.¹
1H NMR (500 MHz, CDCl₃) δ 8.67 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.03 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.82 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.44 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.10 (hept, J = 6.8 Hz, 1H), 1.20 (d, J = 6.8 Hz, 6H).

13C NMR (126 MHz, CDCl₃) δ 205.85, 153.07, 148.99, 137.02, 126.97, 122.58, 34.34, 18.78.

2,2-dimethyl-1-pyridin-2-yl-propan-1-one (1g)

This compound was prepared according to a described² procedure from 2.1 g of 2-picolinonitrile to yield 0.7 g of title compound (21%). Analytical data matched that described.

1-(pyridin-2-yl)propan-1-one (1i)

Prepared from picolinonitrile (2.6 g) and ethylmagnesium bromide (9.2 mL of 3M diethyl ether solution) to yield 1.91 g (57%) of titular compound as yellow oil. The compound is described¹.

1H NMR (500 MHz, CDCl₃) δ 8.67 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.04 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.83 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.46 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 3.24 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 202.67, 153.55, 149.01, 136.94, 127.08, 121.80, 31.19, 8.04.

1-(pyridin-2-yl)heptan-1-one (1j)

Prepared from picolinonitrile (2.08 g) and n-propylmagnesium chloride (13.8 mL of 2M THF solution) to yield 1.7 g (45%) of titular compound as an orange oil. The compound is described³.

1H NMR (500 MHz, CDCl₃) δ 8.66 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.02 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.81 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.44 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 3.20 (t, J = 7.5 Hz, 2H), 1.76 – 1.66 (m, 2H), 1.45 – 1.26 (m, 6H), 0.92 – 0.82 (m, 3H).

13C NMR (126 MHz, CDCl₃) δ 202.34, 153.72, 149.01, 136.96, 127.06, 121.88, 37.84, 31.80, 29.15, 24.07, 22.67, 14.17.

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² Prathapan S., Robinson K. E., Agosta W. C., J. Am. Chem. Soc. 1992, 114, 5, 1838–1843
³ Sharma S., Kumar M., Vishwakarma R. A., Verma M.K., Singh P. P., J. Org. Chem. 2018, 83, 20, 12420–12431
1-(pyrimidin-2-yl)butan-1-one (1k)

Prepared from 2-cyanopyrimidine (2.62 g) and n-propylmagnesium chloride (11 mL of 2M THF solution) to yield 2.71 g (71%) of titular compound as an orange oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.87 (d, $J$ = 4.8 Hz, 1H), 7.41 (t, $J$ = 4.9 Hz, 1H), 3.17 (t, $J$ = 7.1 Hz, 1H), 1.73 (h, $J$ = 7.4 Hz, 1H), 0.95 (t, $J$ = 7.4 Hz, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.87, 160.23, 157.63, 122.93, 40.94, 17.46, 13.73.

HRMS (ESI): Calcd for C$_8$H$_{10}$N$_2$O, [M+Na]$^+$: 173.0685, found: 173.0688.

IR (neat): $\nu$ (cm$^{-1}$) 2965, 2874, 1713, 1561, 1374, 1012, 815, 744.

Rf: 0.46 (EtOAc)

1-(pyrazin-2-yl)butan-1-one (1l)

Prepared from 2-cyanopyrazine (2.1 g) and n-propylmagnesium chloride (11 mL of 2M THF solution) to yield 0.25 g (8%) of titular compound as a red oil. The compound is described$^4$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.23 (d, $J$ = 1.5 Hz, 1H), 8.75 (d, $J$ = 2.5 Hz, 1H), 8.64 (dd, $J$ = 2.5, 1.5 Hz, 1H), 3.17 (t, $J$ = 7.3 Hz, 2H), 1.78 (h, $J$ = 7.4 Hz, 2H), 1.02 (t, $J$ = 7.4 Hz, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.55, 147.80, 143.80, 143.62, 39.91, 17.35, 13.95.

Rf: 0.33 (20% EtOAc in cyclohexane)

3-phenyl-1-(pyridin-2-yl)propan-1-one (1m)

Prepared from picolinonitrile (2.08 g) and phenethylmagnesium chloride (22 mL of 1M THF solution) to yield 2.8 g (66%) of titular compound as yellow oil. The compound is described$^5$.

$^4$ Wang X.-Z., Zeng C.-C., Tetrahedron 2019, 75, 1425-1430

$^5$ Boblak K. N., Klumpp D. A., J. Org. Chem. 2014, 79, 12, 5852–5857
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.66 (ddd, $J$ = 4.8, 1.8, 0.9 Hz, 1H), 8.05 (ddd, $J$ = 7.8, 1.1, 1.1 Hz, 1H), 7.82 (ddd, $J$ = 7.7, 1.8 Hz, 1H), 7.45 (ddd, $J$ = 7.6, 4.8, 1.3 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.23 – 7.15 (m, 1H), 3.61 – 3.55 (m, 2H), 3.12 – 3.05 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.09, 153.44, 149.06, 141.54, 136.97, 128.60, 128.50, 127.21, 126.07, 121.90, 39.51, 29.98.

1-(quinolin-2-yl)butan-1-one (1n)

Prepared from 2-quinolinecarbonitrile (1 g) and n-propylmagnesium chloride (3.9 mL of 2M THF solution, 1.2 eq) to yield 1.18 g (91%) of titular compound as beige solid. The compound is described$^6$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.28 – 8.23 (m, 1H), 8.21 – 8.17 (m, 1H), 8.15 – 8.09 (m, 1H), 7.89 – 7.83 (m, 1H), 7.78 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.64 (ddd, $J$ = 8.1, 6.9, 1.2 Hz, 1H), 3.38 (d, $J$ = 7.6 Hz, 2H), 1.83 (h, $J$ = 7.4 Hz, 2H), 1.06 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.76, 153.35, 147.34, 136.97, 130.69, 130.04, 129.71, 128.55, 127.78, 118.30, 39.52, 17.77, 14.12.

4-phenyl-1-(pyridin-2-yl)butan-1-one (1o)

Prepared from picolinonitrile (1 g) and (3-phenylpropyl)magnesium bromide solution in diethyl ether to yield 1.92 g (85%) of titular compound as yellow oil. (3-phenylpropyl)magnesium bromide solution was prepared by dropwise addition 1-bromo-3-phenylpropane (3.04 mL) to a suspension of magnesium (0.49 g) and iodine (25 mg) in diethyl ether (20 mL) and stirred for 3 hours. The compound is described$^7$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.69 (ddd, $J$ = 4.7, 1.7, 0.9 Hz, 1H), 8.05 (ddd, $J$ = 7.8, 1.1, 1.1 Hz, 1H), 7.84 (ddd, $J$ = 7.7, 7.7, 1.7 Hz, 1H), 7.47 (ddd, $J$ = 7.5, 4.8, 1.2 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 3.27 (t, $J$ = 7.5 Hz, 1H), 2.76 (dd, $J$ = 8.6, 6.8 Hz, 2H), 2.17 – 2.07 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.82, 153.49, 148.92, 141.98, 136.87, 128.53, 128.34, 127.03, 125.85, 121.75, 37.16, 35.38, 25.62.

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$^6$ Siddaraju Y., Lamani M., Prahbu K. R., *J. Org. Chem.* 2014, 79, 9, 3856–3865

$^7$ W. Sun, L. Wang, C. Xia, C. Liu, *Angew. Chem. Int. Ed.* 2018, 57, 5501.
 Preparation of other ketone compounds

**1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (1d)**

To a 50 mL round bottom flask equipped with PTFE-coated magnetic stirbar 1-methyl-1H-pyrazole-3-carboxylic acid (1 g, 7.9 mmol) was charged. 20 mL of DCM are then added; resulting mixture was then cooled to 0 °C (ice/water). 1,1'-Carbonyldiimidazole (1.67 g, 10.3 mmol, 1.3 eq) was then added portionwise. Resulting mixture was stirred at that temperature for 1.5 hours. N,O-dimethylhydroxylamine hydrochloride (1.06 g, 10.3 mmol, 1.3 eq) was added afterwards in a single portion, followed by slow addition of triethylamine (3.3 mL, 23.8 mmol, 3 eq). Cooling was then removed and reaction mixture was then left to stir at room temperature overnight. After aging, reaction mixture was diluted with water. Organic layer was extracted and washed once with sat. NaHCO₃ solution and water, dried over Na₂SO₄ and evaporated at reduced pressure. 1.15 g (77%, rated as 90% pure) of N-methoxy-N,1-dimethyl-1H-pyrazole-3-carboxamide is recovered as a beige, transparent liquid, which is then used in the next step without purification.

To a 100 mL round bottom flask equipped with PTFE-coated magnetic stirbar product of previous transformation (1.15 g, 90%, 6.12 mmol) was charged, followed by dissolution in 30 mL of diethyl ether. Resulting mixture was cooled to -20°C (30% aq. MeOH/dry ice) and n-propylmagnesium chloride (7.65 mL of 2 M solution in diethyl ether) was added dropwise. Reaction mixture was then left to stir overnight at rt. After aging, mixture was then quenched with sat. NH₄Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 0.77 g (83%) of titular compound as a pale yellow liquid.

**1H NMR (500 MHz, CDCl₃)** δ 7.35 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 3.95 (s, 3H), 2.94 (t, J = 7.5 Hz, 2H), 1.79 – 1.68 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

**13C NMR (126 MHz, CDCl₃)** δ 196.36, 151.46, 131.71, 106.99, 40.83, 39.63, 17.82, 14.00.

**HRMS (ESI):** Calcd for C₉H₁₂N₂O, [M+Na]⁺: 175.0842, found: 175.0844.

**IR (neat): v (cm⁻¹) 2962, 1678, 1469, 1360, 1209, 1059, 954, 892, 771.

**Rf:** 0.22 (20% EtOAc in cyclohexane)
**1-(1-methyl-1H-pyrazol-5-yl)butan-1-one (1e)**

To an oven-dried two-neck flask equipped with a PTFE-coated magnetic stirbar, under the atmosphere of argon N-methylpyrazole (0.83 mL, 10 mmol) was charged, followed by dry THF (15 mL) and TMEDA (1.72 mL, 1.15 eq). Reaction mixture was then cooled to -78°C (dry ice/acetone) and n-butyllithium (4.4 mL of 2.5 M solution in hexane, 1.1 eq) was added dropwise. Upon completion of addition, reaction was stirred for 1h at that temperature. After aging, a solution of N-methoxy-N-methylbutyramide (1.44 g, 1.1 eq) in 30 mL of THF was added dropwise. Reaction was then left in the cooling bath to slowly warm up to rt overnight. Mixture was then quenched by addition of sat. NH₄Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 0.34 g (22%) of titular compound as a pale yellow liquid.

$^1$H NMR (500 MHz, CDCl₃) δ 7.44 (d, $J = 2.1$ Hz, 1H), 6.81 (d, $J = 2.1$ Hz, 1H), 4.15 (s, 3H), 2.84 - 2.77 (m, 2H), 1.73 (h, $J = 7.4$ Hz, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl₃) δ 191.93, 138.65, 137.62, 111.32, 42.53, 40.35, 17.83, 13.88.

HRMS (ESI): Calcd for C₈H₁₂N₂O, [M+H]⁺: 153.1022, found: 153.1020.

IR (neat): ν (cm⁻¹) 2962, 1678, 1453, 1318, 1218, 966, 785.

Rf: 0.42 (20% EtOAc in cyclohexane)
N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (1p)

To a 250 mL round bottom flask, glutaryl chloride (3.2 mL, 25 mmol) was charged, followed by addition of DCM (63 mL) and N,O-dimethylhydroxylamine hydrochloride (5.12 g, 52.5 mmol, 2.1 eq). Resulting mixture was cooled to 0 °C (ice/water) and pyridine (8.5 mL, 105 mmol, 4.2 eq) was added dropwise. After completion, reaction is stirred for 3.5 hours at room temperature, after which 0.5 M hydrochloric acid solution was added. Organic layer was separated and extracted additionally once with 0.5 M HCl and twice with sat. NaHCO₃ solution. Remaining organic layer was dried over Na₂SO₄ and evaporated at reduced pressure to yield 5 g of N,N-dimethoxy-N,N-dimethylglutaramide as a brown liquid, which was used in the next step without purification.

To an oven-dried 100 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (2.14 mL, 22 mmol, 2.4 eq) was added, followed by dry THF (50 mL). To this mixture isopropylmagnesium bromide (8.21 mL of 2.9 M solution in 2-MeTHF, 23.8 mmol, 2.6 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of N,N-dimethoxy-N,N-dimethylglutaramide (2 g, 9.6 mmol) in 10 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring for 4 hours at room temperature. After completion of these steps, reaction was quenched by addition of sat. NH₄Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-50% EtOAc in cyclohexane) to yield 0.63 g (29%) of titular compound as a brown liquid.

1H NMR (500 MHz, CDCl₃) δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.03 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.82 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.45 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H), 3.67 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H), 3.17 (s, 3H), 2.56 (t, J = 7.5 Hz, 2H), 2.08 (p, J = 7.3 Hz, 2H).

13C NMR (126 MHz, CDCl₃) δ 201.50, 174.24, 153.48, 149.01, 136.94, 127.14, 121.78, 61.29, 37.23, 32.27, 31.25, 18.92.

HRMS (ESI): Calcd for C₁₂H₁₆N₂O₃, [M+Na]⁺: 259.1053, found: 259.1056.

IR (neat): ν (cm⁻¹) 2931, 1698, 1651, 1384, 978, 769.

Rf: 0.1 (20% EtOAc in cyclohexane)
6-((tert-butyldiphenylsilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (1q)

Preparation of ketone 1r was performed with known procedures.\textsuperscript{8,9}

Isopropylmagnesium chloride (3 eq, 52.5 mmol, 18 mL of 2.9 M solution in 2-MeTHF) was added dropwise to a mixture of 2-oxepanone (2 g, 17.5 mmol) and N,O-dimethylhydroxylamine hydrochloride (2.56 g, 26.3 mmol, 1.5 eq) in THF (60 mL) at 0 °C. The resulting mixture was then warmed to r.t. After 1 h, it was cooled to 0 °C, and of sat. NH\textsubscript{4}Cl solution was added, followed by water. The phases were separated, and the aqueous layer was extracted with DCM twice. The combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure to provide 6-hydroxy-N-methoxy-N-methylhexanamide, which was used without purification in the next reaction.

Into a 100 mL round-bottom flask equipped with PTFE-coated magnetic stirbar product of previous transformation (2 g, 11.4 mmol) was charged and subsequently dissolved in DCM (25 mL). Reaction was then cooled to 0 °C (ice/water); imidazole (1.1 g, 14.8 mmol, 1.3 eq) and DMAP (139 mg, 1.14 mmol, 0.1 eq) were added, followed by dropwise addition of TBDPS–Cl (3 mL, 11.6 mmol, 1.02 eq). Cooling bath was then removed and reaction was stirred for 1 hour, by which time TLC control (20% EtOAc in cyclohexane) indicated full consumption of the material. Reaction mixture was quenched by addition of water. Layers were separated and organics were additionally washed twice with water and once with brine. Organics were then dried over Na\textsubscript{2}SO\textsubscript{4} and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-25% EtOAc in cyclohexane) to yield 2.7 g of TBDPS-protected alcohol, which was used in the next step.

To an oven-dried 100 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (0.57 mL, 5.8 mmol, 1.2 eq) was added, followed by dry THF (25 mL). To this mixture isopropylmagnesium bromide (2.1 mL of 2.9 M solution in 2-MeTHF, 6.1 mmol, 1.25 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of previously obtained silyl ether (2 g, 4.8 mmol) in 5 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring overnight at room temperature. After completion of these steps, reaction was quenched by addition of sat. NH\textsubscript{4}Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na\textsubscript{2}SO\textsubscript{4} and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-30% EtOAc in cyclohexane) to yield 0.37 g (18%) of titular compound as a pale yellow oil.

\begin{align*}
^{1}H \text{ NMR (500 MHz, CDCl}_3) & \delta 8.69 \text{ (ddd, } J = 4.8, 1.8, 0.9 \text{ Hz, 1H)}, 8.05 \text{ (ddd, } J = 7.8, 1.1, 1.1 \text{ Hz, 1H)}, 7.85 \text{ (ddd, } J = 7.7, 7.7, 1.7 \text{ Hz, 1H)}, 7.72 – 7.63 \text{ (m, 4H)}, 7.48 \text{ (ddd, } J = 7.5, 4.8, 1.3 \text{ Hz, 1H)}, 7.45 – 
\end{align*}

\textsuperscript{8} Bissember A. C., Levina A., Fu. G. C., J. Am. Chem. Soc. 2012, 134, 34, 14232–14237
\textsuperscript{9} Zhang C.-H., Gao Q., Li M., Wang J.-F., Yu C.-M., Mao B., Org. Lett. 2021, 23, 10, 3949–3954
7.28 (m, 7H), 3.67 (t, J = 6.4 Hz, 2H), 3.22 (d, J = 7.5 Hz, 2H), 1.78 – 1.67 (m, 2H), 1.67 – 1.58 (m, 2H), 1.53 – 1.43 (m, 2H), 1.04 (s, 9H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.02, 153.50, 148.89, 137.23, 135.72, 134.27, 129.62, 127.72, 127.17, 122.01, 63.93, 37.93, 32.59, 27.02, 25.73, 23.93, 19.36.

HRMS (ESI): Calcd for C$_{27}$H$_{33}$NO$_2$Si, [M+Na]$^+$: 454.2173, found: 454.2176.

IR (neat): ν (cm$^{-1}$) 3052, 2933, 2859, 1698, 1463, 1110, 705.

Rf: 0.6 (20% EtOAc in cyclohexane)
1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (1r)

Compound was prepared according to a modified Representative procedure A. 4H-1,2,4-triazole-3-carbonitrile (0.941 g, 10 mmol) and solution of n-propylmagnesium chloride (2.5 eq, 25 mmol, 12.5 mL of 2 mol/L solution in diethyl ether) in THF (25 mL) were used. During acidification, 18.8 mL (3.75 eq, 37.5 mmol of HCl) of 2M HCl was used. These amendments yield 0.7 g (50%) of titular compound as white crystalline solid.

1-(4H-1,2,4-triazol-3-yl)butan-1-one (0.2 g, 1.44 mmol) was charged into a threaded culture tube with PTFE-coated magnetic stirbar and dissolved in THF (2 mL). 3,4-Dihydro-2H-pyran (0.66 mL, 5 eq) and methanesulfonic acid (5 μL, 5% mol) were added sequentially. The culture tube was sealed with a cap and then subjected to stirring in an heating block at 85°C overnight. After aging, reaction mixture was cooled to room temperature, diluted with EtOAc and extracted with sat. NaHCO₃ solution and brine. Organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-100% EtOAc in cyclohexane) to yield 0.2 g (62%) of titular compound as a transparent honey-like oil.

1H NMR (500 MHz, CDCl₃) δ 8.34 (s, 1H), 5.52 (dd, J = 9.0, 2.8 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.77 – 3.67 (m, 1H), 3.05 (t, J = 7.4 Hz, 2H), 2.24 – 2.14 (m, 1H), 2.11 – 1.97 (m, 2H), 1.86 – 1.61 (m, 6H), 0.99 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 193.98, 160.16, 143.27, 86.90, 67.87, 41.66, 30.83, 24.80, 21.67, 17.49, 13.91.

HRMS (ESI): Calcd for C₁₁H₁₇N₃O₂, [M+Na]⁺: 246.1213, found: 246.1217.

IR (neat): ν (cm⁻¹) 2939, 2872, 1702, 1445, 1198, 1088, 1043, 998, 914.

Rf: 0.32 (50% EtOAc in cyclohexane)
1-(thiazol-2-yl)butan-1-one (1s)

To an oven-dried, 50 mL two-neck flask equipped with a PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromothiazole (0.9 mL) was added, followed by dry THF (15 mL) and TMEDA (1.65 mL, 1.1 eq). Reaction mixture was then cooled to -78°C (dry ice/acetone) and n-butyllithium (4 mL of 2.5 M solution in hexane, 1 eq) was added dropwise. Resulting mixture was then stirred for 30 min at this temperature. After aging, a solution of N-methoxy-N-methylbutyramide (1.31 g, 1 eq) in 5 mL of THF was added dropwise. The vessel was then allowed to naturally warm up inside the bath to room temperature overnight. Reaction was then quenched by addition of sat. NH₄Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then diluted with DCM and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 1 g (64%) of titular compound as a brown oil.

1H NMR (500 MHz, CDCl₃) δ 8.00 (d, J = 3.0 Hz, 1H), 7.66 (d, J = 3.0 Hz, 1H), 3.14 (t, J = 7.5 Hz, 1H), 1.81 (h, J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 194.19, 167.55, 144.78, 126.17, 40.55, 17.72, 13.92.

HRMS (ESI): Calcd for C₇H₉NOS, [M+H]⁺: 156.0478, found: 156.0476.

IR (neat): ν (cm⁻¹) 2964, 2875, 1683, 1391, 1226, 965, 747, 618.

Rf: 0.6 (20% EtOAc in cyclohexane)
**3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (1t)**

To a 250 mL round bottom flask equipped with PTFE-coated magnetic stirbar 3-cyclopentylpropionic acid (4.28 mL, 30 mmol) was charged. 60 mL of DCM are then added; resulting mixture was then cooled to 0 °C (ice/water). 1,1'-Carbonyldiimidazole (5.35 g, 33 mmol, 1.1 eq) was then added portionwise. Resulting mixture was stirred at that temperature for 1.5 hours. N,O-dimethylhydroxylamine hydrochloride (3.21 g, 33 mmol, 1.1 eq) was added afterwards in a single portion, followed by slow addition of triethylamine (12.5 mL, 90 mmol, 3 eq). Cooling was then removed and reaction mixture was then left to stir at room temperature overnight. After aging, reaction mixture was diluted with water. Organic layer was extracted and washed once with sat. NaHCO₃ solution and water, dried over Na₂SO₄ and evaporated at reduced pressure. 5 g (90%) of 3-cyclopentyl-N-methoxy-N-methylpropanamide is recovered as a beige, transparent liquid, which is then used in the next step without purification.

To an oven-dried 25 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (0.975 mL, 10 mmol, 1 eq) was added, followed by dry THF (3 mL). To this mixture isopropylmagnesium bromide (3.9 mL of 2.9 M solution in 2-MeTHF, 11 mmol, 1.1 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of 3-cyclopentyl-N-methoxy-N-methylpropanamide (1.9 g, 10.3 mmol, 1.03 eq) in 5 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring at room temperature overnight. After completion of these steps, reaction was quenched by addition of sat. NH₄Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (X-Y% EtOAc in cyclohexane) to yield 1.05 g (52%) of titular compound as an orange liquid.

**1H NMR (500 MHz, CDCl₃)** \(\delta\) 8.68 (ddd, \(J = 4.8, 1.8, 0.9\) Hz, 1H), 8.03 (dd, \(J = 7.9, 1.1, 1\) Hz, 1H), 7.82 (dd, \(J = 7.7, 1.7, 1\) Hz, 1H), 7.45 (dd, \(J = 7.6, 1.2\) Hz, 1H), 3.26 – 3.20 (m, 2H), 1.92 – 1.77 (m, 3H), 1.77 – 1.71 (m, 2H), 1.67 – 1.56 (m, 2H), 1.55 – 1.45 (m, 2H), 1.22 – 1.09 (m, 2H).

**13C NMR (126 MHz, CDCl₃)** \(\delta\) 202.50, 153.73, 149.05, 136.99, 127.09, 121.93, 40.00, 37.16, 32.77, 30.34, 25.34.

**HRMS (ESI):** Calcd for C₁₃H₁₇NO, \([M+H]^+\): 204.1383, found: 204.1384.

**IR (neat):** \(\nu\) (cm\(^{-1}\)) 2949, 2866, 1697, 1584, 1216, 995, 890, 752, 631.

**Rf:** 0.32 (50% EtOAc in cyclohexane)
**tert-butyl (6-oxo-6-(pyridin-2-yl)hexyl)carbamate (1u)**

![Chemical Structure]

To an oven-dried 100 mL two-neck flask equipped with a PTFE-coated stirbar under the atmosphere of argon 2-bromopyridine (0.73 mL, 7.5 mmol, 1.5 eq), N,N,N’,N’-tetramethylethylenediamine (1.12 mL, 7.5 mmol, 1.5 eq) and THF (20 mL) were charged. Resulting mixture is then cooled to -78 °C (acetone/dry ice) and n-butyllithium (3 mL of 2.5 M solution in hexanes, 7.5 mmol, 1.5 eq) was added dropwise into the solution. Reaction mixture was then stirred at this temperature for 2 hours. Upon aging, a solution of tert-butyl 2-oxopiperidine-1-carboxylate (1 g, 5 mmol, 1 eq) in THF (10 mL) was added dropwise and reaction mixture is stirred at -78 °C for 2 hours. Reaction is then allowed to reach room temperature, after which water is added. Resulting biphasic mixture is extracted with EtOAc three times, organic extracts are dried over Na₂SO₄ and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-40% EtOAc in cyclohexane) to yield 0.8 g (58%) of titular compound as a yellow liquid.

**1H NMR (500 MHz, CDCl₃)** δ 8.68 – 8.63 (m, 1H), 8.03 – 7.97 (m, 1H), 7.81 (ddd, J = 7.8, 1.8 Hz, 1H), 7.45 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.73 – 4.71 (brs, 1H), 3.21 (t, J = 7.3 Hz, 2H), 3.18 – 3.12 (m, 2H), 1.75 (p, J = 7.6 Hz, 2H), 1.57 (p, J = 7.1 Hz, 2H), 1.41 (s, 9H).

**13C NMR (126 MHz, CDCl₃)** δ 201.84, 156.13, 153.41, 149.03, 137.03, 127.22, 121.88, 79.14, 40.36, 37.28, 29.61, 28.53, 21.21.

**HRMS (ESI):** Calcd for C₁₅H₂₂N₂O₃, [M+Na]⁺: 301.1523, found: 301.1529.

**IR (neat):** ν (cm⁻¹) 3373, 2961, 1696, 1521, 1336, 1273, 1171.

**Rf:** 0.19 (20% EtOAc in cyclohexane).
Preparation of aryl components

**N,N-dibenzyl-4-iodoaniline (2b)**

![Chemical structure](image)

This compound was synthesized according to a described procedure\(^\text{10}\) from 2.2 g of 4-iodoaniline to yield 2.67 g (67\%) of titular compound as white needles. Analytical data of obtained sample matched those described.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.37 (m, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.24 (m, 2H), 7.24 – 7.20 (m, 4H), 6.55 – 6.48 (m, 2H), 4.63 (s, 4H).

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 148.71, 137.90, 128.89, 127.24, 126.68, 115.01, 54.47.

**1-benzyl-5-iodo-1H-indole (2c)**

![Chemical structure](image)

This compound was synthesized according to a described procedure\(^\text{11}\) from 0.6 g of 5-iodoindole to yield 0.65 g (78\%) of titular compound as pale yellow flakes. Analytical data of obtained sample matched those described.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.90 (dd, \(J = 1.7, 0.6\) Hz, 1H), 7.32 (dd, \(J = 8.6, 1.6\) Hz, 1H), 7.26 – 7.15 (m, 4H), 7.06 – 6.94 (m, 5H), 6.40 (dd, \(J = 3.1, 0.9\) Hz, 1H), 5.21 (s, 2H)

\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 137.16, 135.54, 131.43, 130.13, 129.93, 129.23, 128.98, 128.55, 127.93, 126.82, 111.87, 101.18, 83.24, 50.38.

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\(^\text{10}\) Goldup S. M., Leigh D.A., Lusby P. J., McBurney R. T., Slawin A. M. Z., *Angew. Chem. Int. Ed.* **2008**, *47*, 3381 –3384

\(^\text{11}\) Arendt K. A., Doyle A. G., *Angew. Chem. Int. Ed.* **2015**, *54*, 9876 –9880
3. Products of α-functionalization

- Optimization studies for α-functionalization

Table 3.1. Base and solvent optimization for α-functionalization

| Entry | Base (X) | n | T, °C | Solvent, [C] | Yield, α | Yield, β | Comment |
|-------|----------|---|-------|--------------|----------|----------|---------|
| 1     | Cs₂CO₃ (1) | 2 | 100   | Toluene, 0.1 M | 45       | 1        | Initial base screening |
| 2     | Rb₂CO₃ (1) | 2 | 100   | HFIP, 0.1 M | 1        | 5        | |
| 3     | NaOtBu (1) | 2 | 100   | DCE, 0.1 M | 12       | 6        | |
| 4     | KOH (1)    | 2 | 100   | H₂O, 0.1 M | 22       | 3        | |
| 5     | NaOH (1)   | 2 | 100   | PEG400, 0.1 M | 2       | 4        | |
| 6     | CsOH (1)   | 2 | 100   | t-AmyLOH, 0.1 M | 23      | 12       | |
| 7     | Cs₂CO₃ (1) | 2 | 100   | t-BuOH, 0.1 M | 21       | 9        | |
| 8     | Cs₂CO₃ (1) | 2 | 100   | AcOH, 0.1 M | 0        | 3        | |
| 9     | Cs₂CO₃ (1) | 2 | 100   | Dioxane, 0.1 M | 13      | 0        | |
| 10    | Cs₂CO₃ (1) | 2 | 100   | DMSO, 0.1 M | 0        | 0        | |
| 11    | Cs₂CO₃ (1) | 2 | 100   | TFT, 0.1 M | 68       | 0        | |
| 12    | Cs₂CO₃ (1) | 2 | 100   | TFE, 0.1 M | 12       | 10       | |
| 13    | Cs₂CO₃ (1.5) | 2 | 100 | TFT, 0.1 M | 68       | 0        | Base quantity determination |
| 14    | Cs₂CO₃ (2) | 2 | 100   | m-xylene, 0.1 M | 72      | 0        | Secondary solvent screening |
| 15    | Cs₂CO₃ (2) | 2 | 100   | mesitylene, 0.1 M | 95     | 0        | |
| 16    | Cs₂CO₃ (2) | 2 | 100   | TCE, 0.1 M | 6        | 0        | |
| 17    | Cs₂CO₃ (2) | 2 | 100   | GVL, 0.1 M | 0        | 0        | |
| 18    | Cs₂CO₃ (2) | 2 | 100   | DME, 0.1 M | 69       | 0        | |
| 19    | Cs₂CO₃ (2) | 2 | 100   | 2-MeTHF, 0.1 M | 76     | 0        | |
| 20    | Cs₂CO₃ (2) | 2 | 100   | MTBE, 0.1 M | 84       | 0        | |

*Performed on 0.1 mmol scale, using 0.2 mmol (1 eq) of 1a and appropriate quantity of 2a with appropriate base, additives and solvent. Yield was determined by ¹H NMR with 1,1,2-trichloroethylene as an external standard.
Table 3.2. Scale optimization for α-functionalization

\[
\text{Cs}_2\text{CO}_3, \text{X% mol} \ [\text{Pd}] \\
\text{solvent, [C], T, 14 h}
\]

![Chemical structure of 1a and 3a](image)

| Entry | \(n\) | \(X\) | \(T, ^\circ\text{C}\) | Solvent, [C] | [Pd] | Scale, mmol | Yield, \(\alpha\) | Comment |
|-------|-----|-----|---------|-------------|-------|------------|-------------|---------|
| 29    | 2   | 10  | 100     |             |       | 0.1        | 95 (63)     | Scale up to 0.25 mmol |
| 30    | 2   | 10  | 100     |             |       | 0.25       | 66 (53)     | Temperature screen |
| 31    | 2   | 10  | 90      | Mesitylene, 0.1M | Pd(OAc)\(_2\) | 0.25       | 19          |         |
| 32    | 2   | 10  | 110     |             |       | 0.25       | 65 (38)     |         |
| 33    | 2   | 10  | 100     |             |       | 0.5        | 72          | 250 rpm stirring |
| 34    | 2   | 10  | 100     | Mesitylene, 0.2M | Pd(OAc)\(_2\) | 0.5        | 80 (77)     | 1000 rpm stirring |
| 35    | 1.25 | 5   | 100     | Mesitylene, 0.2M | PdI\(_2\) | 0.5        | 74          | Eq of aryl iodides |
| 36    | 1.5  | 5   | 120     |             |       | 0.5        | 90 (71)     |         |
| 37    | 1.25 | 5   | 120     |             |       | 0.5        | 56          | Other Pd salts |
| 38    | 1.25 | 5   | 120     |             |       | 0.5        | 85          |         |
| 39    | 1.25 | 5   | 120     | Mesitylene, 0.4M | Pd(OAc)\(_2\) | 0.5        | 88 (75)     | Finalized conditions |

*Performed on 0.1 mmol scale, using 0.2 mmol (1 eq) of 1a and appropriate quantity of 2a with appropriate base, additives and solvent. Yield was determined by \(^1\text{H NMR with 1,1,2-trichloroethylene as an external standard.})*
Representative procedure B - preparation of 2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one 3a

To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar cesium carbonate (326 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 μL, 0.5 mmol), 1-fluoro-4-iodobenzene (73 μL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 91 mg (75%) of 2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one as a yellow liquid that solidified upon standing.

Similarly, this transformation was performed at 2.5 mmol and 12.5 mmol scale to yield 500 mg (83%) and 2 g (66%) of titular compound.

2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)

Prepared as stated above. Compound was also prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 1-fluoro-4-bromobenzene (69 μL, 1.25 eq) to yield titular compound in 69% yield. Compound consistency and analytical data match in both cases.

**1H NMR (500 MHz, CDCl3)** δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.77 (ddd, J = 7.8, 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.37 – 7.32 (m, 2H), 6.98 – 6.90 (m, 2H), 5.28 (t, J = 7.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.81 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

**13C NMR (126 MHz, CDCl3)** δ 201.61, 161.89 (d, J = 244.8 Hz), 153.15, 148.95, 136.99, 135.04 (d, J = 3.2 Hz), 130.56 (d, J = 7.9 Hz), 127.12, 122.81, 115.36 (d, J = 21.2 Hz), 51.62, 26.28, 12.28.
$^{19}$F NMR (471 MHz, CDCl$_3$) δ -117.29 (s).

HRMS (ESI): Calcd for C$_{15}$H$_{14}$FNO, [M+H]$^+$: 244.1132, found: 244.1135.

Mp: 65°C

IR (neat): ν (cm$^{-1}$) 3054, 2965, 2919, 1693, 1506, 1219, 994, 821, 773.

Rf: 0.5 (20% EtOAc in cyclohexane)

According to this procedure, following compounds were synthesized:

![Chemical structure](image)

1-(pyridin-2-yl)-2-(p-tolyl)butan-1-one (3b)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 4-iodotoluene (136 mg, 1.25 eq) to yield 81 mg (68%) of titular compound as a dark blue solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.64 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.97 (ddd, $J = 7.9, 1.1, 1.1$ Hz, 1H), 7.73 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.36 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.30 – 7.19 (m, 2H), 7.08 – 7.00 (m, 2H), 5.25 (t, $J = 7.6$ Hz, 1H), 2.25 (s, 3H), 2.22 – 2.10 (m, 1H), 1.95 – 1.83 (m, 1H), 0.89 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.86, 153.46, 148.93, 136.90, 136.41, 136.32, 129.30, 128.96, 126.94, 122.81, 52.14, 26.23, 21.17, 12.39.

HRMS (ESI): Calcd for C$_{16}$H$_{17}$NO, [M+H]$^+$: 240.1383, found: 240.1385.

Mp: 55°C

IR (neat): ν (cm$^{-1}$) 2963, 2923, 2873, 1688, 1580, 1435, 1214, 994, 802.

Rf: 0.64 (20% EtOAc in cyclohexane)

![Chemical structure](image)

1-(pyridin-2-yl)-2-(m-tolyl)butan-1-one (3c)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodotoluene (136 mg) to yield 100 mg (84%) of titular compound as a dark green oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.67 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 8.00 (ddd, $J = 7.8, 1.1, 1.1$ Hz, 1H), 7.75 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.39 (ddd, $J = 7.5, 4.7, 1.2$ Hz, 1H), 7.22 – 7.17 (m, 2H), 7.17 –
7.09 (m, 1H), 7.00 – 6.96 (m, 1H), 5.26 (t, J = 7.6 Hz, 1H), 2.29 (s, 3H), 2.22 – 2.14 (m, 1H), 1.96 – 1.84 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 201.86, 153.45, 148.95, 139.29, 138.12, 136.90, 129.61, 128.40, 127.63, 126.97, 126.27, 122.81, 52.44, 26.35, 21.55, 12.44.

HRMS (ESI): Calcd for C\(_{16}\)H\(_{17}\)NO, [M+H]+: 240.1383, found: 240.1386.

IR (neat): \(\nu\) (cm\(^{-1}\)) 3054, 2964, 1693, 1461, 1345, 1211, 1090, 995, 781, 689, 617.

Rf: 0.57 (20% EtOAc in cyclohexane)

\(\text{2-(4-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3d)}\)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 4-iodochlorobenzene (77 µL) to yield 107 mg (82%) of titular compound as a green solid.

\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.77 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.25 – 7.19 (m, 2H), 5.27 (t, J = 7.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.81 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 201.36, 153.07, 148.98, 137.91, 137.02, 132.70, 130.46, 128.71, 127.19, 122.83, 51.87, 26.18, 12.29.

HRMS (ESI): Calcd for C\(_{16}\)H\(_{17}\)NO, [M+H]+: 260.0837, found: 260.0840.

Mp: 49°C

IR (neat): \(\nu\) (cm\(^{-1}\)) 3055, 2960, 2923, 1694, 1490, 1329, 1275, 1215, 1091, 991, 810, 751.

Rf: 0.56 (20% EtOAc in cyclohexane)

\(\text{2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)}\)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 2,4-difluoriodobenzene (75 µL) to yield 90 mg (69%) of titular compound as a yellow crystalline solid.
\[ \text{1H NMR (500 MHz, CDCl}\textsubscript{3}) \delta 8.64 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.01 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.32 – 7.23 (m, 1H), 6.82 – 6.72 (m, 2H), 5.49 (dd, J = 8.4, 6.6 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.90 – 1.76 (m, 1H), 0.96 – 0.90 (m, 3H). \]

\[ \text{13C NMR (126 MHz, CDCl}\textsubscript{3}) \delta 201.03, \delta 162.45 (dd, J = 108.1, 11.6 Hz), 160.48 (dd, J = 110.1, 11.6 Hz), 152.97, 149.15, 136.94, 130.37 (dd, J = 9.6, 5.7 Hz), 127.17, 122.67, 122.65 (dd, J = 15.6, 3.8 Hz), 111.43 (d, J = 3.8 Hz), 103.88 (dd, J = 26.9, 25.2 Hz), 44.79 (d, J = 1.4 Hz), 25.67, 12.10. \]

\[ \text{19F NMR (471 MHz, CDCl}\textsubscript{3}) \delta -113.48 (d, J = 7.2 Hz), -113.87 (d, J = 7.3 Hz). \]

\[ \text{HRMS (ESI): Calcd for C}_{16}\textsubscript{H}_{17}\textsubscript{NO}, [M+H]\textsuperscript{+}: 262.1038, \text{found: 262.1041.} \]

\[ \text{Mp: 90°C} \]

\[ \text{IR (neat): } \nu \textsubscript{(cm\textsuperscript{-1})} 2962, 2934, 2875, 1696, 1602, 1429, 1278, 1141, 964, 851, 783. \]

\[ \text{Rf: 0.54 (20% EtOAc in cyclohexane)} \]

\[ \text{2-(4-(dibenzylamino)phenyl)-1-(pyridin-2-yl)butan-1-one (3f)} \]

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and N,N-dibenzyl-4-iodoaniline (200 mg, 1 eq) to yield 116 mg (55%) of titular compound as a yellow oil.

\[ \text{1H NMR (500 MHz, CDCl}\textsubscript{3}) \delta 8.53 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.87 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.59 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.22 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.19 – 7.14 (m, 4H), 7.15 – 7.04 (m, 8H), 6.58 – 6.50 (m, 2H), 5.10 (t, J = 7.6 Hz, 1H), 4.46 (s, 4H), 2.12 – 2.00 (m, 1H), 1.82 – 1.70 (m, 1H), 0.80 (t, J = 7.4 Hz, 3H). \]

\[ \text{13C NMR (126 MHz, CDCl}\textsubscript{3}) \delta 201.97, 153.63, 148.84, 148.22, 138.78, 136.78, 129.79, 128.67, 127.11, 126.93, 126.79, 126.77, 122.77, 112.58, 54.26, 51.09, 26.17, 12.47. \]

\[ \text{HRMS (ESI): Calcd for C}_{29}\textsubscript{H}_{28}N_{2}O, [M+H]\textsuperscript{+}: 421.2274, \text{found: 421.2271.} \]

\[ \text{IR (neat): } \nu \textsubscript{(cm\textsuperscript{-1})} 3083, 2963, 1690, 1516, 1452, 1357, 1231, 995, 729. \]

\[ \text{Rf: 0.58 (20% EtOAc in cyclohexane)} \]
**2-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (3g)**

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodoanisole (75 μL) to yield 79 mg (62%) of titular compound as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.66 (ddd, $J = 4.8$, 1.8, 0.9 Hz, 1H), 7.99 (ddd, $J = 7.9$, 1.1, 1.1 Hz, 1H), 7.74 (ddd, $J = 7.7$, 7.7, 1.7 Hz, 1H), 7.38 (ddd, $J = 7.5$, 4.8, 1.3 Hz, 1H), 7.16 (t, $J = 7.9$ Hz, 1H), 7.01 – 6.92 (m, 2H), 6.71 (ddd, $J = 8.3$, 2.6, 1.0 Hz, 1H), 5.27 (t, $J = 7.5$ Hz, 1H), 3.76 (s, 3H), 2.25 – 2.12 (m, 1H), 1.97 – 1.85 (m, 1H), 0.92 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.57, 159.71, 153.35, 148.91, 140.91, 136.90, 129.42, 126.99, 122.78, 121.50, 114.70, 112.27, 55.25, 52.49, 26.18, 12.37.

HRMS (ESI): Calcd for C$_{16}$H$_{17}$NO$_2$, [M+H]$^+$: 256.1332, found: 256.1335.

IR (neat): ν (cm$^{-1}$) 3055, 2964, 1694, 1598, 1486, 1461, 1260, 1150, 1048, 995, 877, 781.

Rf: 0.5 (20% EtOAc in cyclohexane)

![Image of 2-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (3g)]

**2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)butan-1-one (3h)**

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 1-iodo-3,4-methylenedioxybenzene (155 mg) to yield 74 mg (55%) of titular compound as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.65 (ddd, $J = 4.7$, 1.8, 0.9 Hz, 1H), 7.99 (ddd, $J = 7.8$, 1.1, 1.1 Hz, 1H), 7.74 (ddd, $J = 7.7$, 7.7, 1.7 Hz, 1H), 7.37 (ddd, $J = 7.5$, 4.7, 1.2 Hz, 1H), 6.91 (d, $J = 1.7$ Hz, 1H), 6.83 (dd, $J = 8.0$, 1.7 Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 5.90 – 5.83 (m, 2H), 5.20 (t, $J = 7.6$ Hz, 1H), 2.18 – 2.07 (m, 1H), 1.92 – 1.74 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.56, 153.27, 148.90, 147.72, 146.43, 136.89, 133.01, 127.04, 122.75, 122.34, 109.34, 108.27, 100.94, 51.88, 26.15, 12.25.

HRMS (ESI): Calcd for C$_{16}$H$_{15}$NO$_3$, [M+H]$^+$: 270.1125, found: 270.1126.

Mp: 69°C

IR (neat): ν (cm$^{-1}$) 2964, 2907, 1681, 1482, 1247, 1038, 933, 849, 800, 694.

Rf: 0.55 (20% EtOAc in cyclohexane)
methyl 3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzoate (3i)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and methyl 3-iodobenzoate (164 mg, 1.5 eq) to yield 92 mg (65%) of titular compound as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.67 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 8.09 – 8.05 (m, 1H), 8.01 (ddd, $J = 7.9, 1.1, 1.1$ Hz, 1H), 7.85 (ddd, $J = 7.7, 1.7, 1.2$ Hz, 1H), 7.77 (ddd, $J = 7.7, 7.7, 1.8$ Hz, 1H), 7.64 – 7.58 (m, 1H), 7.41 (ddd, $J = 7.5, 4.8, 1.2$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 5.35 (t, $J = 7.5$ Hz, 1H), 3.89 (s, 3H), 2.26 – 2.15 (m, 1H), 1.98 – 1.86 (m, 1H), 0.91 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.36, 167.22, 153.05, 149.03, 139.90, 137.00, 133.72, 130.50, 130.31, 128.62, 128.20, 127.19, 122.82, 52.32, 52.21, 26.32, 12.35.

HRMS (ESI): Calcd for C$_{17}$H$_{17}$NO$_3$, [M+H]$^+$: 284.1281, found: 284.1282.

IR (neat): $\nu$ (cm$^{-1}$) 2963, 1721, 1583, 1435, 1280, 1196, 1107, 995, 752.

Rf: 0.4 (20% EtOAc in cyclohexane)

3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzaldehyde (3j)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodobenzaldehyde (116 mg) to yield 57 mg (45%) of titular compound as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.96 (s, 1H), 8.66 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 1H), 8.00 (ddd, $J = 7.8, 1.1, 1.1$ Hz, 1H), 7.94 – 7.89 (m, 1H), 7.76 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.72 – 7.64 (m, 2H), 7.46 – 7.37 (m, 2H), 5.40 5.40 (t, $J = 7.6$ Hz, 1H), 2.28 – 2.17 (m, 1H), 1.98 – 1.86 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.15, 192.44, 152.84, 149.02, 140.68, 137.02, 136.75, 135.23, 130.70, 129.21, 128.05, 127.27, 122.78, 52.10, 26.30, 12.29.

HRMS (ESI): Calcd for C$_{16}$H$_{17}$NO$_2$, [M+H]$^+$: 254.1176, found: 254.1180.

IR (neat): $\nu$ (cm$^{-1}$) 2966, 2735, 1697, 1583, 1459, 1234, 995, 789.

Rf: 0.33 (20% EtOAc in cyclohexane)
2-(4-acetylphenyl)-1-(pyridin-2-yl)butan-1-one (3k)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 4-iodoacetophenone (154 mg) to yield 66 mg (49%) of titular compound as a white solid.

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 8.66 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 8.01 (ddd, $J = 7.9, 1.1, 1.1$ Hz, 1H), 7.89 – 7.83 (m, 2H), 7.78 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.52 – 7.46 (m, 2H), 7.41 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 5.36 (t, $J = 7.6$ Hz, 1H), 2.54 (s, 3H), 2.28 – 2.15 (m, 1H), 1.98 – 1.85 (m, 1H), 0.91 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.02, 197.95, 153.00, 149.02, 145.10, 137.04, 135.86, 129.33, 128.67, 127.27, 122.84, 52.68, 26.70, 26.20, 12.32.

HRMS (ESI): Calcd for C$_{17}$H$_{17}$NO$_2$, [M+H]$^+$: 268.1332, found: 268.1335.

Mp: 51°C

IR (neat): ν (cm$^{-1}$) 3052, 2968, 2879, 1668, 1601, 1414, 1360, 1270, 1010, 956, 810, 748.

Rf: 0.25 (20% EtOAc in cyclohexane)

3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzonitrile (3l)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodobenzonitrile (172 mg) to yield 51 mg (41%) of titular compound as a white solid.

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 8.67 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 8.02 (ddd, $J = 7.8, 1.1, 1.1$ Hz, 1H), 7.79 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.75 – 7.70 (m, 1H), 7.64 (dt, $J = 7.9, 1.5$ Hz, 1H), 7.49 – 7.44 (m, 1H), 7.45 – 7.42 (m, 2H), 7.36 (t, $J = 7.8$ Hz, 1H), 5.35 (t, $J = 7.6$ Hz, 1H), 2.25 – 2.14 (m, 1H), 1.94 – 1.82 (m, 1H), 0.89 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 200.70, 197.95, 153.00, 149.02, 145.10, 137.04, 135.86, 129.33, 128.67, 127.44, 122.84, 119.00, 112.57, 51.89, 26.22, 12.23.

HRMS (ESI): Calcd for C$_{16}$H$_{14}$N$_2$O, [M+H]$^+$: 251.1179, found: 251.1178.
Mp: 48°C
IR (neat): ν (cm⁻¹) 3057, 2959, 2229, 1689, 1581, 1480, 1306, 1207, 1145, 995, 932, 810, 786, 693.
Rf: 0.26 (20% EtOAc in cyclohexane)

1-(pyridin-2-yl)-2-(o-toly)butan-1-one (3m)
Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 2-iodotoluene (80 μL) to yield 77 mg (64%) of titular compound as a dark green solid.

1H NMR (500 MHz, CDCl₃) δ 8.60 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 7.99 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.74 (td, J = 7.7, 7.7, 1.7 Hz, 1H), 7.36 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.15 – 7.10 (m, 1H), 7.13 – 7.01 (m, 2H), 5.43 (t, J = 7.4 Hz, 1H), 2.60 (s, 3H), 2.23 – 2.11 (m, 1H), 1.89 – 1.76 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 202.34, 153.58, 148.92, 138.16, 137.34, 136.85, 130.57, 127.23, 126.94, 126.65, 126.16, 122.53, 48.55, 26.59, 20.28, 12.35.

HRMS (ESI): Calcd for C₁₆H₁₇NO, [M+H]^+: 240.1383, found: 240.1388.

Mp: 56°C
IR (neat): ν (cm⁻¹) 3050, 2969, 2935, 1686, 1581, 1435, 1310, 1215, 995, 758, 685.
Rf: 0.52 (20% EtOAc in cyclohexane)

2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3n)
Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 2-iodochlorobenzene (76 μL) to yield 108 mg (83%) of titular compound as a dark green liquid.

1H NMR (500 MHz, CDCl₃) δ 8.64 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.16 (td, J = 7.5, 1.5 Hz, 1H), 7.11 (td, J = 7.7, 1.8 Hz, 1H), 5.71 (t, J = 7.3 Hz, 1H), 2.24 – 2.11 (m, 1H), 1.92 – 1.80 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 201.58, 153.24, 149.19, 137.64, 136.84, 134.90, 129.82, 129.11, 127.93, 127.02, 126.93, 122.56, 49.29, 26.06, 12.25.
2-(1-benzyl-1H-indol-5-yl)-1-(pyridin-2-yl)butan-1-one (3o)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and N-benzyl-5-iodoindole (208 mg) to yield 94 mg (53%) of titular compound as a light brown solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.53 – 8.46 (m, 1H), 7.83 (d, $J$ = 7.9 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.46 (td, $J$ = 7.7, 1.2 Hz, 1H), 7.15 – 7.06 (m, 5H), 7.04 (d, $J$ = 8.5 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.89 (d, $J$ = 3.2 Hz, 1H), 6.34 (d, $J$ = 3.1 Hz, 1H), 5.27 (t, $J$ = 7.5 Hz, 1H), 5.04 (s, 2H), 2.20 – 2.08 (m, 1H), 1.92 – 1.80 (m, 1H), 0.82 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.09, 153.59, 148.77, 137.48, 136.68, 135.52, 130.26, 128.93, 128.74, 128.43, 127.62, 126.94, 126.66, 122.99, 122.71, 121.30, 109.67, 101.61, 52.30, 50.09, 26.98, 26.54, 12.47.

HRMS (ESI): Calcd for C$_{24}$H$_{22}$N$_2$O, [M+H]$^+$: 260.0837, found: 260.0841

Mp: 91°C

IR (neat): ν (cm$^{-1}$) 2968, 1686, 1580, 1481, 1318, 1181, 1010, 722.

Rf: 0.58 (20% EtOAc in cyclohexane)

2-phenyl-1-(pyridin-2-yl)butan-1-one (3p)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and iodobenzene (69 μL) to yield 86 mg (76%) of titular compound as a greenish blue liquid. Analytical data matched with that described in literature.$^{12}$

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$^{12}$ Li B. X., Le D. N., Mack K. A., McClory A., Lim N.-K., Cravillion T., Savage S., Han C., Collum D. B., Zhang H., Gosselin F., *J. Am. Chem. Soc.* **2017**, *139*, 31, 10777–10783
1H NMR (500 MHz, CDCl₃) δ 8.66 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.28 – 7.21 (m, 2H), 7.19 – 7.14 (m, 1H), 5.29 (t, J = 7.6 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.98 – 1.85 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 201.78, 153.40, 148.95, 139.41, 136.92, 129.11, 128.56, 127.00, 126.83, 122.81, 52.54, 26.28, 12.39.

Rf: 0.59 (20% EtOAc in cyclohexane)

2-(naphthalen-2-yl)-1-(pyridin-2-yl)butan-1-one (3q)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 2-iodonaphtalene (159 mg) to yield 89 mg (65%) of titular compound as a green liquid.

1H NMR (500 MHz, CDCl₃) δ 8.67 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.02 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.81 – 7.75 (m, 3H), 7.72 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.59 (dd, J = 8.5, 1.8 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.35 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 5.48 (t, J = 7.6 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.11 – 1.99 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, CDCl₃) δ 201.57, 153.30, 148.91, 136.91, 133.62, 132.53, 128.16, 127.87, 127.84, 127.65, 127.33, 126.99, 125.97, 125.68, 122.80, 52.72, 26.24, 12.41.

HRMS (ESI): Calcd for C₁₉H₁₇NO, [M+Na]+: 298.1202, found: 298.1205.

IR (neat): ν (cm⁻¹) 3055, 2964, 1693, 1582, 1342, 1214, 995, 815, 745.

Rf: 0.5 (20% EtOAc in cyclohexane)

2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)

Prepared from 1-(pyridin-2-yl)propan-1-one (68 mg) and 1-fluoro-4-iodobenzene (58 μL, 1 eq) to yield 67 mg (59%) of titular compound as an yellow oil that solidified upon standing.

1H NMR (500 MHz, CDCl₃) δ 8.65 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.39 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.00 – 6.90 (m, 2H), 5.48 (q, J = 7.1 Hz, 1H), 1.53 (d, J = 7.1 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.78, 161.80 (d, $J = 244.8$ Hz), 152.83, 148.92, 136.98, 136.66 (d, $J = 3.2$ Hz), 130.09 (d, $J = 8.0$ Hz), 127.11, 122.89, 115.38 (d, $J = 21.2$ Hz), 44.17, 18.34.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -117.33 (s).

HRMS (ESI): Calcd for C$_{14}$H$_{12}$FNO, [M+H]$^+$: 230.0976, found: 230.0979.

Mp: 34°C

IR (neat): $\nu$ (cm$^{-1}$) 3062, 2979, 1694, 1505, 1327, 1223, 1160, 958, 841, 751.

Rf: 0.54 (20% EtOAc in cyclohexane)

**2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)**

Prepared from 1-(pyridin-2-yl)heptan-1-one (96 mg) and 1-fluoro-4-iodobenzene (116 $\mu$L, 2 eq) to yield 100 mg (70%) of titular compound as a dark brown liquid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.66 (ddd, $J = 4.8$, 2.6, 0.8 Hz, 1H), 8.00 (ddd, $J = 7.9$, 1.1, 1.1 Hz, 1H), 7.75 (ddd, $J = 7.7$, 7.7, 1.7 Hz, 1H), 7.44 – 7.32 (m, 3H), 6.99 – 6.89 (m, 2H), 5.39 (t, $J = 7.6$ Hz, 1H), 2.20 – 2.09 (m, 1H), 1.90 – 1.79 (m, 1H), 1.38 – 1.18 (m, 6H), 0.89 – 0.79 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.61, 161.84 (d, $J = 244.8$ Hz), 153.10, 148.94, 136.95, 135.28 (d, $J = 3.2$ Hz), 130.51 (d, $J = 7.9$ Hz), 127.08, 122.80, 115.34 (d, $J = 21.2$ Hz), 49.84, 33.13, 31.88, 27.39, 22.57, 14.11.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -117.30 (s).

HRMS (ESI): Calcd for C$_{18}$H$_{20}$FNO, [M+H]$^+$: 286.1602, found: 286.1605.

IR (neat): $\nu$ (cm$^{-1}$) 2929, 2859, 1697, 1508, 1225, 770.

Rf: 0.66 (20% EtOAc in cyclohexane)

**3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)**

Prepared from 3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (102 mg) and 1-fluoro-4-iodobenzene (87 $\mu$L, 1.5 eq) to yield 66 mg (44%) of titular compound as a brown liquid.
1H NMR (500 MHz, CDCl3) δ 8.67 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.00 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.00 – 6.90 (m, 2H), 5.48 (t, J = 7.6 Hz, 1H), 2.14 (dt, J = 13.4, 7.5 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.84 – 1.74 (m, 1H), 1.73 – 1.52 (m, 4H), 1.51 – 1.37 (m, 2H), 1.25 – 1.07 (m, 2H).

13C NMR (126 MHz, CDCl3) δ 201.66, 161.84 (d, J = 244.9 Hz), 153.05, 148.98, 136.93, 135.38 (d, J = 3.2 Hz), 130.56 (d, J = 7.9 Hz), 127.08, 122.81, 115.33 (d, J = 21.2 Hz), 48.94, 39.45, 38.22, 33.13, 32.61, 25.23, 25.21.

19F NMR (471 MHz, CDCl3) δ -117.33.

HRMS (ESI): Calcd for C19H20FNO, [M+H]+: 298.1602, found: 298.1604.

IR (neat): ν (cm⁻¹) 2948, 2865, 1696, 1508, 1224, 995, 635.

Rf: 0.6 (20% EtOAc in cyclohexane)

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2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)

Prepared from 3-phenyl-1-(pyridin-2-yl)propan-1-one (106 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 88 mg (58%) of titular compound as a dark solid.

1H NMR (500 MHz, CDCl3) δ 8.59 (d, J = 4.8 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.22 – 7.05 (m, 5H), 6.90 (t, J = 8.6 Hz, 2H), 5.72 (t, J = 7.6 Hz, 1H), 3.52 (dd, J = 13.9, 7.7 Hz, 1H), 3.11 (dd, J = 13.8, 7.6 Hz, 1H).

13C NMR (126 MHz, CDCl3) δ 200.59, 161.90 (d, J = 245.4 Hz), 152.74, 148.93, 139.71, 136.88, 134.52 (d, J = 3.2 Hz), 130.64 (d, J = 8.0 Hz), 129.21, 128.28, 127.12, 126.17, 122.81, 51.72, 39.14.

19F NMR (471 MHz, CDCl3) δ -116.87.

HRMS (ESI): Calcd for C20H16FNO, [M+H]+: 306.1289, found: 306.1289.

Mp: 90°C

IR (neat): ν (cm⁻¹) 3053, 2918, 1689, 1503, 1353, 1222, 1158, 953, 809, 696.

Rf: 0.5 (20% EtOAc in cyclohexane)
2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)
Prepared from 4-phenyl-1-(pyridin-2-yl)butan-1-one (113 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 120 mg (75%) of titular compound as an orange oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.65 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.99 (ddd, $J = 7.9, 1.1, 1.1$ Hz, 1H), 7.77 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.41 (ddd, $J = 7.5, 4.8, 1.3$ Hz, 1H), 7.39 – 7.35 (m, 2H), 7.29 – 7.20 (m, 2H), 7.22 – 7.13 (m, 3H), 7.04 – 6.91 (m, 2H), 5.42 (t, $J = 7.4$ Hz, 1H), 2.65 – 2.44 (m, 3H), 2.22 – 2.11 (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.17, 161.96 (d, $J = 245.1$ Hz), 152.98, 148.97, 141.92, 137.00, 136.48, 134.85 (d, $J = 3.1$ Hz), 130.67, 128.52 (d, $J = 14.8$ Hz), 127.18, 126.01, 122.88, 115.50 (d, $J = 21.2$ Hz), 49.62, 34.80, 33.95.

$^{19}$F NMR (471 MHz, CDCl$_3$) δ -117.02.

HRMS (ESI): Calcd for C$_{21}$H$_{18}$FNO, [M+H]$^+$: 320.1445, found: 320.1445.

IR (neat): $\nu$ (cm$^{-1}$) 3058, 2928, 1695, 1506, 1339, 1224, 995, 824, 749, 700.

Rf: 0.5 (20% EtOAc in cyclohexane)

4-(4-fluorophenyl)-N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (3w)
Prepared from N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (118 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 120 mg (73%) of titular compound as an dark brown liquid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.64 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 7.99 (ddd, $J = 7.8, 1.1, 1.1$ Hz, 1H), 7.76 (ddd, $J = 7.7, 1.7$ Hz, 1H), 7.44 – 7.33 (m, 3H), 6.99 – 6.85 (m, 2H), 5.47 – 5.40 (m, 1H), 3.55 (s, 3H), 3.14 (s, 3H), 2.50 – 2.33 (m, 3H), 2.27 – 2.16 (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 200.87, 174.07, 161.98 (d, $J = 245.3$ Hz), 152.91, 149.00, 136.96, 134.56 (d, $J = 3.2$ Hz), 130.71 (d, $J = 8.0$ Hz), 127.15, 122.85, 115.50 (d, $J = 21.3$ Hz), 61.25, 49.39, 32.33, 29.86, 27.72.

$^{19}$F NMR (471 MHz, CDCl$_3$) δ -116.89 (s).
HRMS (ESI): Calcd for C₁₈H₁₉FN₂O₃, [M+Na]⁺: 353.1272, found: 353.1272.

IR (neat): ν (cm⁻¹) 2938, 1705, 1659, 1507, 1224, 995.

Rf: 0.11 (50% EtOAc in cyclohexane)

5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-1-(pyridin-2-yl)pentan-1-one (3x)
Prepared from 6-((tert-butyldiphenylsilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (216 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 162 mg (62%) of titular compound as an yellow oil.

₁H NMR (500 MHz, CDCl₃) δ 8.67 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.00 (dt, J = 7.8, 1.1 Hz, 1H), 7.79 (td, J = 7.7, 1.7 Hz, 1H), 7.62 (dt, J = 7.9, 1.3 Hz, 4H), 7.48 – 7.30 (m, 10H), 6.97 – 6.88 (m, 2H), 5.38 (t, J = 7.8 Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H), 2.17 – 2.06 (m, 1H), 1.91 – 1.80 (m, 1H), 1.67 – 1.50 (m, 2H), 1.38 – 1.28 (m, 2H), 1.00 (s, 9H).

₁³C NMR (126 MHz, CDCl₃) δ 201.34, 165.08, 161.91 (d, J = 244.8 Hz), 152.89, 148.79, 137.25, 135.70, 135.01 (d, J = 3.3 Hz), 130.57 (d, J = 7.9 Hz), 129.62, 127.70, 127.19, 122.95, 115.41 (d, J = 21.2 Hz), 63.79, 49.89, 32.88, 26.97, 23.96, 19.33.

₁⁹F NMR (376 MHz, CDCl₃) δ -117.32.

HRMS (ESI): Calcd for C₃₃H₃₆FNO₂Si, [M+H]⁺: 526.2572, found: 526.2582.

IR (neat): ν (cm⁻¹) 2932, 2859, 1696, 1507, 1428, 1225, 1109, 822, 705.

Rf: 0.66 (20% EtOAc in cyclohexane)

tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)
Prepared from tert-butyl (5-oxo-5-(pyridin-2-yl)pentyl)carbamate (139 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 67 mg (36%) of titular compound as an orange oil.

₁H NMR (500 MHz, CDCl₃) δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.98 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.41 – 7.30 (m, 2H), 6.97 –
6.89 (m, 2H), 5.36 (t, J = 7.6 Hz, 1H), 4.71 (bs, 1H), 3.27 – 3.01 (m, 1H), 2.17 – 2.11 (m, 1H), 1.92 – 1.81 (m, 1H), 1.47 – 1.36 (m, 11H).

\[ ^{13}\text{C NMR (126 MHz, CDCl}_3\] \(\delta\) 201.12, 161.94 (d, J = 245.3 Hz), 156.04, 152.81, 148.99, 137.05, 134.64 (d, J = 3.2 Hz), 130.54 (d, J = 8.0 Hz), 127.23, 122.85, 115.47 (d, J = 21.3 Hz), 79.14, 49.40, 40.28, 30.20, 28.53, 27.93, 27.02.

\[ ^{19}\text{F NMR (471 MHz, CDCl}_3\] \(\delta\) -116.93.

HRMS (ESI): Calcd for C_{21}H_{25}FN_2O_3, [M+Na]^+: 395.1741, found: 395.1741.

IR (neat): \(\nu\) (cm\(^{-1}\)) 3364, 2975, 2932, 1692, 1506, 1224, 1162, 995, 817, 732.

Rf: 0.24 (20% EtOAc in cyclohexane)

\[
\text{2-(4-fluorophenyl)-1-(pyrimidin-2-yl)butan-1-one (3z)}
\]

Prepared from 1-(pyrimidin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (73 \(\mu\)L) to yield 61 mg (50%) of titular compound as an orange solid.

\[ ^{1}\text{H NMR (500 MHz, CDCl}_3\] \(\delta\) 8.86 (d, J = 4.9 Hz, 2H), 7.37 (t, J = 4.8 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.98 – 6.89 (m, 1H), 5.08 (d, J = 7.5 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.94 – 1.82 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

\[ ^{13}\text{C NMR (126 MHz, CDCl}_3\] \(\delta\) 199.02, 162.03 (d, J = 245.4 Hz), 160.23, 157.68, 134.15 (d, J = 3.1 Hz), 130.71 (d, J = 8.0 Hz), 122.84, 115.58 (d, J = 21.3 Hz), 53.68, 26.15, 12.20.

\[ ^{19}\text{F NMR (471 MHz, CDCl}_3\] \(\delta\) -116.77 (s).

HRMS (ESI): Calcd for C_{14}H_{13}FN_2O, [M+H]^+: 245.1085 , found: 245.1085.

Mp: 72°C

IR (neat): \(\nu\) (cm\(^{-1}\)) 3046, 2972, 2922, 2877, 1713, 1560, 1505, 1406, 1217, 1009, 835, 775,

Rf: 0.14 (20% EtOAc in cyclohexane)
2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)

Prepared from 1-(pyrazin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (73 μL) to yield 86 mg (70%) of titular compound as a light orange solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.19 (d, $J = 1.5$ Hz, 1H), 8.69 (d, $J = 2.4$ Hz, 1H), 8.61 (dd, $J = 2.5$, 1.5 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.00 – 6.91 (m, 2H), 5.10 (t, $J = 7.6$ Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.82 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 200.81, 162.07 (d, $J = 245.7$ Hz), 147.74, 147.39, 144.65, 143.51, 134.23 (d, $J = 3.1$ Hz), 130.56 (d, $J = 8.1$ Hz), 115.64 (d, $J = 21.3$ Hz), 52.30, 26.05, 12.23.

$^{19}$F NMR (471 MHz, CDCl$_3$) δ -116.63 (s).

HRMS (ESI): Calcd for C$_{14}$H$_{13}$FN$_2$O, [M+H]$^+$: 245.1085, found: 245.1082.

Mp: 96°C

IR (neat): $\nu$ (cm$^{-1}$) 2972, 1690, 1503, 1225, 1007, 818.

Rf: 0.32 (20% EtOAc in cyclohexane)

2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)

Prepared from 1-(quinolin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (116 μL, 2 eq) to yield 115 mg (79%) of titular compound as a brown solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.24 – 8.22 (m, 1H), 8.22 – 8.20 (m, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.86 – 7.81 (m, 1H), 7.78 (ddd, $J = 8.4$, 6.9, 1.4 Hz, 1H), 7.63 (ddd, $J = 8.1$, 6.9, 1.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 6.99 – 6.88 (m, 2H), 5.55 (t, $J = 7.6$ Hz, 1H), 2.30 – 2.18 (m, 1H), 2.01 – 1.89 (m, 1H), 0.95 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.69, 161.84 (d, $J = 244.8$ Hz), 152.52, 147.15, 136.99, 135.29 (d, $J = 3.1$ Hz), 130.61 (d, $J = 7.9$ Hz), 130.03, 129.62, 128.68, 127.70, 118.90, 115.35 (d, $J = 21.2$ Hz), 51.52, 26.14, 12.32.

$^{19}$F NMR (471 MHz, CDCl$_3$) δ -117.38 (s).

HRMS (ESI): Calcd for C$_{19}$H$_{16}$FNO, [M+H]$^+$: 294.1289, found: 294.1289.

Mp: 73°C

IR (neat): $\nu$ (cm$^{-1}$) 2963, 1691, 1599, 1504, 1331, 1220, 993, 809.

Rf: 0.69 (20% EtOAc in cyclohexane)
2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)

Prepared from 1-(thiazol-2-yl)butan-1-one (78 mg) and 1-fluoro-4-iodobenzene (116 μL, 2 eq) to yield 52 mg (42%) of titular compound as a brown oil.

^{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.98 (d, \(J = 3.0\) Hz, 1H), 7.63 (d, \(J = 3.0\) Hz, 1H), 7.43 - 7.34 (m, 2H), 7.02 - 6.93 (m, 2H), 4.94 (t, \(J = 7.6\) Hz, 1H), 2.26 - 2.14 (m, 1H), 1.96 - 1.84 (m, 1H), 0.91 (t, \(J = 7.4\) Hz, 3H).

^{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 193.68, 167.08, 163.11, 161.16, 144.86, 134.17 (d, \(J = 3.2\) Hz), 130.45 (d, \(J = 7.9\) Hz), 126.76, 115.58 (d, \(J = 21.3\) Hz), 53.83, 26.36, 12.21.

^{19}F NMR (471 MHz, CDCl\textsubscript{3}) \(\delta\) -116.62 (s).

HRMS (ESI): Calcd for C\textsubscript{13}H\textsubscript{12}FNOS, [M+H]\textsuperscript{+}: 250.0696, found: 250.0695.

IR (neat): \(\nu\) (cm\textsuperscript{-1}) 2965, 1676, 1507, 1383, 1220, 1088, 959, 815, 757.

Rf: 0.54 (20% EtOAc in cyclohexane)

2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)

Prepared from 1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (112 mg) and 1-fluoro-4-iodobenzene (87 μL, 1.5 eq) to yield 102 mg (76%) of titular compound as a light yellow oil. The compound was recovered as an inseparable 1/1 mixture of diastereomers.

^{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.28 (d, \(J = 3.5\) Hz, 1H), 7.37 - 7.27 (m, 1H), 6.98 - 6.87 (m, 2H), 5.47 (ddd, \(J = 8.9, 7.2, 2.9\) Hz, 1H), 4.73 (td, \(J = 7.6, 3.7\) Hz, 1H), 4.06 - 3.93 (m, 1H), 3.74 - 3.62 (m, 1H), 2.15 (dddd, \(J = 18.1, 16.5, 10.5, 3.1\) Hz, 2H), 2.07 - 1.91 (m, 2H), 1.90 - 1.77 (m, 1H), 1.74 - 1.58 (m, 3H), 0.86 (td, \(J = 7.3, 1.1\) Hz, 3H).

^{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 193.24, 161.98 (d, \(J = 245.2\) Hz), 159.67 (d, \(J = 6.5\) Hz), 143.37 (d, \(J = 29.2\) Hz), 134.33 (dd, \(J = 3.2, 1.9\) Hz), 130.41 (d, \(J = 7.9\) Hz), 115.39 (dd, \(J = 21.3, 1.3\) Hz), 86.72 (d, \(J = 2.4\) Hz), 67.61 (d, \(J = 33.8\) Hz), 54.99 (d, \(J = 5.7\) Hz), 30.56 (d, \(J = 16.5\) Hz), 25.98 (d, \(J = 2.5\) Hz), 24.69, 21.43 (d, \(J = 24.1\) Hz), 12.10 (d, \(J = 2.7\) Hz).
\[^{19}\text{F}\text{ NMR (471 MHz, CDCl}_3\text{)} \delta -116.93 \text{ (d, } J = 5.5 \text{ Hz).}\]

\text{HRMS (ESI): Calcd for } C_{17}H_{20}FN_3O_2, [M+Na]^+: 340.1432, \text{ found: 340.1429.}\n
\text{IR (neat): } \nu (\text{cm}^{-1}) 2964, 2872, 1710, 1508, 1223, 1043, 913, 822, 648.\n
\text{Rf: 0.22 (50\% EtOAc in cyclohexane)}

\[
\text{2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)}
\]

\text{Prepared from 1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (76 mg) and 1-fluoro-4-iodobenzene (116 \mu L, 2 eq) to yield 53 mg (43\%) of titular compound as an orange oil.}

\[^{1}\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.40 – 7.32 \text{ (m, 2H)}, 7.30 \text{ (d, } J = 2.4 \text{ Hz, 1H)}, 7.00 – 6.90 \text{ (m, 2H)}, 6.73 \text{ (d, } J = 2.3 \text{ Hz, 1H)}, 4.74 \text{ (t, } J = 7.6 \text{ Hz, 1H)}, 3.93 \text{ (s, 3H)}, \delta 2.22 – 2.10 \text{ (m, 1H)}, 1.89 – 1.77 \text{ (m, 1H)}, 0.88 \text{ (t, } J = 7.4 \text{ Hz, 3H).}\n
\[^{13}\text{C NMR (126 MHz, CDCl}_3\text{)} \delta 195.92, 161.87 \text{ (d, } J = 244.6 \text{ Hz)}, 150.88, 135.53 \text{ (d, } J = 3.1 \text{ Hz)}, 131.89, 130.23 \text{ (d, } J = 7.9 \text{ Hz)}, 115.24 \text{ (d, } J = 21.2 \text{ Hz)}, 107.65, 53.98, 39.64, 26.42, 12.25.\n
\[^{19}\text{F NMR (471 MHz, CDCl}_3\text{)} \delta -117.53 \text{ (s)}\]

\text{HRMS (ESI): Calcd for } C_{14}H_{15}FN_2O, [M+Na]^+: 269.1061, \text{ found: 269.1064.}\n
\text{IR (neat): } \nu (\text{cm}^{-1}) 2964, 1680, 1508, 1466, 1361, 1212, 1061, 819, 792.\n
\text{Rf: 0.24 (20\% EtOAc in cyclohexane)}
4. Products of β-functionalization

- Optimization studies for β-functionalization

**Table 4.1. Screening for β-functionalization with silver**

| Base (eq) | Additive (eq) | Solvent, C | T, °C | [Pd] | Yield 4a, % |
|-----------|---------------|------------|-------|------|-------------|
| AgOAc (1) | None          | Toluene    | 100   | Pd(OAc)$_2$ | 6           |
| AgOAc (1) | TFA (1.5)     | HFIP       |       |      | 18          |
| Ag$_2$CO$_3$ (1) | | Diox | | | 0 |
| Ag$_2$CO$_3$ (1) | None | Toluene | 100 |  | 4 |
| AgOAc (2) | None | | | | 5 |
| AgOAc (3) | TFA (1.5) | | | | 5 |
| AgTFA (1.5) | TFA (1.5) | DCE | 11 | | |
| AgTFA (1.5) | TFA (1.5) | m-xylene | 19 | | |
| AgTFA (1.5) | TFA (1.5) | mesitylene | 17 | | |
| AgTFA (1.5) | TFA (1.5) | TFT | 17 | | |
| AgTFA (1.5) | TFA (1.5) | toluene | 15 | Pd(TFA)$_2$ | |
| AgTFA (3) | TFA (3) | | | | 23 |
| Ag$_3$PO$_4$ (1) | TFA (3) | m-xylene | 19 | | |
| AgOTf (3) | TFA (3) | | | | 6 |
| AgTFA (3) | TFA (3) | Toluene, 0.1M | 26 | | |
| AgTFA (3) | TFA (3), LiOTf (3) | Toluene | 12 | | |
| AgTFA (3) | TFA (3), LiCl (3) | Toluene, 0.4M | 19 | Pd(OAc)$_2$ | |
| AgTFA (3) | TFA (3) | | | 16 |
| AgTFA (3) | TFA (3), NaCl (3) | Toluene | 18 | | |
| AgTFA (3) | TFA (3), KCl (3) | Toluene | 6 | | |
| AgTFA (3) | TFA (3) | | | | 16 |
| AgOAc (3) | None | Toluene | 140 | | 6 |
| AgTFA (3) | TFA (3) | m-xylene, 0.1M | 100 | | 27 |
| AgTFA (3) | TFA (1.5) | Toluene | 90 | | 15 |

*Performed on 0.2 mmol scale, using 0.2 mmol (1 eq) of 1a and 0.4 mmol (2 eq) of 2a with appropriate base, additives and solvent. Yield was determined by $^1$H NMR with 1,1,2-trichloroethylene as an external standard.*
Table 4.2. Ligand screening for β-functionalization

![Chemical structures](attachment:image)

| Ligand | Yield (%) | Ligand | Yield (%) | Ligand | Yield (%) | Ligand | Yield (%) | Ligand | Yield (%) |
|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|
| HOAc   | 0/21^b    | HOAc   | 0/21^b    | HOAc   | 0/19^b    | HOAc   | 0/15^b    | HOAc   | 0/24^b    |
| Boc    | 8/11^c    | Boc    | 8/10^c    | Boc    | 10/12^c   | Boc    | 10/13^c   | Boc    | 9/15^c    |
| \[(BnO)\_2PO\_2H\] | 0/23^b | \[(BnO)\_2PO\_2H\] | 0/22^b | \[(BnO)\_2PO\_2H\] | 11/8^c | \[(BnO)\_2PO\_2H\] | 8/15^c | \[(BnO)\_2PO\_2H\] | 5/13^c |
| | 0/27^b | 0/19^c | 0/31^b | 0/21^c | 0/40^b | 0/39^c | 0/16^b | 6/20^c | 0/13^b | 9/15^c |
| | | | | | | | | | | |
| | | | | | | | | | |
| IAd    | 3/11^c    | | 2/10^c | - | 10/11^c | - | 3/12^c | - | 3/4^c |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

^a Performed on 0.1 mmol scale, using 0.1 mmol (1 eq) of 1a and 0.2 mmol (2 eq) of 2a with appropriate base, additives and solvent. Yield was determined by ^1^H NMR with 1,1,2-trichloroethylene as an external standard. Yield listed as % yield of 3a/4a. ^b^ 1 eq of KOAc used as base. ^c^ 1.5 eq of K$_2$CO$_3$ used as a base.
### Table 4.3. Oxidant-free base screening

| Entry # | Base                        | Yield 3a/4a, % |
|---------|-----------------------------|----------------|
| 1       | NaOAc                       | 0/10           |
| 2       | Na$_2$CO$_3$                | 0/17           |
| 3       | KOAc                        | 0/40           |
| 4       | K$_2$CO$_3$                 | 0/39           |
| 5       | CsOAc                       | 0/30           |
| 6       | Cs$_2$CO$_3$                | 10/42          |
| 7       | AgOAc                       | 0/9            |
| 8       | Ag$_2$CO$_3$                | 0/5            |
| 9       | Na$_2$HPO$_4$ x 2H$_2$O     | 0/6            |
| 10      | KHCO$_3$                    | 0/15           |
| 11      | K$_2$HPO$_4$                | 0/6            |

*a Performed on 0.1 mmol scale, using 0.1 mmol (1 eq) of 1a and 0.2 mmol (2 eq) of 2a with appropriate base, additives and solvent. Yield was determined by $^1$H NMR with 1,1,2-trichloroethylene as an external standard.
Table 4.4. Additional ligand/base screening

| Entry # | L1  | Base   | X, eq | Solvent        | C, M | Yield 4a, % |
|---------|-----|--------|-------|----------------|------|------------|
| 1       |     |        |       |                |      | 49         |
| 2       | L3  |        | 1     | t-AmOH         |      | 33         |
| 3       |     |        |       | MeOH           | 1.5  | 39         |
| 4       | L4  | K2CO3  | 1.5   | t-AmOH         |      | 49         |
| 5       |     |        |       | EtOH           |      | 15         |
| 6       |     |        |       | TFE            |      | 27         |
| 7       |     |        |       | MTBE           | 1.5  | 28         |
| 8       |     |        |       | CPME           |      | 40         |
| 9       |     |        |       | DME            |      | 31         |
| 10      |     |        | 1.5   | DME            |      | 17         |
| 11      |     |        |       | THF            | 2.0  | 17         |
| 12      |     |        |       | 2-MeTHF        | 1    | 34         |
| 13      |     |        |       | toluene        | 1.5  | 35         |
| 14      |     |        |       | TFT            | 0.2  | 29         |
| 15      |     |        |       | DCE            | 0.2  | 19         |
| 16      |     |        |       | mesitylene     | 0.2  | 31         |
| 17      |     |        |       | m-xylene       | 0.2  | 13         |
| 18      |     |        |       | o-xylene       | 0.2  | 25         |
| 19      |     |        |       | dioxane        | 0.2  | 26         |
| 20      |     |        |       | t-AmOH         | 0.2  | 18         |
| 21      |     |        |       | Rb2CO3         | 0.2  | 40         |
| 22      |     |        |       | RbOAc          | 0.2  | 39         |
| 23      |     |        |       | Cs2CO3         | 0.2  | 38         |
| 24      |     |        |       | K2CO3          | 0.2  | 42         |
| 25      |     |        |       | KOAc           | 0.2  | 25         |
| 26      |     |        |       | RbCO3          | 0.2  | 37         |
| 27      |     |        |       | NaAc           | 0.2  | 28         |
| 28      |     |        |       | K2CO3          | 0.2  | 20         |
| 29      |     |        |       | KOAc           | 0.2  | 32         |
| 30      |     |        |       | Rb2CO3         | 0.2  | 46         |
|         |     |        |       | KOAc           | 0.2  | 50 (50)    |

*Performed on 0.2 mmol scale, using 0.2 mmol (1 eq) of 1a and 0.4 mmol (2 eq) of 2a with appropriate base, additives and solvent. Yield was determined by 1H NMR with 1,1,2-trichloroethylene as an external standard. Isolated yield stated in parenthesis. Reaction performed on 0.5 mmol scale.
To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar rubidium carbonate (116 mg, 0.5 mmol, 1 eq) and 3-cyanopyridin-2-one (12 mg, 0.1 mmol, 20% mol) were charged. Tube was then introduced to the glovebox, where palladium acetate (11.2 mg, 0.05 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 μL, 0.5 mmol), 1-fluoro-4-iodobenzene (116 μL, 1 mmol, 2 eq) and tert-amyl alcohol (2.5 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 100°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-15% EtOAc in cyclohexane) to yield 60 mg (50%) of 3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one as a yellow liquid.

**3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)**

Prepared as stated above. Compound was also prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 1-fluoro-4-bromobenzene (110 μL, 2 eq) to yield titular compound in 25% yield. Compound consistency and analytical data match in both cases.

$^{1}$H NMR (500 MHz, CDCl₃) $\delta$ 8.59 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.91 (ddd, $J = 7.8, 1.1, 1.1$ Hz, 1H), 7.73 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1H), 7.38 (ddd, $J = 7.6, 4.8, 1.3$ Hz, 1H), 7.21 – 7.13 (m, 2H), 6.93 – 6.82 (m, 2H), 3.54 – 3.33 (m, 3H), 1.25 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 200.62, 161.41 (d, $J = 243.5$ Hz), 153.57, 149.00, 142.48 (d, $J = 3.2$ Hz), 137.03, 128.49 (d, $J = 7.7$ Hz), 127.24, 121.97, 115.20 (d, $J = 21.1$ Hz), 45.98, 34.84, 22.58.
$^{19}$F NMR (471 MHz, CDCl$_3$) δ -118.43 (s).

HRMS (ESI): Calcd for C$_{15}$H$_{14}$FNO, [M+Na]$^+$: 266.0952, found: 266.0953.

IR (neat): ν (cm$^{-1}$) 2964, 1696, 1510, 1360, 1221, 995, 834, 771.

Rf: 0.5 (20% EtOAc in cyclohexane)

According to this procedure, following compounds were synthesized:

![Chemical Structure](image)

### 3-phenyl-1-(pyridin-2-yl)butan-1-one (4b)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and iodobenzene (111 μL, 2 eq) to yield 46 mg (41%) of titular compound as a dark yellow liquid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.58 (ddd, $J$ = 4.7, 1.7, 0.9 Hz, 1H), 7.91 (ddd, $J$ = 7.8, 1.1, 1.1 Hz, 1H), 7.71 (ddd, $J$ = 7.7, 7.7, 1.7 Hz, 1H), 7.35 (ddd, $J$ = 7.5, 4.7, 1.3 Hz, 1H), 7.24 – 7.16 (m, 4H), 7.11 – 7.06 (m, 1H), 3.56 – 3.37 (m, 3H), 1.26 (d, $J$ = 6.7 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 200.77, 153.67, 148.98, 146.88, 136.84, 128.51, 127.15, 127.11, 126.21, 121.94, 45.89, 35.46, 22.40.

HRMS (ESI): Calcd for C$_{15}$H$_{15}$NO, [M+H]$^+$: 226.1226, found: 226.1225.

IR (neat): ν (cm$^{-1}$) 2961, 1694, 1582, 1493, 1394, 1352, 1297, 1221, 1146, 995, 907, 762.

Rf: 0.46 (20% EtOAc in cyclohexane)

![Chemical Structure](image)

### 3-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (4c)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodoanisole (119 μL, 2 eq) to yield 42 mg (33%) of titular compound as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.67 (ddd, $J$ = 4.7, 1.7, 0.9 Hz, 1H), 7.99 (ddd, $J$ = 7.8, 1.1, 1.1 Hz, 1H), 7.80 (ddd, $J$ = 7.7, 7.7, 1.7 Hz, 1H), 7.44 (ddd, $J$ = 7.5, 4.7, 1.2 Hz, 1H), 7.20 (t, $J$ = 7.9 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.87 – 6.82 (m, 1H), 6.71 (ddd, $J$ = 8.2, 2.6, 0.9 Hz, 1H), 3.78 (s, 3H), 3.65 – 3.42 (m, 3H), 3.33 (d, $J$ = 6.8 Hz, 3H).
13C NMR (126 MHz, CDCl3) δ 200.74, 159.75, 153.66, 148.98, 148.62, 136.98, 129.47, 127.16, 121.96, 119.52, 113.01, 111.41, 55.25, 45.80, 35.53, 22.35.

HRMS (ESI): Calcd for C_{16}H_{17}NO_{2}, [M+Na]^+: 278.1151, found: 278.1151.

IR (neat): ν (cm⁻¹) 2961, 1697, 1600, 1260, 1045, 995, 773, 701.

Rf: 0.41 (20% EtOAc in cyclohexane)

1-(pyridin-2-yl)-3-(m-tolyl)butan-1-one (4d)
Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and 3-iodotoluene (128 μL, 2 eq) to yield 46 mg (38%) of titular compound as a dark yellow liquid.

1H NMR (500 MHz, CDCl3) δ 8.68 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.00 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.81 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.45 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.13 – 7.06 (m, 2H), 7.03 – 6.95 (m, 1H), 3.62 – 3.43 (m, 3H), 2.32 (s, 3H), 1.32 (d, J = 6.5 Hz, 3H).

13C NMR (126 MHz, CDCl3) δ 200.76, 153.62, 148.90, 146.86, 138.03, 137.12, 128.43, 127.94, 127.19, 127.01, 124.11, 122.05, 45.93, 35.42, 22.46, 21.62.

HRMS (ESI): Calcd for C_{16}H_{17}NO, [M+H]^+: 240.1383, found: 240.1383.

IR (neat): ν (cm⁻¹) 2963, 1697, 1583, 1358, 1308, 1218, 995, 772, 706.

Rf: 0.5 (20% EtOAc in cyclohexane)

methyl 3-(4-oxo-4-(pyridin-2-yl)butan-2-yl)benzoate (4e)
Prepared from 1-(pyridin-2-yl)butan-1-one (74 μL) and methyl 3-iodobenzoate (262 mg, 2 eq) to yield 37 mg (26%) of titular compound as an yellow liquid.

1H NMR (500 MHz, CDCl3) δ 8.65 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.84 (ddd, J = 7.7, 1.7, 1.2 Hz, 1H), 7.79 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.43 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 3.89 (s, 3H), 3.65 – 3.45 (m, 3H), 1.35 (d, J = 7.0 Hz, 3H).

13C NMR (126 MHz, CDCl3) δ 200.42, 167.33, 153.49, 148.99, 147.22, 136.99, 131.99, 130.36, 128.55, 128.20, 127.56, 127.23, 121.92, 52.13, 45.69, 35.34, 22.31.

HRMS (ESI): Calcd for C_{17}H_{17}NO_{3}, [M+Na]^+: 306.1101, found: 306.1100.

IR (neat): ν (cm⁻¹) 2957, 1720, 1584, 1435, 1286, 1204, 995, 755.

Rf: 0.32 (20% EtOAc in cyclohexane)
5. Products of post-functionalization

- Synthesis of 6-ethylbenzo[f]quinolin-5-ol 5a

![Chemical structure of 5a](image)

To an oven-dried microwave vial (30 mL) equipped with PTFE-coated magnetic stirbar 2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (130 mg, 0.5 mmol, synthesized via Representative procedure B) and potassium carbonate (138 mg, 1 mmol, 2 eq) were charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 11.2 mg, 0.05 mmol), tricyclohexylphosphine (28 mg, 0.1 mmol), and pivalic acid (10.2 mg, 0.1 mmol) were charged. Reaction was then sealed with a septum and reintroduced into a separate glovebox, where DMF (5 mL) was added. Septum was then replaced with a crimp cap and removed from the glovebox. Reaction mixture was then stirred in a heating block at 140 °C for 14 hours, after which it was cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 90 mg (85%) of 6-ethylbenzo[f]quinolin-5-ol as a deep red oil.

**6-ethylbenzo[f]quinolin-5-ol (5a)**

Prepared as stated above.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.70 (ddd, \(J = 4.8, 1.8, 1.0\) Hz, 1H), 7.89 (ddd, \(J = 8.0, 1.1, 1.1\) Hz, 1H), 7.76 (ddd, \(J = 8.0, 7.5, 1.8\) Hz, 1H), 7.64 (ddd, \(J = 7.7, 1.3, 0.7\) Hz, 1H), 7.52 (ddd, \(J = 8.2, 0.9, 0.9\) Hz, 1H), 7.33 (ddd, \(J = 8.3, 7.2, 1.3\) Hz, 1H), 7.30 – 7.23 (m, 1H), 7.19 (ddd, \(J = 7.5, 4.8, 1.2\) Hz, 1H), 3.29 (q, \(J = 7.5\) Hz, 2H), 1.35 (t, \(J = 7.5\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 154.23, 151.34, 149.74, 148.69, 136.46, 130.40, 125.24, 122.61, 122.28, 122.02, 120.97, 120.28, 111.44, 17.61, 14.34.

HRMS (ESI): Calcd for C\(_{15}\)H\(_{13}\)NO, [M+H]\(^+\): 224.1070, found: 224.1074

IR (neat): \(\nu\) (cm\(^{-1}\)) 3059, 2928, 1604, 1455, 1347, 1249, 1128, 743.

Rf: 0.75 (20% EtOAc in cyclohexane)
6. Products of control experiments

- Synthesis of 2-(4-fluorophenyl)-1-phenylbutan-1-one 3af

To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar sodium tert-butoxide (96 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-phenylbutan-1-one (75 μL, 0.5 mmol), 1-fluoro-4-iodobenzene (73 μL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2×2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 91 mg (75%) of 2-(4-fluorophenyl)-1-phenylbutan-1-one as an orange oil.

2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)

Prepared as stated above. This compound is described.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 – 7.92 (m, 2H), 7.53 – 7.46 (m, 1H), 7.44 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.04 – 6.92 (m, 2H), 4.44 (t, $J$ = 7.3 Hz, 1H), 2.24 – 2.12 (m, 1H), 1.90 – 1.77 (m, 1H), 0.90 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 200.20, 162.01 (d, $J$ = 245.5 Hz), 137.02, 135.42 (d, $J$ = 3.2 Hz), 133.06, 129.90 (d, $J$ = 7.9 Hz), 128.73, 128.70, 115.84 (d, $J$ = 21.3 Hz), 54.62, 27.34, 12.35.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -116.79 (s).
To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar rubidium carbonate (116 mg, 0.5 mmol, 1 eq) and 3-cyanopyridin-2-one (12 mg, 0.1 mmol, 20% mol) was charged. Tube was then introduced to the glovebox, where palladium acetate (11.2 mg, 0.05 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 μL, 0.5 mmol), 1-phenylbut-2-en-1-one (73 mg, 0.5 mmol), 1-fluoro-4-iodobenzene (116 μL, 1 mmol, 2 eq) and tert-amyl alcohol (2.5 mL) are added via syringe. Septum was then replaced in a flow of argon with a screw cap and reaction mixture was then stirred in a heating block at 100°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then diluted with CDCl₃ and 1,1,2-trichloroethylene is added, after which the mixture is analyzed via ¹H NMR.
To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar cesium carbonate (when used, 326 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) and sodium tert-butoxide (when used, 96 mg, 1 mmol, 2 eq) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 μL, 0.5 mmol), butyrophenone (75 μL, 0.5 mmol, 1 eq) 1-fluoro-4-iodobenzene (73 μL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then diluted with CDCl₃ and 1,1,2-trichloroethylene is added, after which the mixture is analyzed via ¹H NMR to determine the ratio of products 3a and 3af.
7. NMR spectra – starting materials

1-(pyridin-2-yl)butan-1-one (1a)
1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (1d)
1-(1-methyl-1H-pyrazol-5-yl)butan-1-one (1e)
2-methyl-1-(pyridin-2-yl)propan-1-one (1f)
1-(pyridin-2-yl)propan-1-one (1i)
1-(pyridin-2-yl)heptan-1-one (1j)
1-(pyrimidin-2-yl)butan-1-one (1k)
1-(pyrazin-2-yl)butan-1-one (1)
3-phenyl-1-(pyridin-2-yl)propan-1-one (1m)
1-(quinolin-2-yl)butan-1-one (1n)
4-phenyl-1-(pyridin-2-yl)butan-1-one (1o)
N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (1p)
6-((tert-butyldiphenylysilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (1q)
1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (1r)
1-(thiazol-2-yl)butan-1-one (1s)
3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (1t)
N,N-dibenzyl-4-iodoaniline (2b)
1-benzyl-5-iodo-1H-indole (2c)

$\text{I} \quad \text{Bn}$

$\text{I} \quad \text{Bn}$
6. NMR spectra – products of α-functionalization

2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)
2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)
1-(pyridin-2-yl)-2-(p-tolyl)butan-1-one (3b)
1-(pyridin-2-yl)-2-(m-tolyl)butan-1-one (3c)
2-(4-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3d)
2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)
2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)
2-(4-(dibenzylamino)phenyl)-1-(pyridin-2-yl)butan-1-one (3f)
2-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (3g)
2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)butan-1-one (3h)
methyl 3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzoate (3i)
3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzaldehyde (3j)

![Chemical structure of 3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzaldehyde (3j)]

- **Formula:** C_{28}H_{24}N_{2}O_{3}
- **Properties:**
  - Molecular weight: 428.5 g/mol
  - Density: 1.32 g/cm³

**NMR Spectral Data:**
- **Chemical Shifts:** 3.17, 1.07, 1.05, 1.00, 2.05, 2.06, 1.05, 0.99, 0.93, 0.97, 0.96
- **Resonance Peaks:**
  - 7.26 (CDCl₃), 7.39 (CDCl₃), 7.40 (CDCl₃), 7.41 (CDCl₃), 7.42 (CDCl₃), 7.43 (CDCl₃), 7.47 (CDCl₃), 7.67 (CDCl₃), 7.68 (CDCl₃), 7.69 (CDCl₃), 7.70 (CDCl₃), 7.75 (CDCl₃), 7.76 (CDCl₃), 7.78 (CDCl₃), 7.91 (CDCl₃), 7.92 (CDCl₃), 8.00 (CDCl₃), 8.01 (CDCl₃), 8.02 (CDCl₃), 8.65 (CDCl₃), 8.66 (CDCl₃), 8.66 (CDCl₃), 8.67 (CDCl₃), 9.96 (CDCl₃)
- **Chemical Bonds:**
  - Carbon-to-carbon double bond at 12.29 (CDCl₃), 26.30 (CDCl₃), 52.10 (CDCl₃)
  - Carbon-to-hydrogen bond at 122.78 (CDCl₃), 127.27 (CDCl₃), 128.05 (CDCl₃), 129.21 (CDCl₃), 130.70 (CDCl₃), 135.23 (CDCl₃), 136.75 (CDCl₃), 137.02 (CDCl₃), 140.68 (CDCl₃), 149.02 (CDCl₃), 152.84 (CDCl₃)
  - Nitrogen-to-carbon bond at 192.44 (CDCl₃), 201.15 (CDCl₃), 76.58 (CDCl₃)
2-(4-acetylphenyl)-1-(pyridin-2-yl)butan-1-one (3k)
3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzonitrile (3l)
1-(pyridin-2-yl)-2-(o-tolyl)butan-1-one (3m)
2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3n)
2-(1-benzyl-1H-indol-5-yl)-1-(pyridin-2-yl)butan-1-one (3o)
2-phenyl-1-(pyridin-2-yl)butan-1-one (3p)
2-(naphthalen-2-yl)-1-(pyridin-2-yl)butan-1-one (3q)
2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)
2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)
2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)
2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{F} & \\
\end{align*}
\]
3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)
3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)
2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)
2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)
2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)
2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)
4-(4-fluorophenyl)-N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (3w)
5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-1-(pyridin-2-yl)pentan-1-one (3x)
tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)
tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)
2-(4-fluorophenyl)-1-(pyrimidin-2-yl)butan-1-one (3z)
2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)
2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)
2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)
2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)
2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)
2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)
2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)
2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)
2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)
2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)
7. NMR spectra – products of β-functionalization

3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)
3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)
3-phenyl-1-(pyridin-2-yl)butan-1-one (4b)
3-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (4c)
1-(pyridin-2-yl)-3-(m-tolyl)butan-1-one (4d)
methyl 3-(4-oxo-4-(pyridin-2-yl)butan-2-yl)benzoate (4e)
8. NMR spectra – post-functionalization products

6-ethylbenzo[f]quinolin-5-ol (5a)
9. NMR spectra – products of control experiments

2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)
2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)