Uniting Amide Synthesis and Activation by P^{III}/P^{V}-Catalyzed Serial Condensation: Three-Component Assembly of 2-Amidopyridines

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I. General Materials and Methods

All reagents were purchased from commercial vendors (Sigma-Aldrich, Alfa Aesar, Acros, TCI, Oakwood Chemical, Combi-Blocks) and used without further purification unless otherwise indicated. Indicated substrates were synthesized according to literature procedure. *N*,*N*-Diisopropylethylamine (Sigma Aldrich, purified by redistillation, 99.5%, Sure/Seal™), 2,6-lutidine (Sigma Aldrich, purified by redistillation, >99%, Sure/Seal™), and acetonitrile (Sigma Aldrich, anhydrous, 99.8%, Sure/Seal™) were used as is, under N_2 atmosphere. All other solvents were ACS grade or better and were used without further purification unless otherwise noted. Diethyl 2-bromo-2-methylmalonate (Sigma Aldrich, 98%) was stored under ambient atmosphere. Diphenylsilane (Oakwood, 97%) was stored under N_2 atmosphere. All liquids were handled with gastight syringe. Reactions conducted in 4 mL vials used white polypropylene vial caps with PTFE faced foamed polyethylene liner from Wheaton (Item# W238520-1325, "white cap") or Black open-top screw cap, 13-425, phenolic, with red PTFE/white silicone septum from VWR (Item# 66065-242, "black septum cap"). Column chromatography was carried out on silica gel (SiliFlash® Irregular Silica Gel, P60 40-63μm). Preparatory TLC was carried out using SiliaPlate Preparative TLC Plates, Glass-Backed, Silica, 1000 μm, 20x20 cm, F254 (TLG-R10011B-341). ^{1}H, ^{13}C, and ^{31}P NMR were collected with Bruker Neo 600 (QCI-F helium cryoprobe), Bruker Neo 500 (BBO Prodigy nitrogen cryoprobe or BBFO SmartProbe), or Bruker AVANCE III HD 400 (BBO Prodigy nitrogen cryoprobe) spectrometers and processed using MestReNova software. ^{1}H NMR chemical shifts are given in ppm with respect to solvent residual peak ($CDCl_3$, δ 7.26 ppm, acetone-d_6, δ 2.05 ppm). $^{13}C\{^{1}H\}$ NMR shifts are given in ppm with respect to solvent peak ($CDCl_3$ δ 77.16 ppm, acetone-d_6, δ 29.84 ppm). ^{31}P NMR shifts are given in ppm with respect to 85% H_3PO_4 (δ 0.0 ppm) as an external standard. Multiplicities are described as s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. Coupling constants are reported in Hertz (Hz). High-resolution mass spectra were obtained at the Mass Spectrometry Laboratory in the Department of Chemistry Instrumentation Facility, MIT, using Agilent QTOF 6545 with ESI ionization source.

II. Optimization of Reaction Conditions

A. Optimization with Propylamine (3)

Optimization-scale reactions were conducted at 0.125 mmol of limiting substrate. To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 98%, TCI) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**•[O]). The vial was capped with a black septum cap, and the septum was punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Solvent (MeCN or 1,2-DCE, 0.5–3.0 M) was added under N_2, followed by propylamine (**3**, 98%, Acros) and acetic acid (**2**, glacial, 99.5%, Fisher). To this mixture, base (EtN^iPr_2 or 2,6-lutidine, 0–2.0 equiv.), halenium source (DEMBM or DEBM, 0–2.2 equiv.), and silane (Ph_2SiH_2 or $PhSiH_3$, 0–3.0 equiv.) were added. The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After 16 h, the reaction was cooled to ambient temperature with stirring at 300 rpm. Then, approximately 50 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added to quench the reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 1,3,5-trimethoxybenzene (85.0 mg, 98%, 0.500 mmol) in MeCN in a 1 mL volumetric flask – was added. The reaction was diluted to homogeneity with ~ 1 mL $CDCl_3$. An aliquot was transferred to an NMR tube, diluted to total volume ~0.6 mL, and analyzed by ^{1}H NMR spectroscopy. The yield was determined by relative integration between 1,3,5-trimethoxybenzene (δ = 6.04 ppm, s, 2 H, 0.2 equiv., integrate to 60), and product **5** (δ = 8.52 ppm, d, 1H). Number of scans = 8 and relaxation delay = 4 seconds.

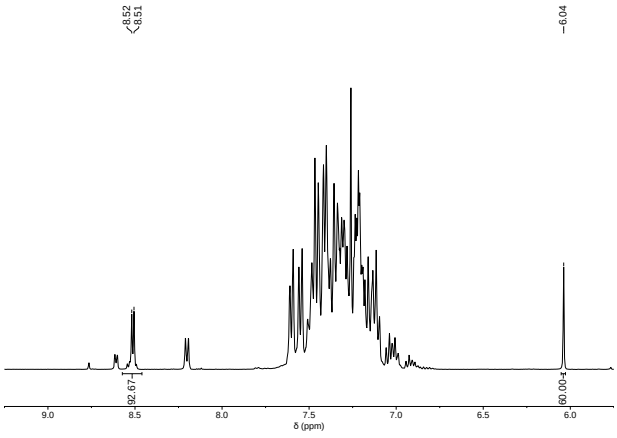
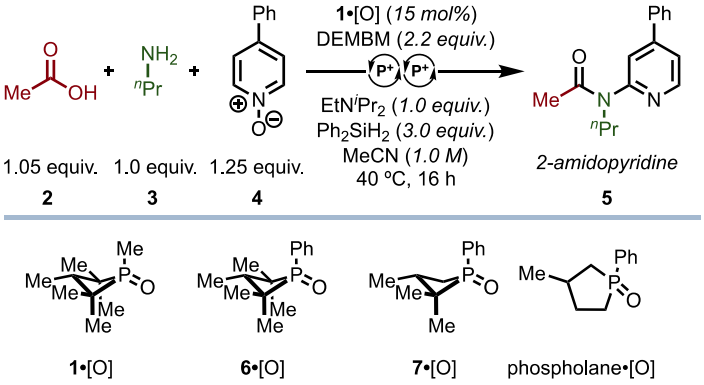


Figure S1. Representative ^{1}H NMR spectrum for yield determination for optimization of dehydrative coupling of **2**, **3**, and **4** by **1**•[O] (optimal conditions, 93% **5**).



Entry	deviation from standard	Yield of **5** (%)[a]
1	none	93
2	10% **1**·[O]	89
3	5% **1**·[O]	63
4	0% **1**·[O]	0
5	2.0 equiv EtN^{i}Pr$_2$	71
6	0 equiv EtN^{i}Pr$_2$	78
7	2,6-lutidine in place of EtN^{i}Pr$_2$	88
8	**6**·[O] in place of **1**·[O]	85
9	**7**·[O] or phospholane·[O] in place of **1**·[O]	0
10	MeCN (3.0 M)	93
11	MeCN (0.5 M)	93
12	1,2-DCE in place of MeCN	90
13	1.05 equiv **2**	88
14	2.0 equiv DEMBM, 2.5 equiv Ph$_2$SiH$_2$	81
15	DEBM in place of DEMBM	43
16	1.5 equiv PhSiH$_3$ in place of Ph$_2$SiH$_2$	73
17	No DEMBM	0
18	No Ph$_2$SiH$_2$	0

Table S1. Expanded table of optimized conditions and variations for coupling of **2**, **3**, and **4** by **1**•[O]. [a]Yield determined by ^{1}H NMR against internal standard on 0.125 mmol scale reaction. DEMBM = diethyl(methyl)bromomalonate, 1,2-DCE = 1,2-dichloroethane. DEBM = diethylbromomalonate.

B. Optimization with 4-Fluoroaniline (9)

Optimization-scale reactions were conducted at 0.125 mmol of limiting substrate. To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 98%, TCI) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**·[**O**]). The vial was capped with a black septum cap, and the septum was punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.125 mL, 1.0 M) was added under N_2, followed by 4-fluoroaniline (**9**, 12.0 μL, 99%, 125 μmol, 1.00 equiv.) and acetic acid (**2**, 7.5 μL, 99.5%, 131 μmol, 1.05 equiv.). To this mixture, base (EtN^iPr_2 or 2,6-lutidine, 0 or 1.0 equiv.), DEMBM (98%, 0 or 2.2 equiv.), and Ph_2SiH_2 (97%, 0 or 3.0 equiv.) were added. The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After 16 h, the reaction was cooled to ambient temperature with stirring at 300 rpm. Then, approximately 50 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added to quench the reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 4,4′-difluorobenzophenone (110.2 mg, 0.5 mmol, 98%) in MeCN in a 1 mL volumetric flask – was added. The reaction was diluted to homogeneity with ~ 1 mL $CHCl_3$, and an aliquot was transferred to an NMR tube, diluted to total volume ~0.6 mL with $CDCl_3$, and analyzed by ^{19}F NMR spectroscopy. The yield was determined by relative integration between 4,4′-difluorobenzophenone (δ = -105.76 ppm, 2 F, 0.2 equiv., integrate to 40), aniline **9** (δ = -127.3 ppm, 1 F), amide **11** (also prepared according to literature procedure)[1] (δ = -118.8 ppm, 1 F), and product **10** (δ = -113.9, brs, 1F). Number of scans = 8 and relaxation delay = 8 seconds.

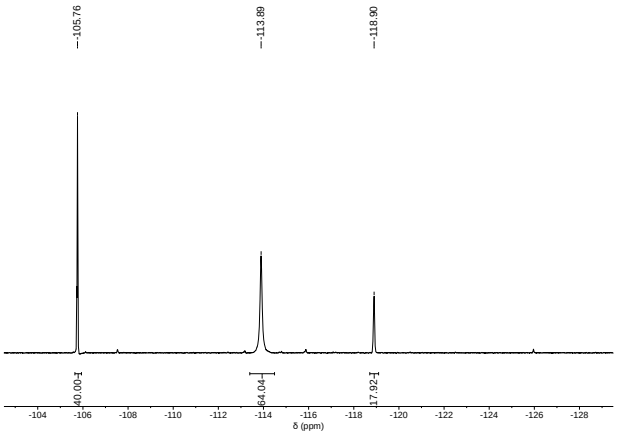
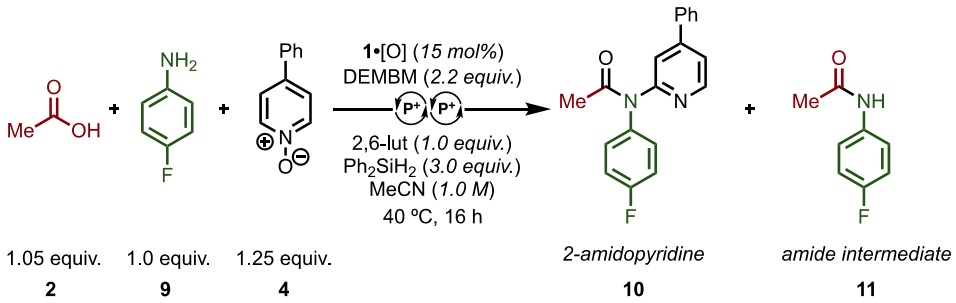


Figure S2. Representative ^{19}F NMR spectrum for yield determination for optimization of coupling of **2**, **9**, and **4** by **1**·[**O**] (sup-optimal conditions showing 64% **10** and 18% **11**).



1.05 equiv. **2** | 1.0 equiv. **9** | 1.25 equiv. **4** | *2-amidopyridine* **10** | *amide intermediate* **11**

Entry	deviation from standard	Yield of **10** (%)[a]	Yield of **11** (%)[a]
1	none	84	8
2	0 equiv DEMBM	0	10
3	0 equiv Ph_2SiH_2	0	0
4	0% **1**·[O]	0	7
5	EtN^iPr_2 in place of 2,6-lutidine	72	12
6	0 equiv 2,6-lutidine	7	5

Table S2. Table of optimized conditions and variations for coupling of **2**, **9**, and **4** by **1**•[O]. [a]Yield determined by ^{19}F NMR against internal standard on 0.125 mmol scale reaction.

III. Synthetic Examples

A. General Procedures

General Procedure for Acid Scope (GP1)

To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (109.2 mg, 98%, 0.625 mmol, 1.25 equiv.), 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (13.1 mg, 75.0 μmol, 0.150 equiv.), and acid if solid (0.525 mmol, 1.05 equiv.). The vial was capped with a black septum cap. The septum was punctured with a needle under N_2 atmosphere. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.500 mL, 1.0 M) was added, followed by propylamine (42.0 μL, 98%, 0.500 mmol, 1.00 equiv.) and acid if liquid (0.525 mmol, 1.05 equiv.). Next, *N*,*N*-diisopropylethylamine (87.5 μL, 99.5%, 0.500 mmol, 1.00 equiv.) was added, unless otherwise indicated, followed by diethyl 2-bromo-2-methylmalonate (215 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (287 μL, 97%, 1.50 mmol, 3.00 equiv.). The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm for 16 h. After that time, the reaction vessel was removed from the heating block and cooled to ambient temperature with stirring at 300 rpm. Then, approximately 200 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added. The reaction was transferred to a 40 mL vial with washing with EtOAc. The crude reaction was concentrated, dissolved in acetone, and adsorbed onto silica gel under vacuum. The crude residue was then purified by flash column chromatography on silica gel (dry loading) by eluting with the indicated solvent and further purified if needed by flash column chromatography or preparatory TLC with the indicated solvent.

General Procedure for Alkyl Amine Scope (GP2)

To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (109.2 mg, 98%, 0.625 mmol, 1.25 equiv.), 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (13.1 mg, 0.075 mmol, 0.150 equiv.), and amine if solid (0.500 mmol, 1.00 equiv.). The vial was capped with a black septum cap. The septum was punctured with a needle under N_2 atmosphere. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.500 mL, 1.0 M) was added, followed by amine if liquid (0.500 mmol, 1.00 equiv.) and acetic acid (30.2 μL, 99.5%, 0.525 mmol, 1.05 equiv.). Next, *N*,*N*-diisopropylethylamine (87.5 μL, 99.5%, 0.500 mmol, 1.00 equiv.) was added, unless otherwise indicated, followed by diethyl 2-bromo-2-methylmalonate (215 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (287 μL, 97%, 1.50 mmol, 3.00 equiv.). The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm for 16 h. After that time, the reaction vessel was removed from the heating block and cooled to ambient temperature with stirring at 300 rpm. Then, approximately 200 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added. The reaction was transferred to a 40 mL vial with washing with EtOAc. The crude reaction was concentrated, dissolved in acetone, and adsorbed onto silica gel under vacuum. The crude residue was then purified by flash column chromatography on silica gel (dry loading) by eluting with the indicated solvent and further purified if needed by flash column chromatography or preparatory TLC with the indicated solvent.

General Procedure for Aryl Amine Scope (GP3)

To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (109.2 mg, 98%, 0.625 mmol, 1.25 equiv.), 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (13.1 mg, 0.075 mmol, 0.150 equiv.), and amine if solid (0.500 mmol, 1.00 equiv.). The vial was capped with a black septum cap. The septum was punctured with a needle under N_2 atmosphere. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.500 mL, 1.0 M) was added, followed by amine if liquid (0.50 mmol, 1.00 equiv.) and acetic acid (30.2 μL, 99.5%, 0.525 mmol, 1.05 equiv.). Next, 2,6-lutidine (58.8 μL, 99%, 0.500 mmol, 1.00 equiv.) was added, unless otherwise indicated, followed by diethyl 2-bromo-2-methylmalonate (215 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (287 μL, 97%, 1.50 mmol, 3.00 equiv.). The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block, unless otherwise indicated, and stirred at 300 rpm for 16 h. After that time, the reaction vessel was removed from the heating block and cooled to ambient temperature with stirring at 300 rpm. Then, approximately 200 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added. The reaction was transferred to a 40 mL vial with washing with EtOAc. The crude reaction was concentrated, dissolved in acetone, and adsorbed onto silica gel under vacuum. The crude residue was then purified by flash column chromatography on silica gel (dry loading) by eluting with the indicated solvent and further purified if needed by flash column chromatography or preparatory TLC with the indicated solvent.

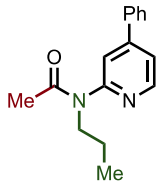
General Procedure for Aryl Amine + Benzoic Acid Scope (GP4)

To a 4 mL vial with magnetic stir bar was added 4-phenylpyridine N-oxide (109.2 mg, 98%, 0.625 mmol, 1.25 equiv.), 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (13.1 mg, 0.075 mmol, 0.150 equiv.), amine if solid (0.500 mmol, 1.00 equiv.), and acid (0.525 mmol, 1.05 equiv.). The vial was capped with a black septum cap. The septum was punctured with a needle under N_2 atmosphere. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.500 mL, 1.0 M) was added, followed by amine if liquid (0.500 mmol, 1.00 equiv.). Next, 2,6-lutidine (58.8 μL, 99%, 0.500 mmol, 1.00 equiv.) was added, unless otherwise indicated, followed by diethyl 2-bromo-2-methylmalonate (215 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (287 μL, 97%, 1.50 mmol, 3.00 equiv.). The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (80 °C) aluminum heating block and stirred at 300 rpm for 16 h. After that time, the reaction vessel was removed from the heating block and cooled to ambient temperature with stirring at 300 rpm. Then, approximately 200 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added. The reaction was transferred to a 40 mL vial with washing with EtOAc. The crude reaction was concentrated, dissolved in acetone, and adsorbed onto silica gel under vacuum. The crude residue was then purified by flash column chromatography on silica gel (dry loading) by eluting with the indicated solvent and further purified if needed by flash column chromatography or preparatory TLC with the indicated solvent.

General Procedure for Pyridine N-Oxide Scope (GP5)

To a 4 mL vial with magnetic stir bar was added the indicated pyridine N-oxide (0.625 mmol, 1.25 equiv.) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (13.1 mg, 75.0 μmol, 0.150 equiv.). The vial was capped with a black septum cap. The septum was punctured with a needle under N_2 atmosphere. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (0.500 mL, 1.0 M) was added, followed by propylamine (42.0 μL, 98%, 0.500 mmol, 1.00 equiv.) and acetic acid (30.2 μL, 99.5%, 0.525 mmol, 1.05 equiv.). Next, *N*,*N*-diisopropylethylamine (87.5 μL, 99.5%, 0.500 mmol, 1.00 equiv.) was added, followed by diethyl 2-bromo-2-methylmalonate (215 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (287 μL, 97%, 1.50 mmol, 3.00 equiv.). The black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm for 16 h, unless otherwise indicated. After that time, the reaction vessel was removed from the heating block and cooled to ambient temperature with stirring at 300 rpm. Then, approximately 200 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added. The reaction was transferred to a 40 mL vial with washing with EtOAc. The crude reaction was concentrated, dissolved in acetone, and adsorbed onto silica gel under vacuum. The crude residue was then purified by flash column chromatography on silica gel (dry loading) by eluting with the indicated solvent and further purified if needed by flash column chromatography or preparatory TLC with the indicated solvent.

B. Analytical Data



***N*-(4-Phenylpyridin-2-yl)-*N*-propylacetamide** (**5**).

Prepared according to **GP1** using acetic acid (30.2 μL, 99.5%).

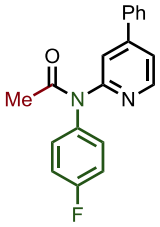
Purification: Column eluted with 50% EtOAc/hexanes. Impure fractions further purified by second column eluted with 50% EtOAc/hexanes.

Yield: 86% (109.5 mg). Light orange oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.2 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.53 – 7.49 (m, 2H), 7.49 – 7.41 (m, 3H), 3.89 – 3.78 (m, 2H), 2.05 (s, 3H), 1.60 (h, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.31, 156.58, 151.15, 149.74, 137.48, 129.66, 129.39, 127.17, 120.35, 119.71, 49.77, 23.33, 21.70, 11.46.

HRMS (ESI) calculated for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1497.



***N*-(4-Fluorophenyl)-*N*-(4-phenylpyridin-2-yl)acetamide (10)**.

Prepared according to **GP3** using 4-fluoroaniline (48.0 μL, 99%).

Purification: Column eluted with 50%, then 60% Et_2O/hexanes.

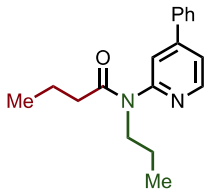
Yield: 78% (119.4 mg). Faint yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.3 Hz, 1H), 7.67 (s, 1H), 7.62 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.37 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.10, 163.02, 160.56, 155.88, 150.92, 149.30, 138.08 (d, *J* = 3.3 Hz), 137.68, 130.20 (d, *J* = 8.5 Hz), 129.50, 129.27, 127.24, 119.50 (d, *J* = 79.4 Hz), 116.52 (d, *J* = 22.8 Hz), 24.41.

^{19}F NMR (565 MHz, $CDCl_3$) δ -113.82.

HRMS (ESI) calculated for $C_{19}H_{16}FN_2O$ $[M+H]^+$ 307.1241, found 307.1243.



***N*-(4-Phenylpyridin-2-yl)-*N*-butyramide** (**14**).

Prepared according to **GP1** using butyric acid (48.7 μL, 99%).

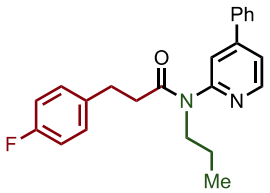
Purification: Column eluted with 35% EtOAc/hexanes. Further purified by second column eluted with 25% EtOAc/hexanes.

Yield: 78% (109.5 mg). Viscous yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.44 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.40 (brs, 1H), 3.86 – 3.80 (m, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.66 (h, *J* = 7.7 Hz, 2H), 1.59 (dt, *J* = 14.9, 7.4 Hz, 2H), 0.93 – 0.87 (m, 3H), 0.88 – 0.84 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.92, 156.46, 151.06, 149.79, 137.49, 129.63, 129.37, 127.15, 120.33, 119.98, 49.73, 36.93, 21.73, 18.98, 13.99, 11.46.

HRMS (ESI) calculated for $C_{18}H_{23}N_2O$ $[M+H]^+$ 283.1805, found 283.1809.



3-(4-Fluorophenyl)-*N*-(4-phenylpyridin-2-yl)-*N*-propylpropanamide (**15**).

Prepared according to **GP1** using 3-(4-fluorophenyl)propionic acid (90.1 mg, 98%).

Purification: Column eluted with 40% EtOAc/cyclohexane. Impure fractions further purified by preparatory TLC eluted with 40% EtOAc/cyclohexane.

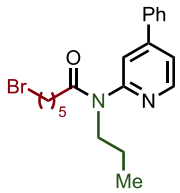
Yield: 78% (140.5 mg). Viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 2H), 7.50 (q, *J* = 6.9, 6.5 Hz, 3H), 7.44 (d, *J* = 5.3 Hz, 1H), 7.16 (brs, 1H), 7.06 (dd, *J* = 8.3, 5.5 Hz, 2H), 6.87 (t, *J* = 8.5 Hz, 2H), 3.85 – 3.77 (m, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 1.58 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.86, 161.44 (d, *J* = 243.7 Hz), 156.25, 151.25, 149.85, 137.09 (d, *J* = 3.2 Hz), 129.98 (d, *J* = 7.8 Hz), 129.71, 129.38, 127.13, 120.55, 119.83, 115.21 (d, *J* = 21.1 Hz), 49.93, 36.93, 30.94, 21.62, 11.45.

^{19}F NMR (565 MHz, $CDCl_3$) δ -117.26 (tt, *J* = 9.4, 5.6 Hz).

HRMS (ESI) calculated for $C_{23}H_{24}FN_2O$ $[M+H]^+$ 363.1867, found 363.1876.



6-Bromo-*N*-(4-phenylpyridin-2-yl)-*N*-propylhexanamide (**16**).

Prepared according to **GP1** using 6-bromohexanoic acid (104 mg, 98%).

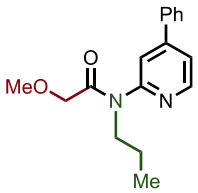
Purification: Column eluted with 40% EtOAc/cyclohexane. Impure fractions further purified by preparatory TLC eluted with 40% EtOAc/cyclohexane.

Yield: 74% (144.3 mg). Viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.54 – 7.43 (m, 4H), 7.40 (brs, 1H), 3.82 (t, *J* = 7.7 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 1.80 (p, *J* = 7.0 Hz, 2H), 1.62 (ddt, *J* = 30.4, 15.0, 7.5 Hz, 4H), 1.39 (h, *J* = 7.5, 6.5 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.63, 156.37, 151.20, 149.83, 137.40, 129.68, 129.39, 127.15, 120.45, 119.86, 49.82, 34.76, 33.81, 32.65, 27.92, 24.65, 21.70, 11.46.

HRMS (ESI) calculated for $C_{20}H_{26}BrN_2O$ $[M+H]^+$ 389.1223, found 389.1232.



2-Methoxy-*N*-(4-phenylpyridin-2-yl)-*N*-propylacetamide (**17**).

Prepared according to **GP1** using methoxyacetic acid (49.6 μL, 99%).

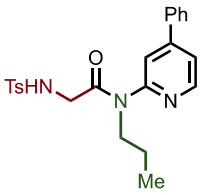
Purification: Column eluted with 40% EtOAc/hexanes. Impure fractions further purified by preparatory TLC eluted with 40% EtOAc/hexanes.

Yield: 70% (98.9 mg). Yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.3 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.44 (d, *J* = 4.4 Hz, 2H), 4.07 (s, 2H), 3.92 – 3.80 (m, 2H), 3.35 (s, 3H), 1.61 (h, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.56, 155.30, 151.28, 149.52, 137.42, 129.70, 129.39, 127.15, 120.42, 118.53, 71.78, 59.30, 49.66, 21.59, 11.42.

HRMS (ESI) calculated for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1598, found 285.1607.



2-((4-Methylphenyl)sulfonamido)-*N*-(4-phenylpyridin-2-yl)-*N*-propylacetamide (**18**).

Prepared according to **GP1** using *N*-(*p*-toluenesulfonyl)glycine (124 mg, 97%).

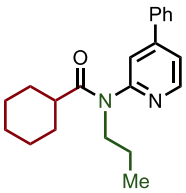
Purification: Column eluted with 25% acetone/hexanes. Further purified by preparatory TLC eluted with 4% MeOH/CH_2Cl_2.

Yield: 61% (128.3 mg). Pale yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.2 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 6.9 Hz, 2H), 7.56 – 7.48 (m, 3H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 3H), 5.61 (brs, 1H), 4.00 – 3.37 (m, 4H), 2.40 (s, 3H), 1.48 (h, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.40, 154.30, 151.91, 149.87, 143.66, 137.16, 136.14, 129.90, 129.78, 129.47, 127.43, 127.20, 121.21, 118.61, 45.20, 21.64, 21.36, 11.28.

HRMS (ESI) calculated for $C_{23}H_{26}N_3O_3S$ $[M+H]^+$ 424.1689, found 424.1701.



***N*-(4-Phenylpyridin-2-yl)-*N*-propylcyclohexanecarboxamide** (**19**).

Prepared according to **GP1** using cyclohexanecarboxylic acid (68.7 mg, 98%).

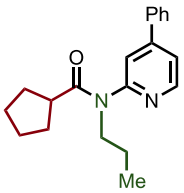
Purification: Column eluted with 10%, then 15% EtOAc/CH_2Cl_2.

Yield: 77% (124.0 mg). Chalky colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.39 (brs, 1H), 3.81 (t, *J* = 7.6 Hz, 2H), 2.29 (brs, 1H), 1.79 (d, *J* = 12.4 Hz, 2H), 1.71 (d, *J* = 14.2 Hz, 2H), 1.63 – 1.52 (m, 5H), 1.29 – 1.17 (m, 1H), 1.04 (q, *J* = 13.0 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.40, 156.65, 151.02, 149.82, 137.58, 129.66, 129.43, 127.19, 120.34, 119.84, 49.81, 42.78, 29.78, 25.84, 25.80, 21.80, 11.48.

HRMS (ESI) calculated for $C_{21}H_{27}N_2O$ $[M+H]^+$ 323.2118, found 323.2115.



***N*-(4-Phenylpyridin-2-yl)-*N*-propylcyclopentanecarboxamide** (**20**).

Prepared according to **GP1** using cyclopentanecarboxylic acid (58.1 μL, 98%).

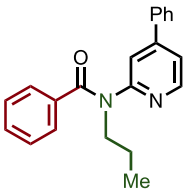
Purification: Column eluted with 25% EtOAc/hexanes. Further purified by second column eluted with 50% Et_2O/hexanes.

Yield: 83% (128.4 mg). White semi-crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 5.2 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.51 (dd, *J* = 8.3, 6.4 Hz, 2H), 7.49 – 7.47 (m, 1H), 7.45 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.40 (brs, 1H), 3.83 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.67 (brs, 1H), 1.92 – 1.81 (m, 2H), 1.77 – 1.65 (m, 4H), 1.59 (h, *J* = 7.4 Hz, 2H), 1.44 (d, *J* = 5.1 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.78, 156.71, 150.99, 149.90, 137.51, 129.67, 129.42, 120.24, 49.95, 43.04, 31.43, 26.47, 21.75, 11.50.

HRMS (ESI) calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$ 309.1961, found 209.1964.



***N*-(4-Phenylpyridin-2-yl)-*N*-propylbenzamide** (**21**).

Prepared according to **GP1** using benzoic acid (65.4 mg, 98%).

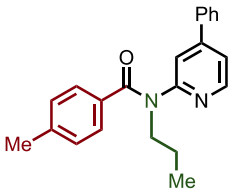
Purification: Column eluted with 25% EtOAc/hexanes. Further purified by preparatory TLC eluted with 50% Et_2O/hexanes.

Yield: 70% (110.0 mg). Viscous yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.1 Hz, 1H), 7.42 – 7.35 (m, 5H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 3.5 Hz, 2H), 6.86 (s, 1H), 4.15 (t, *J* = 7.6 Hz, 2H), 1.73 (h, *J* = 8.3, 7.6 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.86, 156.82, 149.87, 149.19, 137.60, 136.76, 130.13, 129.32, 129.12, 128.70, 128.20, 127.01, 120.99, 119.08, 49.83, 21.63, 11.57.

HRMS (ESI) calculated for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648, found 317.1658.



4-Methyl-*N*-(4-phenylpyridin-2-yl)-*N*-propylbenzamide (**22**).

Prepared according to **GP1** using *p*-toluic acid (73.7 mg, 97%).

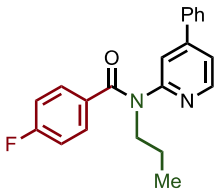
Purification: Column eluted with 10% acetone/cyclohexane. Further purified by second column eluted with 7.5% EtOAc/CH_2Cl_2.

Yield: 71% (117.2 mg). Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.2 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.21 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.85 (s, 1H), 4.16 – 4.08 (m, 2H), 2.28 (s, 3H), 1.71 (h, *J* = 7.8 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.97, 157.09, 149.76, 149.15, 140.43, 137.72, 133.85, 129.31, 129.13, 128.87, 128.84, 127.06, 120.98, 118.95, 49.89, 21.67, 21.46, 11.59.

HRMS (ESI) calculated for $C_{22}H_{23}N_2O$ $[M+H]^+$ 331.1805, found 331.1816.



4-Fluoro-*N*-(4-phenylpyridin-2-yl)-*N*-propylbenzamide (**23**).

Prepared according to **GP1** using 4-fluorobenzoic acid (75.1 mg, 98%).

Purification: Column eluted with 25% EtOAc/hexanes. Further purified by preparatory TLC eluted with 50% Et_2O/hexanes.

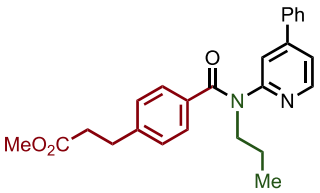
Yield: 60% (100.2 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.43 – 7.34 (m, 5H), 7.27 – 7.21 (m, 3H), 6.92 (t, *J* = 8.6 Hz, 2H), 6.88 (s, 1H), 4.23 – 4.02 (m, 2H), 1.72 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.73, 163.62 (d, *J* = 251.0 Hz), 156.91, 150.19, 149.42, 137.44, 132.81 (d, *J* = 3.2 Hz), 131.08 (d, *J* = 8.6 Hz), 129.51, 129.26, 126.98, 120.04 (d, *J* = 213.7 Hz), 115.27 (d, *J* = 21.8 Hz), 50.20, 21.60, 11.58.

^{19}F NMR (565 MHz, $CDCl_3$) δ -109.48 (ddd, *J* = 13.7, 8.5, 5.5 Hz).

HRMS (ESI) calculated for $C_{21}H_{20}FN_2O$ $[M+H]^+$ 335.1554, found 335.1561.



Methyl 3-(4-((4-phenylpyridin-2-yl)(propyl)carbamoyl)phenyl)propanoate (**24**).

Prepared according to **GP1** using 4-(3-methoxy-3-oxopropyl)benzoic acid (112 mg, 98%).

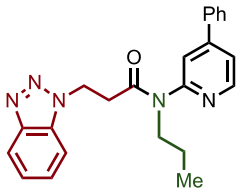
Purification: Column eluted with 40% acetone/hexanes. Further purified by preparatory TLC eluted with 2.5% MeOH/CH_2Cl_2.

Yield: 63% (126.0 mg). Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) 8.47 (d, *J* = 5.2 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.40 – 7.27 (m, 2H), 7.21 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.14 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.83 (s, 1H), 4.17 – 4.10 (m, 2H), 3.58 (s, 3H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.71 (h, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.04, 170.68, 156.90, 149.81, 149.17, 142.92, 137.64, 134.77, 129.34, 129.13, 129.08, 128.12, 126.99, 120.97, 119.03, 51.72, 49.84, 35.44, 30.77, 21.63, 11.56.

HRMS (ESI) calculated for $C_{25}H_{27}N_2O_3$ $[M+H]^+$ 403.2016, found 403.2013.



3-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-*N*-(4-phenylpyridin-2-yl)-*N*-propylpropanamide (**25**).

Prepared according to **GP1** using 3-benzotriazol-1-yl propionic acid (103 mg, 97%) and 2,6-lutidine (58.8 μL, 99%) in place of *N*,*N*-diisopropylethylamine.

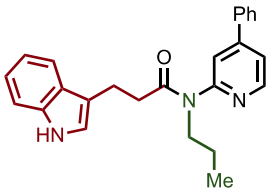
Purification: Column eluted with 50%, then 70% EtOAc/hexanes.

Yield: 60% (115.2 mg). Faint yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.52 – 7.44 (m, 4H), 7.42 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.33 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.17 (brs, 1H), 4.97 (t, *J* = 6.8 Hz, 2H), 3.80 – 2.98 (m, 2H), 3.07 – 2.97 (m, 2H), 1.51 (h, *J* = 7.5 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.71, 155.54, 151.69, 149.85, 145.91, 137.17, 133.33, 129.75, 129.38, 127.41, 127.22, 123.96, 120.88, 119.81, 119.32, 110.13, 50.09, 44.26, 35.29, 21.44, 11.34.

HRMS (ESI) calculated for $C_{23}H_{24}N_5O$ $[M+H]^+$ 386.1975, found 386.1972.



3-(1*H*-Indol-3-yl)-*N*-(4-phenylpyridin-2-yl)-*N*-propylpropanamide (**26**).

Prepared according to **GP1** using 3-indolepropionic acid (99.9 mg, 99%).

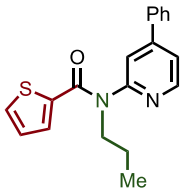
Purification: Column eluted with 7.5% acetone/CH_2Cl_2. Further purified by preparatory TLC eluted with 50% acetone/hexanes.

Yield: 71% (136.9 mg). Colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.2 Hz, 1H), 8.13 (brs, 1H), 7.53 – 7.43 (m, 6H), 7.39 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.17 (brs, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 3.88 – 3.80 (m, 2H), 3.15 (t, *J* = 7.7 Hz, 2H), 2.65 (t, *J* = 7.9 Hz, 2H), 1.59 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.74, 156.27, 151.17, 149.74, 137.32, 136.30, 129.56, 129.29, 127.32, 127.14, 121.91, 121.80, 120.45, 120.01, 119.21, 118.81, 115.44, 111.19, 49.88, 35.91, 21.63, 21.39, 11.46.

HRMS (ESI) calculated for $C_{25}H_{26}N_3O$ $[M+H]^+$ 384.2070, found 384.2077.



***N*-(4-Phenylpyridin-2-yl)-*N*-propylthiophene-2-carboxamide** (**27**).

Prepared according to **GP1** using 2-thiophenecarboxylic acid (68.0 mg, 99%).

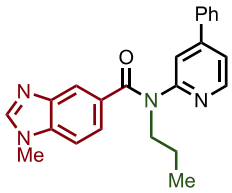
Purification: Column eluted with 5%, then 7.5% EtOAc/CH_2Cl_2.

Yield: 71% (136.9 mg). Faint yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.2 Hz, 1H), 7.48 – 7.39 (m, 6H), 7.34 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 6.85 – 6.79 (m, 2H), 4.07 – 4.01 (m, 2H), 1.72 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.40, 156.76, 150.61, 149.72, 138.78, 137.40, 131.34, 130.17, 129.58, 129.31, 127.09, 126.87, 121.28, 120.33, 50.85, 21.47, 11.54.

HRMS (ESI) calculated for $C_{19}H_{19}N_2OS$ $[M+H]^+$ 323.1213, found 323.1216.



1-Methyl-*N*-(4-phenylpyridin-2-yl)-*N*-propyl-1*H*-benzo[*d*]imidazole-5-carboxamide (**28**). Prepared according to **GP1** using 1-methyl-1*H*-benzimidazole-5-carboxylic acid (95.4 mg, 97%).

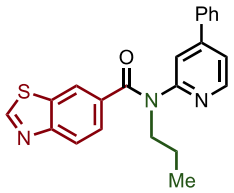
Purification: Column eluted with 3%, then 5% MeOH/CH_2Cl_2. Further purified by preparatory TLC eluted with 10% MeOH/EtOAc.

Yield: 63% (116.9 mg). Pale yellow oil/glassy solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.2 Hz, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 7.39 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.16 – 7.13 (m, 2H), 6.93 (s, 1H), 4.18 – 4.09 (m, 2H), 3.75 (s, 3H), 1.74 (h, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.28, 157.35, 149.69, 149.30, 144.87, 143.19, 137.46, 135.68, 130.89, 129.24, 129.07, 126.90, 124.10, 121.58, 120.69, 118.88, 109.06, 50.32, 31.21, 21.67, 11.60.

HRMS (ESI) calculated for $C_{23}H_{23}N_4O$ $[M+H]^+$ 371.1866, found 371.1867.



***N*-(4-Phenylpyridin-2-yl)-*N*-propylbenzo[*d*]thiazole-6-carboxamide** (**29**).

Prepared according to **GP1** using benzothiazole-6-carboxylic acid (95.4 mg, 97%) and 2,6-lutidine (58.8 μL, 99%) in place of *N*,*N*-diisopropylethylamine.

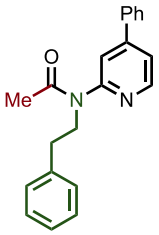
Purification: Column eluted with 40% EtOAc/hexanes. Further purified by preparatory TLC eluted with 50% acetone/hexanes.

Yield: 62% (116.2 mg). Colorless foam.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 1.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.22 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.15 – 7.11 (m, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 4.17 – 4.13 (m, 2H), 1.75 (h, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.08, 156.77, 156.14, 154.04, 150.28, 149.45, 137.33, 134.25, 133.72, 129.46, 129.20, 126.94, 126.70, 123.20, 123.04, 120.57, 119.41, 50.36, 21.64, 11.60.

HRMS (ESI) calculated for $C_{22}H_{20}N_3OS$ $[M+H]^+$ 374.1322, found 374.1318.



***N*-Phenethyl-*N*-(4-phenylpyridin-2-yl)acetamide** (**30**).

Prepared according to **GP2** using phenethylamine (63.6 μL, 99%).

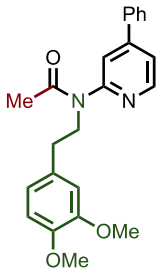
Purification: Column eluted with 50% EtOAc/hexanes. Further purified by preparatory TLC eluted with 20% EtOAc/CH_2Cl_2.

Yield: 84% (132.4 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.14 (t, *J* = 7.6 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.04 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.43, 156.49, 151.01, 149.59, 139.18, 137.36, 129.61, 129.29, 129.05, 128.53, 127.14, 126.45, 120.24, 119.63, 49.83, 34.68, 23.34.

HRMS (ESI) calculated for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648, found 317.1652.



***N*-(3,4-Dimethoxyphenethyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**31**).

Prepared according to **GP2** using 3,4-dimethoxyphenethylamine (92.5 mg, 98%).

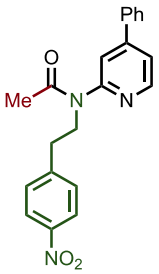
Purification: Column eluted with 30%, then 40% acetone/hexanes. Further purified by preparatory TLC eluted with 70% EtOAc/hexanes.

Yield: 70% (131.6 mg). Light orange oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.2 Hz, 1H), 7.54 (d, *J* = 6.9 Hz, 3H), 7.51 – 7.42 (m, 1H), 7.40 (d, *J* = 4.2 Hz, 1H), 7.08 (brs, 1H), 6.73 – 6.67 (m, 3H), 4.12 (t, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.38, 156.52, 150.94, 149.52, 148.92, 147.60, 137.28, 131.69, 129.61, 129.30, 127.04, 120.99, 120.18, 119.71, 112.11, 111.13, 55.89, 55.86, 49.85, 34.22, 23.32.

HRMS (ESI) calculated for $C_{23}H_{25}N_2O_3$ $[M+H]^+$ 377.1860, found 377.1867.



***N*-(4-Nitrophenethyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**32**).

Prepared according to **GP2** using 4-nitrophenethylamine (84.8 mg, 98%) and 2,6-lutidine (58.8 μL, 99%) in place of *N*,*N*-diisopropylethylamine.

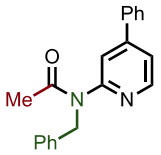
Purification: Column eluted with 70%, then 80% EtOAc/hexanes. Further purified by preparatory TLC eluted with 70% EtOAc/hexanes.

Yield: 66% (118.7 mg). Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.52 – 7.46 (m, 3H), 7.43 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.16 (brs, 1H), 4.22 – 4.10 (m, 2H), 3.15 – 2.98 (m, 2H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.41, 156.29, 151.33, 149.81, 147.09, 146.74, 137.08, 129.92, 129.83, 129.44, 126.98, 123.69, 120.51, 119.46, 48.93, 34.63, 23.23.

HRMS (ESI) calculated for $C_{20}H_{20}N_3O_3$ $[M+H]^+$ 362.1499, found 362.1507.



***N*-Benzyl-*N*-(4-phenylpyridin-2-yl)acetamide (33).**

Prepared according to **GP2** using benzylamine (55.2 μL, 99%).

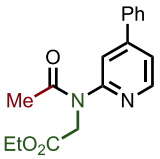
Purification: Column eluted with 50% EtOAc/hexanes. Further purified by preparatory TLC eluted with 50% MeOH/CH_2Cl_2, and then additional preparatory TLC eluted with 60% EtOAc/hexanes.

Yield: 85% (128.3 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.2 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.45 (q, *J* = 8.0, 7.4 Hz, 3H), 7.38 (d, *J* = 5.2 Hz, 1H), 7.31 – 7.10 (m, 6H), 5.15 (s, 2H), 2.12 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.61, 155.98, 150.84, 149.61, 137.76, 137.44, 129.56, 129.29, 128.60, 128.08, 127.36, 127.11, 120.31, 119.71, 51.31, 23.40.

HRMS (ESI) calculated for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492, found 303.1491.



Ethyl *N*-acetyl-*N*-(4-phenylpyridin-2-yl)glycinate (**34**).

Prepared according to **GP2** using glycine ethyl ester hydrochloride (70.5 mg, 99%) and 2,6-lutidine (118 μL, 99%, 2 equiv.) in place of *N*,*N*-diisopropylethylamine.

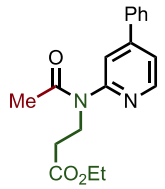
Purification: Column eluted with 20% acetone/hexanes. Further purified by preparatory TLC eluted with 40% EtOAc/hexanes.

Yield: 55% (81.1 mg). Off-white solid.

^{1}H NMR (600 MHz, acetone-d_6) δ 8.48 (d, J = 5.2 Hz, 1H), 7.88 (brs, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.60 – 7.48 (m, 3H), 7.51 – 7.47 (m, 1H), 4.66 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, acetone-d_6) δ 170.99, 170.12, 157.01, 151.04, 149.69, 138.47, 130.24, 130.08, 127.93, 120.02, 118.59, 61.44, 49.75, 23.33, 14.47.

HRMS (ESI) calculated for $C_{17}H_{19}N_2O_3$ $[M+H]^+$ 299.1390, found 299.1392.



Ethyl 3-(*N*-(4-phenylpyridin-2-yl)acetamido)propanoate (**35**).

Prepared according to **GP2** using β-Alanine ethyl ester hydrochloride (78.4 mg, 98%) and 2,6-lutidine (118 μL, 99%, 2 equiv.) in place of *N*,*N*-diisopropylethylamine.

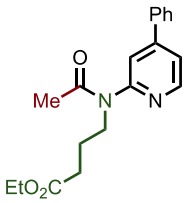
Purification: Column eluted with 70% EtOAc/hexanes. Impure fractions further purified by preparatory TLC eluted with 30% EtOAc/CH_2Cl_2 (plate eluted, dried, and eluted again).

Yield: 75% (116.8 mg). Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.54 – 7.41 (m, 5H), 4.17 (t, *J* = 7.2 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.77, 170.45, 156.23, 151.31, 149.76, 137.35, 129.72, 129.41, 127.16, 120.56, 119.74, 60.65, 44.22, 33.51, 23.23, 14.22.

HRMS (ESI) calculated for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.1547, found 313.1542.



Ethyl 4-(*N*-(4-phenylpyridin-2-yl)acetamido)butanoate (**36**).

Prepared according to **GP2** using ethyl 4-aminobutyrate hydrochloride (85.5 mg, 98%) and 2,6-lutidine (118 μL, 99%, 2 equiv.) in place of *N*,*N*-diisopropylethylamine.

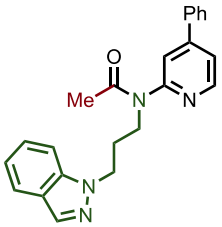
Purification: Column eluted with 20%, then 30%, then 40% EtOAc/CH_2Cl_2. Impure fractions further purified by preparatory TLC eluted with 30% acetone/hexanes (plate eluted, dried, and eluted again).

Yield: 77% (126.0 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.93 (t, *J* = 7.4 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.05 (s, 3H), 1.91 (p, *J* = 7.4 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.17, 170.47, 156.27, 151.24, 149.72, 137.38, 129.66, 129.36, 127.16, 120.41, 119.46, 60.44, 47.22, 31.61, 23.71, 23.28, 14.28.

HRMS (ESI) calculated for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.1703, found 327.1710.



***N*-(3-(1*H*-indazol-1-yl)propyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**37**).

Prepared according to **GP2** using 3-(1*H*-indazol-1-yl)propan-1-amine (97.4 mg, 90%) and 2,6-lutidine (58.8 μL, 99%) in place of *N*,*N*-diisopropylethylamine.

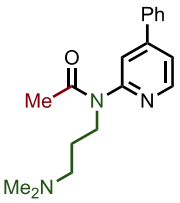
Purification: Column eluted with 80%, then 90% EtOAc/hexanes.

Yield: 90% (167.0 mg). Pale orange oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.2 Hz, 1H), 7.94 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.55 – 7.46 (m, 3H), 7.45 – 7.40 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.48 (t, *J* = 7.1 Hz, 2H), 4.00 (t, *J* = 7.2 Hz, 2H), 2.30 (p, *J* = 7.1 Hz, 2H), 2.05 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.63, 156.10, 151.34, 149.65, 139.53, 137.29, 133.06, 129.67, 129.33, 127.16, 126.26, 124.01, 121.11, 120.56, 120.46, 119.26, 109.14, 46.51, 45.68, 28.62, 23.31.

HRMS (ESI) calculated for $C_{23}H_{23}N_4O$ $[M+H]^+$ 371.1866, found 371.1874.



***N*-(3-(Dimethylamino)propyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**38**).

Prepared according to **GP2** using 3-(dimethylamino)-propan-1-amine (63.6 μL, 99%) with no added *N*,*N*-diisopropylethylamine. Reaction quenched by addition of 400 μL NEt_3.

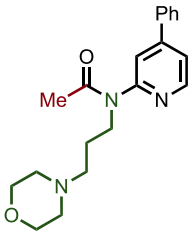
Purification: Column eluted with 5% NEt_3/acetone. The resultant material, containing **38** and **1**•[O] as determined by ^{1}H NMR, was taken up in 20 mL Et_2O, washed with saturated aqueous $NaHCO_3$ (3x20 mL), the combined aqueous layers extracted with Et_2O (3x20 mL), and the combined organic layers dried over $MgSO_4$, filtered, and concentrated.

Yield: 84% (124.4 mg). Dark yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.2 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.48 – 7.40 (m, 3H), 3.91 (t, *J* = 7.5 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.15 (s, 6H), 2.05 (s, 3H), 1.75 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.44, 156.38, 151.25, 149.71, 137.49, 129.67, 129.39, 127.19, 120.38, 119.58, 57.05, 46.42, 45.54, 26.61, 23.37.

HRMS (ESI) calculated for $C_{18}H_{24}N_3O$ $[M+H]^+$ 298.1914, found 298.1916.



***N*-(3-Morpholinopropyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**39**).

Prepared according to **GP2** using 3-(morpholino)-propan-1-amine (74.6 µL, 98%) with no added *N*,*N*-diisopropylethylamine. Reaction quenched by addition of 400 µL NEt_3.

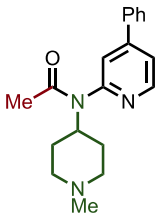
Purification: Column eluted with 1% NEt_3/acetone. Further purified by preparatory TLC eluted with 5% NEt_3/EtOAc.

Yield: 98% (167.1 mg). Yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.1 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.53 – 7.45 (m, 3H), 7.44 – 7.40 (m, 2H), 3.94 (t, *J* = 7.5 Hz, 2H), 3.62 (s, 4H), 2.39 – 2.29 (m, 6H), 2.05 (s, 3H), 1.79 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.40, 156.53, 151.19, 149.65, 137.40, 129.68, 129.38, 127.12, 120.32, 119.46, 67.03, 56.02, 53.68, 46.30, 25.40, 23.32.

HRMS (ESI) calculated for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2020, found 340.2022.



***N*-(1-Methylpiperidin-4-yl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**40**).

Prepared according to **GP2** using 4-amino-1-methylpiperidine (59.0 μL, 98%) with no added *N*,*N*-diisopropylethylamine. Reaction quenched by addition of 400 μL NEt_3.

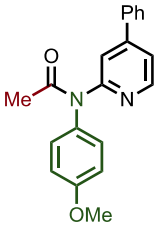
Purification: Column eluted with 4% NEt_3/acetone. The resultant material, containing **40** and **1**•[O] as determined by ^{1}H NMR, was taken up in 20 mL Et_2O, washed with saturated aqueous $NaHCO_3$ (3x20 mL), the combined aqueous layers extracted with Et_2O (3x20 mL), and the combined organic layers dried over $MgSO_4$, filtered, and concentrated.

Yield: 92% (142.1 mg). Golden oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.2 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.54 – 7.44 (m, 4H), 7.31 (s, 1H), 4.63 (t, *J* = 11.9 Hz, 1H), 2.84 (d, *J* = 12.5 Hz, 2H), 2.22 (s, 3H), 2.09 (t, *J* = 11.1 Hz, 2H), 1.93 – 1.87 (m, 2H), 1.83 (s, 3H), 1.54 (qd, *J* = 12.4, 4.0 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.89, 154.05, 151.38, 150.23, 137.16, 129.78, 129.43, 127.18, 122.58, 121.49, 55.37, 52.40, 46.15, 30.68, 23.58.

HRMS (ESI) calculated for $C_{19}H_{24}N_3O$ $[M+H]^+$ 310.1914, found 310.1917.



***N*-(4-Methoxyphenyl)-*N*-(4-phenylpyridin-2-yl)acetamide (41)**.

Prepared according to **GP3** using *p*-anisidine (62.8 mg, 98%).

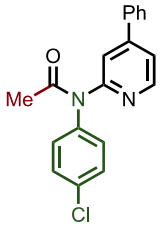
Purification: Column eluted with 30%, then 35% acetone/hexanes. Further purified by preparatory TLC eluted with 20% acetone/toluene.

Yield: 85% (135.5 mg). Sticky yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.2 Hz, 1H), 7.71 (s, 1H), 7.63 – 7.60 (m, 2H), 7.50 – 7.40 (m, 3H), 7.33 (d, *J* = 4.1 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.50, 158.98, 156.11, 150.63, 149.20, 137.90, 134.98, 129.73, 129.36, 129.21, 127.27, 119.55, 119.00, 114.86, 55.58, 24.43.

HRMS (ESI) calculated for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1441, found 319.1451.



***N*-(4-Chlorophenyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**42**).

Prepared according to **GP3** using 4-chloroaniline (65.1 mg, 98%).

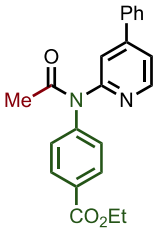
Purification: Column eluted with 50%, then 60% Et_2O/hexanes. Further purified by preparatory TLC eluted with 10% acetone/CH_2Cl_2.

Yield: 70% (112.7 mg). Off-white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.2 Hz, 1H), 7.65 (brs, 1H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.42 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 3H), 7.28 (d, *J* = 8.3 Hz, 2H), 2.15 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.88, 155.75, 151.01, 149.36, 140.61, 137.55, 133.40, 129.74, 129.60, 129.54, 129.27, 127.21, 120.02, 119.19, 24.43.

HRMS (ESI) calculated for $C_{19}H_{16}ClN_2O$ $[M+H]^+$ 323.0946, found 323.0950.



***N*-(4-Ethoxycarbonylphenyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**43**).

Prepared according to **GP3** using ethyl 4-aminobenzoate (48.0 μL, 99%) at 60 ºC.

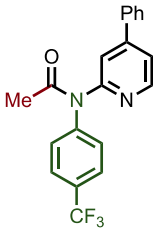
Purification: Column eluted with 15%, then 20% acetone/hexanes.

Yield: 66% (119.2 mg). Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 7.8, 1.7 Hz, 3H), 7.50 – 7.43 (m, 3H), 7.41 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.17 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.71, 165.94, 155.79, 151.17, 146.10, 137.44, 130.84, 129.59, 129.29, 127.71, 127.19, 120.25, 119.47, 61.22, 24.53, 14.44.

HRMS (ESI) calculated for $C_{22}H_{21}N_2O_3$ $[M+H]^+$ 361.1547, found 361.1550.



***N*-(4-Trifluoromethylphenyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**44**).

Prepared according to **GP3** using 4-(trifluoromethyl)aniline (64.1 μL, 98%) at 60 ºC.

Purification: Column eluted with 5%, then 10-20% EtOAc/CH_2Cl_2. Further purified by preparatory TLC eluted with 75% EtOAc/hexanes.

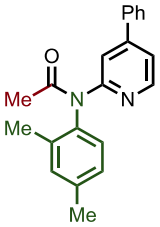
Yield: 67% (119.6 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.2 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 3H), 7.52 – 7.40 (m, 6H), 2.17 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.70, 155.70, 151.37, 149.63, 145.14, 137.34, 129.69, 129.34, 129.13, 128.12, 127.20, 126.59 (q, *J* = 3.7 Hz), 123.96 (q, *J* = 272.2 Hz), 120.47, 119.59, 24.46.

^{18}F NMR (565 MHz, $CDCl_3$) δ -62.50.

HRMS (ESI) calculated for $C_{20}H_{16}F_3N_2O$ $[M+H]^+$ 357.1209, found 357.1210.



***N*-(2,4-Dimethylphenyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**45**).

Prepared according to **GP3** using 2,4-dimethylaniline (62.2 μL, 99%).

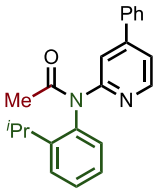
Purification: Column eluted with 5% EtOAc/CH_2Cl_2. Further purified by preparatory TLC eluted with 80% Et_2O/hexanes.

Yield: 81% (128.0 mg). Colorless glassy solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.2 Hz, 1H), 7.91 (brs, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.41 (m, 1H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.56, 155.29, 150.15, 148.84, 138.49, 138.45, 138.19, 136.31, 132.22, 129.42, 129.22, 129.16, 128.06, 127.31, 118.81, 117.79, 24.61, 21.29, 18.12.

HRMS (ESI) calculated for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648, found 317.1652.



***N*-(2-Isopropylphenyl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**46**).

Prepared according to **GP3** using 2-isopropylaniline (73.0 μL, 97%).

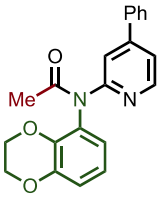
Purification: Column eluted with 5% EtOAc/CH_2Cl_2. Further purified by preparatory TLC eluted with 70% Et_2O/hexanes.

Yield: 70% (115.2 mg). Pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.2 Hz, 1H), 7.91 (brs, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.37 (m, 3H), 7.33 – 7.26 (m, 3H), 3.16 (p, *J* = 6.9 Hz, 1H), 2.11 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.71, 155.65, 150.19, 148.67, 146.82, 139.41, 138.15, 130.03, 129.25, 129.18, 127.35, 127.27, 126.96, 118.84, 117.71, 28.15, 24.87, 23.95, 23.52.

HRMS (ESI) calculated for $C_{22}H_{23}N_2O$ $[M+H]^+$ 331.1805, found 331.1810.



***N*-(1,4-Benzodioxan-5-yl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**47**).

Prepared according to **GP3** using 5-amino-1,4-benzodioxane (77.1 mg, 98%).

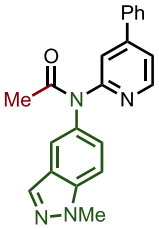
Purification: Column eluted with 15%, then 30% acetone/hexanes. Further purified by preparatory TLC eluted with 10% acetone/CH_2Cl_2.

Yield: 77% (133.3 mg). Colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.2 Hz, 1H), 7.85 (brs, 1H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.52 – 7.38 (m, 3H), 7.30 (d, *J* = 5.2 Hz, 1H), 6.96 – 6.85 (m, 3H), 4.27 (s, 4H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.49, 155.46, 150.22, 148.87, 144.76, 140.48, 138.18, 130.82, 129.19, 129.15, 127.28, 122.49, 121.07, 119.22, 118.36, 117.53, 64.57, 64.32, 23.94.

HRMS (ESI) calculated for $C_{21}H_{19}N_2O_3$ $[M+H]^+$ 347.1390, found 347.1393.



***N*-(1-Methyl-1*H*-indazol-5-yl)-*N*-(4-phenylpyridin-2-yl)acetamide** (**48**).

Prepared according to **GP3** using 1-methyl-1*H*-indazol-5-amine (75.9 mg, 97%).

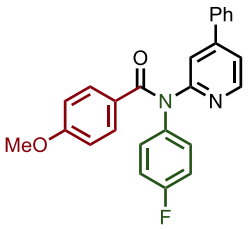
Purification: Column eluted with 20%, then 40% acetone/hexanes. Further purified by preparatory TLC eluted with 25% acetone/CH_2Cl_2.

Yield: 86% (147.5 mg). Brittle light pink foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.2 Hz, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 7.64 – 7.57 (m, 2H), 7.50 – 7.36 (m, 5H), 7.36 – 7.30 (m, 1H), 4.08 (s, 3H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.58, 156.22, 150.69, 149.17, 138.98, 137.80, 135.23, 133.23, 129.37, 129.19, 127.36, 127.23, 124.42, 121.00, 119.57, 118.94, 110.04, 35.83, 24.53.

HRMS (ESI) calculated for $C_{21}H_{19}N_4O$ $[M+H]^+$ 343.1553, found 343.1557.



***N*-(4-Fluorophenyl)-4-methoxy-*N*-(4-phenylpyridin-2-yl)benzamide** (**49**).

Prepared according to **GP4** using 4-fluoroaniline (50.0 μL, 99%) and *p*-anisic acid (81.5 mg, 98%).

Purification: Column eluted with 3%, then 4% acetone/CH_2Cl_2. Further purified by preparatory TLC eluted with 60% EtOAc/hexanes.

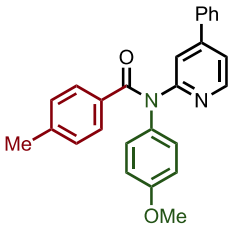
Yield: 43% (85.7 mg). Brittle colorless foam.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.2 Hz, 1H), 7.51 – 7.47 (m, 4H), 7.47 – 7.42 (m, 3H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.31 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.20 – 7.17 (m, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.86, 161.95, 161.62, 160.31, 157.35, 150.61, 149.54, 139.16 (d, *J* = 3.0 Hz), 137.61, 131.45, 129.49 (d, *J* = 1.6 Hz), 129.44, 129.24, 127.90, 127.16, 119.62 (d, *J* = 52.3 Hz), 116.37 (d, *J* = 22.8 Hz), 113.50, 55.44.

^{18}F NMR (565 MHz, $CDCl_3$) ^{19}F NMR (565 MHz, $CDCl_3$) δ -115.10.

HRMS (ESI) calculated for $C_{25}H_{20}FN_2O_2$ $[M+H]^+$ 399.1503, found 399.1509.



***N*-(4-Methoxyphenyl)-4-methyl-*N*-(4-phenylpyridin-2-yl)benzamide** (**50**).

Prepared according to **GP4** using *p*-anisidine (62.8 mg, 98%) and *p*-toluic acid (73.7 mg, 97%).

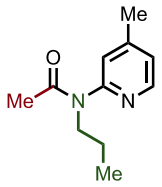
Purification: Column eluted with 3%, then 4% acetone/CH_2Cl_2. Further purified by preparatory TLC eluted with 60% EtOAc/hexanes.

Yield: 50% (97.8 mg). Pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.47 – 7.38 (m, 6H), 7.29 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.21, 158.13, 157.32, 150.29, 149.31, 140.75, 137.70, 135.75, 133.23, 129.25, 129.08, 129.00, 128.66, 127.08, 119.59, 119.15, 114.60.

HRMS (ESI) calculated for $C_{26}H_{23}N_2O_2$ $[M+H]^+$ 395.1754, found 395.1768.



***N*-(4-Methylpyridin-2-yl)-*N*-propylacetamide** (**51**).

Prepared according to **GP5** using 4-methyl pyridine *N*-oxide (69.6 mg, 98%).

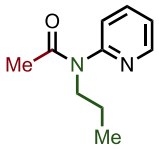
Purification: Column eluted with 50-70% EtOAc/hexanes.

Yield: 82% (78.7 mg). Light orange oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 5.0 Hz, 1H), 7.04 (d, *J* = 5.1 Hz, 1H), 7.00 (s, 1H), 3.76 (t, *J* = 7.7 Hz, 3H), 2.38 (s, 3H), 1.96 (s, 3H), 1.53 (h, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.26, 155.98, 149.93, 149.04, 123.45, 122.61, 49.65, 23.18, 21.58, 21.12, 11.42.

HRMS (ESI) calculated for $C_{11}H_{16}N_2O$ $[M+H]^+$ 193.1335, found 193.1334.



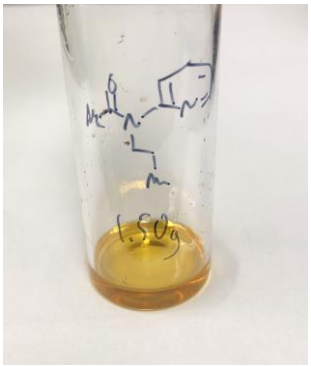
***N*-(Pyridin-2-yl)-*N*-propylacetamide** (**52**).

Prepared according to **GP5** using pyridine *N*-oxide (60.0 mg, 99%).

Purification: Column eluted with 50% EtOAc/hexanes.

Yield: 84% (74.8 mg). Light orange oil.

10.0 mmol scale reaction performed according to modified **GP5** in a 100 mL recovery flask equipped with football-shaped stir bar, in oil bath at 40 ºC under N_2 balloon via needle through septum. Pyridine *N*-oxide (1.21 g, 98%, 12.5 mmol, 1.25 equiv.), 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (261 mg, 1.50 mmol, 0.150 equiv.), propylamine (839 µL, 98%, 10.0 mmol, 1.00 equiv.), acetic acid (604 µL, 99.5%, 10.5 mmol, 1.05 equiv.), *N*,*N*-diisopropylethylamine (1.74 mL, 99.5%, 10.0 mmol, 1.00 equiv.), diethyl 2-bromo-2-methylmalonate (4.22 mL, 98%, 22.0 mmol, 2.20 equiv.) and diphenylsilane (5.57 mL, 97%, 30.0 mmol, 3.00 equiv.) in acetonitrile (10.0 mL, 1.00 M). Quenched after 16 h with 4 mL triethylamine, concentrated, adsorbed onto silica gel, and purified as above.

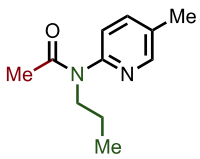
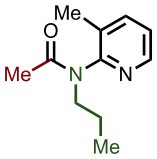


Yield: 84%, 1.50 g. Light orange oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 3.2 Hz, 1H), 7.75 (td, *J* = 7.7, 2.0 Hz, 1H), 7.21 (dd, *J* = 7.5, 4.8 Hz, 2H), 3.79 (dd, *J* = 8.6, 6.7 Hz, 2H), 1.98 (s, 3H), 1.54 (h, *J* = 7.5 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.28, 155.83, 149.40, 138.35, 122.23, 121.88, 49.64, 23.25, 21.61, 11.40.

HRMS (ESI) calculated for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1179, found 179.1177.

***N*-(5-Methylpyridin-2-yl)-*N*-propylacetamide (53a)** and

***N*-(3-Methylpyridin-2-yl)-*N*-propylacetamide** (**53b**).

Prepared according to **GP5** using 3-methylpyridine *N*-oxide (71.1 mg, 96%).

Purification: Column eluted with gradient 10–30% acetone/hexanes to separate **53a** and **53b**, in order of elution. Each individual product was further purified by preparatory TLC eluted with 40% acetone/hexanes.

Yield: **53a**: 39% (37.1 mg). Light yellow oil. **53b**: 32% (31.1 mg). Light yellow oil. **Total**: 71%. Substitution pattern determined by comparison to known compounds.[2]

***N*-(5-Methylpyridin-2-yl)-*N*-propylacetamide (53a)**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (brs, 1H), 7.55 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.07 (brs, 1H), 3.75 (t, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 1.93 (brs, 3H), 1.52 (h, *J* = 7.5 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.32, 149.72, 138.97, 121.49, 49.64, 23.11, 21.53, 18.10, 11.43. Note that some aromatic resonances are not apparent, as previously described for related compounds.[2b]

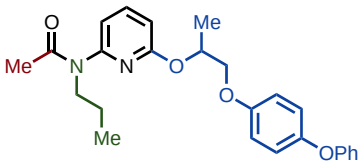
HRMS (ESI) calculated for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341, found 193.1335.

***N*-(3-Methylpyridin-2-yl)-*N*-propylacetamide (53b)**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.7, 2.0 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.35 – 3.29 (m, 1H), 2.27 (s, 3H), 1.75 (s, 3H), 1.57 (h, *J* = 7.5 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 4H). Note that the α-amino methylene protons are non-equivalent due to restricted rotation about the C2–N axis.[3]

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.12, 154.73, 147.52, 140.44, 131.01, 123.64, 49.23, 22.43, 21.27, 17.40, 11.61.

HRMS (ESI) calculated for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341, found 193.1334.



***N*-(6-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-2-yl)-*N*-propylacetamide** (**54**).

Prepared according to **GP5** using pyriproxyfen *N*-oxide (222 mg, 95%).

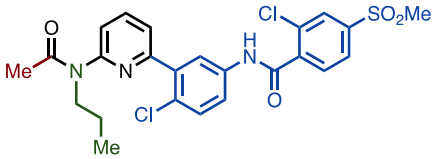
Purification: Column eluted with 30% EtOAc/hexanes.

Yield: 66% (138.0 mg). Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 – 6.87 (m, 6H), 6.77 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 5.49 (h, *J* = 5.9 Hz, 1H), 4.11 (ddd, *J* = 40.7, 9.9, 5.1 Hz, 2H), 3.80 – 3.72 (m, 2H), 2.02 (s, 3H), 1.57 (h, *J* = 7.4 Hz, 2H), 1.47 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.36, 162.75, 158.52, 155.17, 153.29, 150.54, 140.59, 129.73, 122.60, 120.88, 117.76, 115.87, 113.73, 109.91, 71.10, 69.99, 49.52, 23.36, 21.59, 17.00, 11.42.

HRMS (ESI) calculated for $C_{25}H_{29}N_2O_4$ $[M+H]^+$ 421.2122, found 421.2124.



2-Chloro-*N*-(4-chloro-3-(6-(*N*-propylacetamido)pyridin-2-yl)phenyl)-4-(methylsulfonyl) benzamide (**55**).

Prepared according to modified **GP5** using vismodegib *N*-oxide (175 mg, 98%, 0.392 mmol, 1.25 equiv.), propylamine (26.3 µL, 98%, 0.314 mmol, 1.00 equiv.), acetic acid (18.9 µL, 99.5%, 0.329 mmol, 1.05 equiv.), *N*,*N*-diisopropylethylamine (54.9 µL, 99.5%, 0.314 mmol, 1.00 equiv.), diethyl 2-bromo-2-methylmalonate (135 µL, 0.690 mmol, 2.20 equiv.), diphenylsilane (180 µL, 0.941 mmol, 3.00 equiv.), and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (8.2 mg, 0.047 mmol, 0.150 equiv.) in acetonitrile (0.314 mL, 1.0 M), and quenched by addition of 125 µL of NEt_3.

Purification: Column eluted with 30% then 35% EtOAc/CH_2Cl_2. Further purified by second column (dry loaded) eluted with 10% acetone/CH_2Cl_2.

Yield: 63% (103.1 mg). Colorless solid.

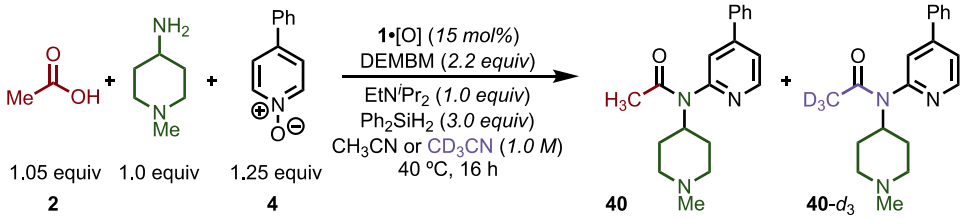
^{1}H NMR (600 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.14 (s, 1H), 8.03 – 7.99 (m, 3H), 7.92 (d, J = 8.0 Hz, 1H), 7.80 (dd, J = 8.8, 2.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.78 (t, J = 7.4 Hz, 2H), 3.35 (s, 3H), 2.01 (s, 3H), 1.49 (h, J = 7.4 Hz, 2H), 0.82 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 169.40, 163.92, 155.02, 154.78, 143.16, 140.86, 139.09, 138.40, 137.76, 130.96, 130.64, 129.97, 128.13, 125.96, 125.82, 122.43, 122.23, 121.09, 120.49, 48.62, 43.09, 23.15, 21.23, 11.19.

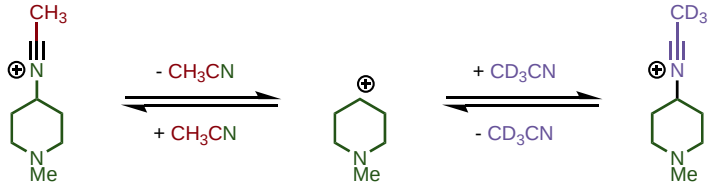
HRMS (ESI) calculated for $C_{24}H_{24}Cl_2N_3O_4S$ $[M+H]^+$ 520.0859, found 520.0863.

IV. Mechanistic Studies

A. Crossover Experiment to Probe for Retro-Ritter/Ritter Exchange



possible exchange (*not observed*):



To each of two 4 mL vials with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 27.3 mg, 98%, 126 μmol, 1.25 equiv.) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**•[O], 3.3 mg, 18.8 μmol, 0.150 equiv.). The vials were each capped with a black septum cap, and the septa were punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. To each vial was added the indicated acetonitrile isotopologue (125 μL, 1.0 M), followed by 4-amino-1-methylpiperidine (16.0 μL, 98%, 0.125 mmol) and acetic acid (**2**, 7.5 μL, 99.5%, 131 μmol, 1.05 equiv.). Next, to each vial was added diethyl 2-bromo-2-methylmalonate (53.8 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (71.8 μL, 97%, 1.50 mmol, 3.00 equiv.). For each vial, the black septum cap was exchanged for a white cap under flow of N_2. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After 16 h, the reaction was cooled to ambient temperature with stirring at 300 rpm. Then, 50 μL of NEt_3 (Sigma Aldrich, for synthesis, stored under ambient atmosphere) was added to quench the reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 1,3,5-trimethoxybenzene (85.0 mg, 98%, 0.500 mmol) in MeCN in a 1 mL volumetric flask – was added. The reaction was diluted to homogeneity with ~ 1 mL $CDCl_3$, and an aliquot was transferred to an NMR tube, diluted to total volume ~0.6 mL, and analyzed by ^{1}H NMR spectroscopy. The yield was determined by relative integration between 1,3,5-trimethoxybenzene (δ = 6.04 ppm, s, 2 H, 0.20 equiv, integrate to 60), and product **40** (δ = 8.5 ppm, d, 1H). Number of scans = 8 and relaxation delay = 4 seconds. A second aliquot from each reaction was diluted in MeOH and analyzed by LC-MS.

Entry	Solvent	Yield of **40**/**40**-d_3 (%)[a]	**40**[b]	**40**-d_3 [b]
1	CH_3CN	91	detected	not detected
2	CD_3CN	91	detected	not detected

Table S3. Crossover-labeling experiment to detect possible retro-Ritter/Ritter exchange. [a]Yield determined by ^{1}H NMR against internal standard. [b]As detected by LC-MS, see **Figure S3**.

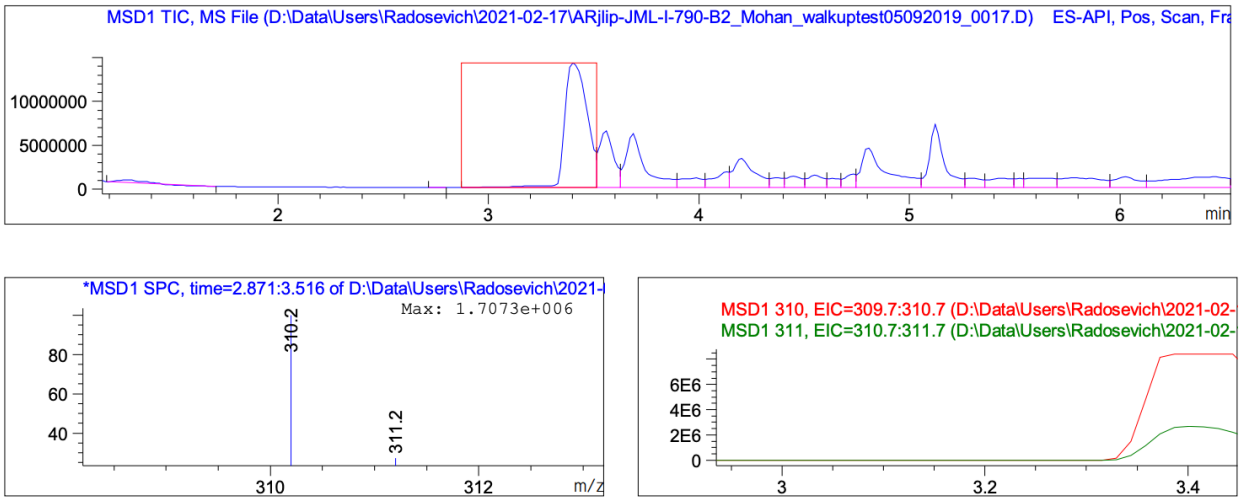
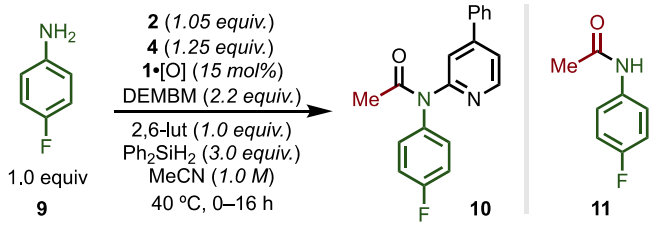


Figure S3. LC-MS trace of crude **entry 2** showing m/z = 310.2 corresponding to **40** (calculated for $C_{19}H_{24}N_3O$ $[M+H]^+$ 310.2), and no m/z = 313.2 corresponding to **40**-d_3 (calculated for $C_{19}H_{21}D_3N_3O$ $[M+H]^+$ 313.2).

B. Time Study with 4-Fluoroaniline (9)



To each of six 4 mL vials with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 27.3 mg, 98%, 126 μmol, 1.25 equiv.) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**•[O], 3.3 mg, 18.8 μmol, 0.15 equiv.). The vials were each capped with a black septum cap, and the septa were punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (125 μL, 1.0 M) was added to each vial under N_2, followed by 4-fluoroaniline (**9**, 12.0 μL, 99%, 125 μmol, 1.00 equiv.) and acetic acid (**2**, 7.5 μL, 99.5%, 131 μmol, 1.05 equiv.). Next, to each vial was added 2,6-lutidine (14.8 μL, 99%, 0.50 mmol, 1.00 equiv.), followed by diethyl 2-bromo-2-methylmalonate (53.8 μL, 98%, 1.10 mmol, 2.20 equiv.) and diphenylsilane (71.8 μL, 97%, 1.50 mmol, 3.00 equiv.). For each vial, the black septum cap was exchanged for a white cap under flow of N_2. The reaction vials were then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After the indicated time, each respective reaction vial was cooled to ambient temperature. Then, 50 μL of NEt_3 was added to quench the reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 4,4′-difluorobenzophenone (110.2 mg, 98%, 0.500 mmol) in MeCN in a 1 mL volumetric flask – was added. The reaction was diluted to homogeneity with ~ 1 mL $CHCl_3$, and an aliquot was transferred to an NMR tube, diluted to total volume ~0.6 mL with $CDCl_3$, and analyzed by ^{19}F NMR spectroscopy. The yield was determined by relative integration between 4,4′-difluorobenzophenone (δ = -105.76 ppm, 2 F, 0.20 equiv, integrate to 40), aniline **9** (δ = -127.3 ppm, 1 F), amide **11** (δ = -118.8 ppm, 1 F), and product **10** (δ = -113.9, brs, 1F). Number of scans = 8 and relaxation delay = 8 seconds. Note that **11** was also independently prepared according to literature procedure,[4] to establish an unambiguous assay (see **Figure S6**).

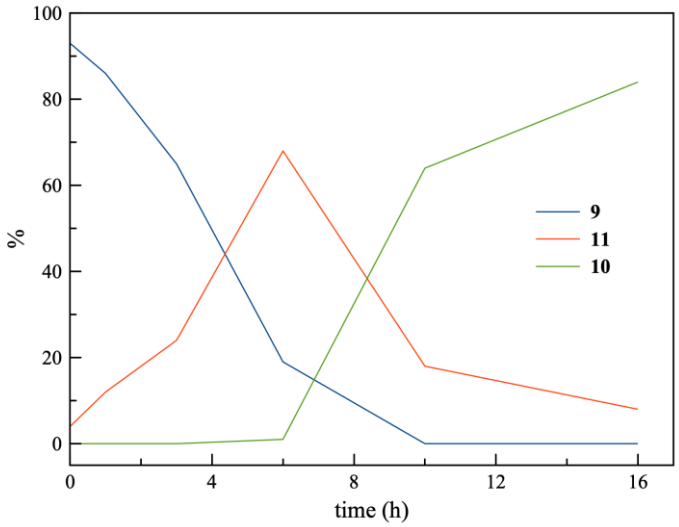


Figure S4. Reaction progress plot for the reaction of **2**, **9**, and **4** catalyzed by **1**•[O] to give **10**.

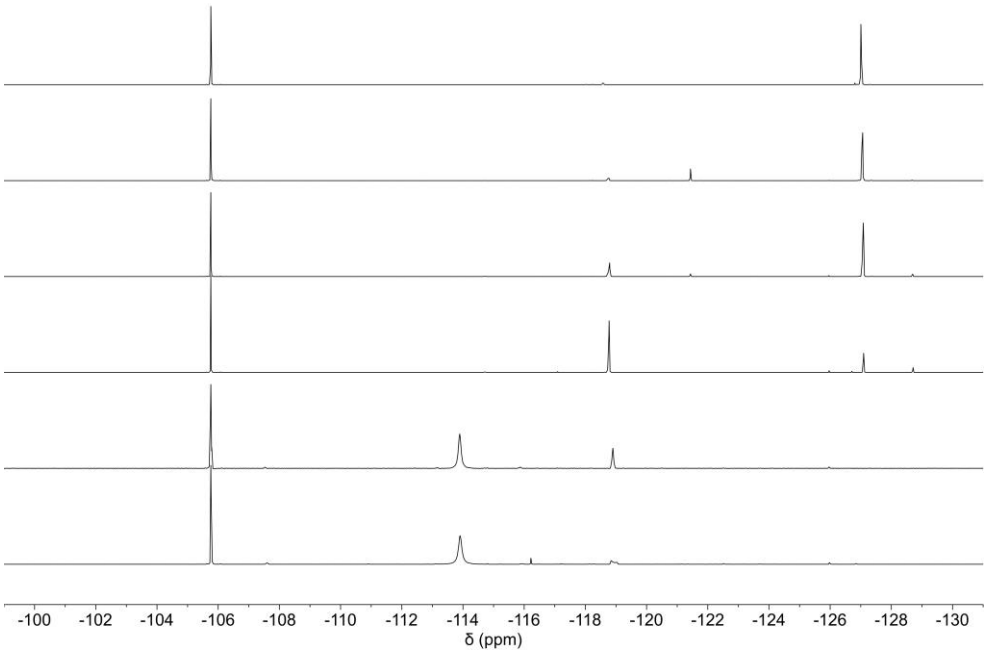


Figure S5. Time-stacked ^{19}F NMR (top-to-bottom: t = 0, 1, 3, 6, 10, and 16 h) for the reaction of **2**, **9**, and **4** catalyzed by **1**•[O] to give **10**.

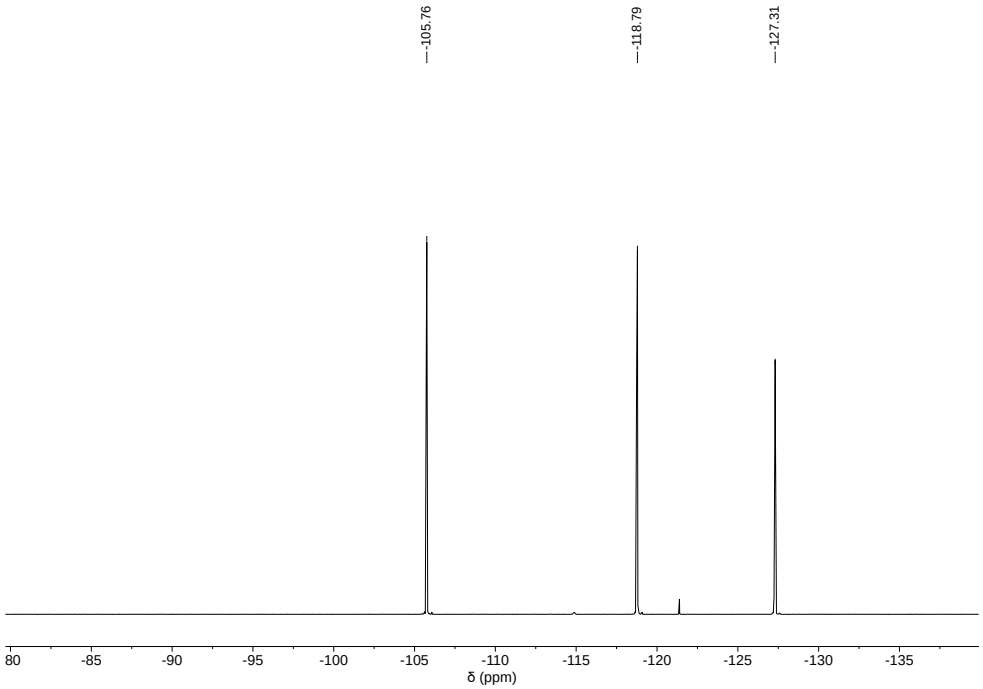
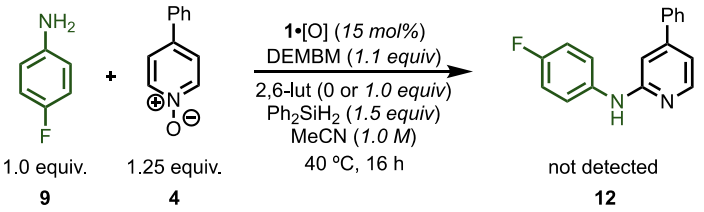


Figure S6. ^{19}F NMR assay in ~2% MeCN in $CDCl_3$ showing 4,4′-difluorobenzophenone (δ = -105.76 ppm, standard), **11** (δ = -118.8 ppm), and **9** (δ = -127.3 ppm).

C. Coupling of 4-Phenylpyridine *N*-Oxide (4) with 4-Fluoroaniline (9)

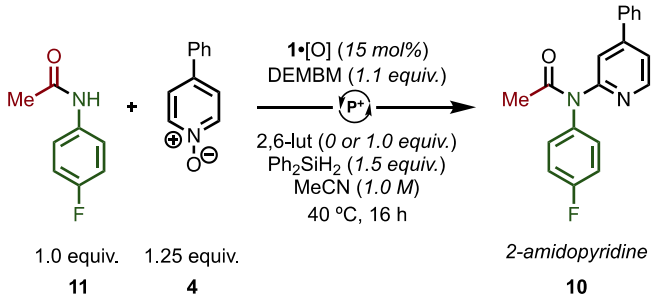


To each of two 4 mL vials with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 27.3 mg, 98%, 126 μmol, 1.25 equiv.) and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**•[O], 3.3 mg, 18.8 μmol, 0.15 equiv.). The vials were each capped with a septum cap, and the septa were punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (125 μL, 1.0 M) was added to each vial under N_2, followed by 4-fluoroaniline (**9**, 12.0 μL, 99%, 125 μmol, 1.00 equiv.). Next, to each vial was added the indicated quantity of 2,6-lutidine. To both vials was then added diethyl 2-bromo-2-methylmalonate (26.9 μL, 98%, 138 μmol, 1.10 equiv.) and diphenylsilane (35.9 μL, 97%, 188 μmol, 1.50 equiv.). For each vial, the black septum cap was exchanged for a white cap under flow of N_2. The reaction vials were then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After 16 hours, the reaction vials were cooled to ambient temperature. Then, 50 μL of NEt_3 was added to quench each reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 4,4′-difluorobenzophenone (110.2 mg, 98%, 0.500 mmol) in MeCN in a 1 mL volumetric flask – was added. The reactions were diluted to homogeneity with ~ 1 mL $CHCl_3$, and an aliquot was transferred from each vial to an NMR tube, diluted to total volume ~0.6 mL with $CDCl_3$, and analyzed by ^{19}F NMR (number of scans = 8 and relaxation delay = 8 seconds). The yield was determined by relative integration between 4,4′-difluorobenzophenone (δ = -105.76 ppm, 2 F, 0.20 equiv, integrate to 40), aniline **9** (δ = -127.3 ppm, 1 F), and diarylamine **12** (δ = -119.4 ppm, 1 F).[5] Number of scans = 8 and relaxation delay = 8 seconds. A second aliquot from each reaction was diluted in MeOH and analyzed by LC-MS, which indicated no presence of **12**.

Entry	2,6-lutidine (X equiv.)	Yield of **12** (%)[a]
1	0	0
2	1	0

Table S4. Direct dehydrative coupling of aniline **9** with pyridine *N*-oxide **4**. [a]Yield determined by ^{19}F NMR against internal standard.

D. Coupling of 4-Phenylpyridine *N*-Oxide (4) with 4-Fluoroacetanilide (11)



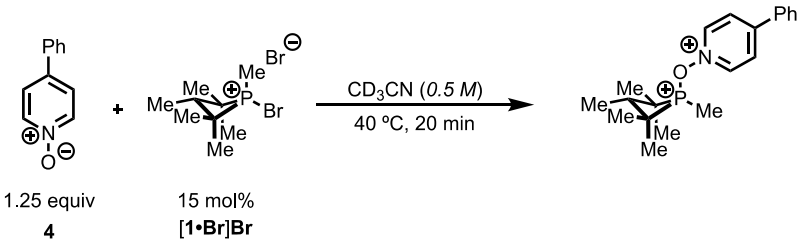
1.0 equiv. **11** 1.25 equiv. **4** *2-amidopyridine* **10**

To two 4 mL vials with magnetic stir bar was added 4-phenylpyridine N-oxide (**4**, 27.3 mg, 98%, 156 μmol, 1.25 equiv.), 4-fluoroacetanilide (**11**, 19.3 mg, 99%, 125 μmol, 1.00 equiv.), and 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide (**1**•[O], 3.3 mg, 18.8 μmol, 0.15 equiv.). The vials were each capped with a black septum cap, and the septa were punctured with a needle under N_2. The atmosphere was exchanged by three evacuation/N_2 backfill cycles. Acetonitrile (125 μL, 1.0 M) was added to each vial under N_2. Next, to each vial was added 2,6-lutidine (0.0 or 1.0 equiv.), followed by diethyl 2-bromo-2-methylmalonate (26.9 μL, 98%, 0.55 mmol, 1.10 equiv.) and diphenylsilane (35.9 μL, 97%, 0.75 mmol, 1.50 equiv.). For each vial, the black septum cap was exchanged for a white cap under flow of N_2. The reaction vials were then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm. After 16 hours, each reaction vial was cooled to ambient temperature. Then, 50 μL of NEt_3 was added to quench the reaction. Then, 50.0 μL (0.50 M, 25.0 μmol, 0.200 equiv.) of an external standard stock solution – freshly prepared from 4,4′-difluorobenzophenone (110.2 mg, 98%, 0.500 mmol) in MeCN in a 1 mL volumetric flask – was added. The reaction was diluted to homogeneity with ~ 1 mL $CHCl_3$, and an aliquot was transferred to an NMR tube, diluted to total volume ~0.6 mL with $CDCl_3$, and analyzed by ^{19}F NMR spectroscopy. The yield was determined by relative integration between 4,4′-difluorobenzophenone (δ = -105.76 ppm, 2 F, 0.20 equiv, integrate to 40), amide **11** (δ = -118.8 ppm, 1 F), and product **10** (δ = -113.9, brs, 1F). Number of scans = 8 and relaxation delay = 8 seconds.

Entry	2,6-lutidine (X equiv.)	Yield of **10** (%)[a]	Remaining **11** (%)[a]
1	0	88	9
2	1	56	28

Table S5. Direct dehydrative coupling of acetanilide **11** with pyridine *N*-oxide **4**. [a]Yield determined by ^{19}F NMR against internal standard.

E. Reaction of 4-Phenylpyridine *N*-Oxide (4) with [1•Br]Br



In a nitrogen-filled glovebox, a 4 mL vial with magnetic stir bar was charged with 4-phenylpyridine *N*-oxide (**4**, 65.5 mg, 98%, 375 μmol, 1.25 equiv.) and 1-bromo-1,2,2,3,4,4-hexamethylphosphetanium bromide[6] ([**1**•Br]Br, 14.3 mg, 45 μmol, 0.15 equiv.). Acetonitrile-d_3 was then added to the vial (600 μL, 0.50 M), and a white PTFE-lined cap was tightly screwed on. The reaction vial was then placed in a thermostatted (40 °C) aluminum heating block and stirred at 300 rpm for 20 min, at which time the vial was cooled to ambient temperature and transferred to an NMR tube, capped, and sealed with electrical tape. The mixture was analyzed by ^{1}H and ^{31}P NMR, which indicated no consumption of **4** and no appreciable reaction of [**1**•Br]Br (>95% of integrable peaks corresponding to [**1**•Br]Br).

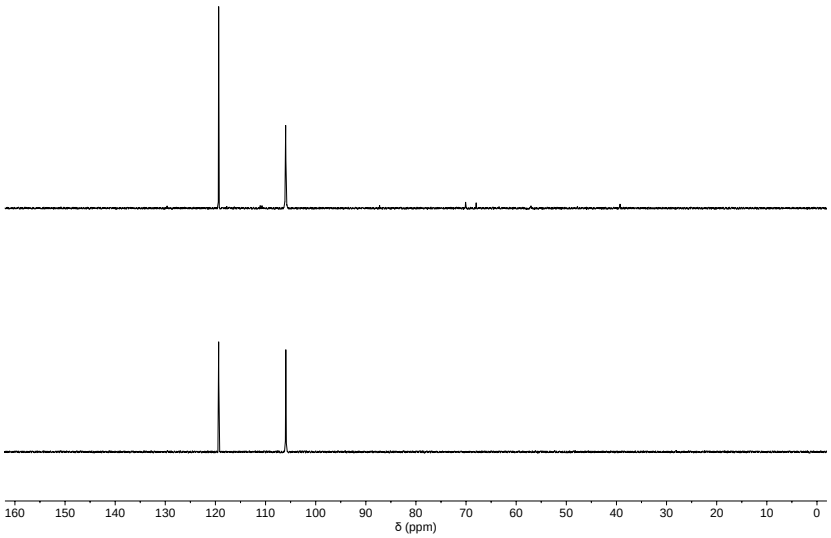


Figure S7. Stacked ^{31}P NMR showing mixture of [**1**•Br]Br and **4** (top) and [**1**•Br]Br (bottom).

F. Proposed Catalytic Cycle

On the basis of the preceding results and literature precedent, the full catalytic cycle below is proposed (using the coupling of **2**, **4**, and **9** as representative examples). First, **1**•[O] is reduced by Ph_2SiH_2 to yield **1**, which undergoes reaction with DEMBM to form [**1**•Br]$^+$. Subsequent activation of **2** to acyloxyphosphonium and attack by **9** would furnish amide intermediate **11** and regenerate **1**•[O]. Upon redox cycling to regenerate [**1**•Br]$^+$, amide **11** would undergo activation via an iminoyloxyphosphonium and elimination of **1**•[O] to produce a nitrilium ion, which could be trapped by **4** to generate *N*-imidoyloxypyridinium **13**. Upon rearrangement and rearomatization, 2-amidopyridine **10** would be formed.

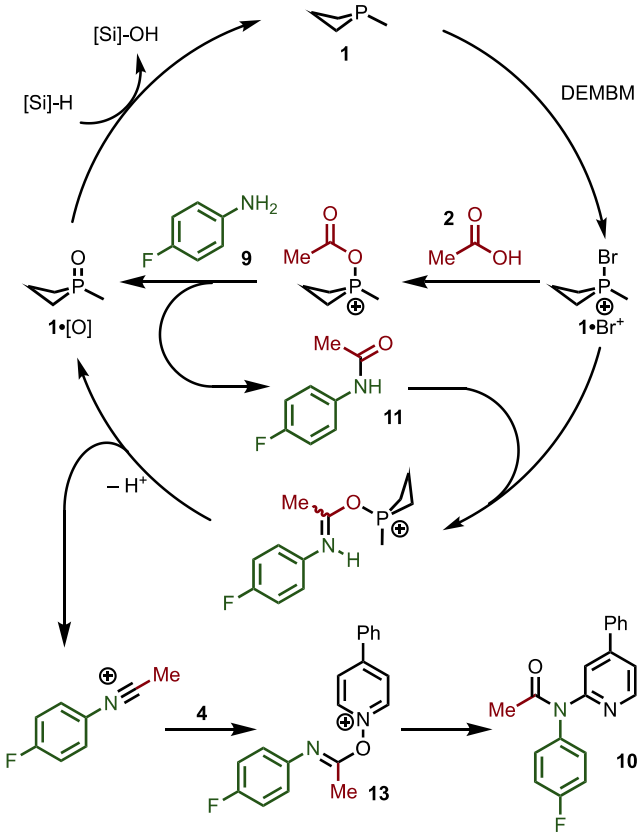
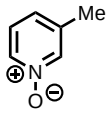


Figure S8. Proposed catalytic cycle for tandem amide coupling and amide activation coupling of amine (**9**), carboxylic acid (**2**), and pyridine *N*-oxide (**4**).

V. Preparation of Substrates

A. Preparation of Pyridine *N*-Oxides

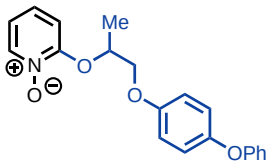


3-Methylpyridine *N*-oxide (**53-SM**).

To a stirred solution of 3-picoline (2.00 mL, 99.5%, 20.5 mmol, 1.00 equiv.) in CH_2Cl_2 (50 mL, 0.40 M) was added in five portions *meta*-chloroperoxybenzoic acid (5.50 g, 77%, 24.5 mmol, 1.20 equiv.). The reaction mixture was stirred for 14 h, then poured into a separatory funnel containing 50 mL $NaOH_{(aq)}$ (1.0 M). The organic layer was separated, and the aqueous layer was back-extracted with 50 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to deliver the product in sufficient purity as a colorless hygroscopic solid (20% yield, 454 mg). The product is fairly water-soluble and more can be extracted from the aqueous phase with washing with CH_2Cl_2. All spectral data was in good agreement with that previously published.[7] Note that the product is very hygroscopic and should be stored in a desiccator and used quickly. Commercial sources are unreliable with respect to hydration.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.98 (d, *J* = 6.4 Hz, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 139.28, 136.86, 136.56, 127.21, 125.40, 18.31.



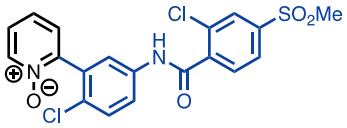
Pyriproxyfen *N*-oxide (**54-SM**).

To a stirred solution of pyriproxyfen (2.00 g, 98%, 6.10 mmol, 1.00 equiv.) in CH_2Cl_2 (30 mL, 0.20 M) was slowly added *meta*-chloroperoxybenzoic acid (1.44 g, 77%, 6.40 mmol, 1.05 equiv.). The reaction mixture was stirred for 18 h, then poured into a 125 mL separatory funnel and washed with CH_2Cl_2 (15 mL). The organic layer was washed with 1M $NaOH_{(aq)}$ (50 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated on rotary evaporator. The crude material was purified by column chromatography on silica gradient eluted with 2-5% MeOH/CH_2Cl_2, yielding the product in 95% purity as a very viscous colorless liquid (61% yield, 1.26 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 6.5, 1.6 Hz, 1H), 7.30 (td, *J* = 7.3, 1.8 Hz, 2H), 7.23 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.06 – 7.03 (m, 1H), 6.98 – 6.90 (m, 5H), 6.84 – 6.80 (m, 2H), 5.25 (pd, *J* = 6.4, 4.1 Hz, 1H), 4.27 – 4.11 (m, 2H), 1.58 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.44, 154.67, 150.79, 140.66, 129.78, 127.37, 122.71, 120.89, 119.15, 117.87, 115.75, 115.06, 76.10, 71.71, 17.33.

HRMS (ESI) calculated for $C_{20}H_{20}NO_4$ $[M+H]^+$ 338.1387, found 338.1395.



Vismodegib *N*-oxide (**55-SM**).

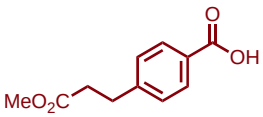
To a stirred solution of vismodegib (973 mg, 98%, 2.31 mmol, 1.00 equiv.) in CH_2Cl_2 (11.5 mL, 0.20 M) was slowly added *meta*-chloroperoxybenzoic acid (545 mg, 77%, 2.43 mmol, 1.05 equiv.). The reaction mixture was stirred for 18 h, then poured into 25 mL of 1M $NaOH_{(aq)}$, washing with CH_2Cl_2 (25 mL). The white biphasic suspension was filtered through filter paper in a Büchner funnel, and the solids were washed with water (25 mL). The collected solids were transferred to a 40 mL vial and dried under high vacuum at 50 ºC overnight, yielding the product as a fluffy colorless solid (650 mg, 65% yield). The product was used without further purification. Note that the organic (CH_2Cl_2) layer contains some product, as well as impurities. The product can be recovered by concentration of the organic layer and suspension in water/Et_2O if desired.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.98 (brs, 1H), 8.37 (d, J = 6.4 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.01 (dd, J = 8.0, 1.7 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 8.8, 2.5 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 7.7, 2.1 Hz, 1H), 7.51 (ddd, J = 8.5, 6.5, 2.1 Hz, 1H), 7.43 (td, J = 7.7, 1.2 Hz, 1H), 3.34 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 163.92, 146.51, 143.16, 140.85, 139.54, 137.59, 133.13, 130.95, 129.95, 129.76, 128.14, 127.98, 127.77, 126.63, 125.98, 124.95, 121.95, 121.59, 43.10.

HRMS (ESI) calculated for $C_{19}H_{15}Cl_2N_2O_4S$ $[M+H]^+$ 437.0124, found 437.0127.

B. Preparation of Carboxylic Acids



Methyl 3-(4-carboxyphenyl)propionate (**21-SM**).

Prepared according to literature procedure.[8] To a stirred solution of 3-(4-carboxyphenyl)propionic acid (2.00 g, 98%, 10.1 mmol, 1.00 equiv.) in MeOH (20 mL, 0.50 M) in a 100 mL pear-shaped flask was added thionyl chloride (37.0 μL, 0.505 mmol, 0.050 equiv.). The reaction mixture was stirred under a balloon of N_2 for 18 h, and then concentrated by rotary evaporator. The crude was suspended in Et_2O (100 mL) and extracted with saturated $NaHCO_{3(aq)}$ (2x50 mL) and water (50 mL). The aqueous extracts were transferred to a 500 mL Erlenmeyer flask and cooled in an ice bath with stirring. Concentrated HCl was added by pipette to reach pH 1. The precipitated white solid was collected by vacuum filtration over filter paper in a Büchner funnel, and the filter-cake was washed with 100 mL water. The collected solids were transferred to a 40 mL vial and dried under high-vac to yield the product as a flaky white solid (1.72 g, 82% yield). All spectral data was in good agreement with that previously published.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 1H), 3.03 (t, *J* = 7.7 Hz, 1H), 2.67 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.13, 171.43, 147.00, 130.64, 128.63, 127.60, 51.91, 35.25, 31.07.

VI. References

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VII. NMR Spectra of Products and Substrates