Nickel-Catalyzed Reductive Arylation of Redox Active Esters for the Synthesis of α-Aryl Nitriles – Role of a Chlorosilane Additive

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Supporting Information 1: Experimental Data

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A. General Information

Unless otherwise noted, all reactions were set up on the benchtop and run under an inert atmosphere of N_2 or Ar using flame-dried glassware and anhydrous solvents. CH_2Cl_2, Et_2O, MeCN, PhMe, and THF were purchased as HPLC-grade (inhibitor-free) from Caledon or Sigma–Aldrich, and were dried using a PureSolv MD 5 solvent purification system and used without further manipulation. DMA was purchased from Acros as Extra-Dry (Cat. #: AC396350010) with or without molecular sieves and were used as received.[1] $NiCl_2$bpy was prepared according to a literature report,[2] and was kept on the benchtop open to air. Zn dust was activated with dilute HCl and was left on the benchtop open to air for periods up to 12 months with no decrease in efficacy.[3] TMSCl (>98%) was purchased from Sigma–Aldrich and used as received. For bottles older than 3 months, or if a pink color is evident, TMSCl was distilled over CaH_2 and kept under an atmosphere of Ar before use. All other commercial reagents and starting materials were used as received. Compounds were purified by flash column chromatography using SiliCycle SilicaFlash P60 silica gel.

GC-MS data was obtained on a Shimadzu GCMS-QP2010 SE; yields represent peak areas calibrated against each compound's response factor relative to n-dodecane internal standard. ^{1}H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz, Agilent DD2 500 MHz, or Bruker AvanceIII 400 MHz spectrometers. TLC samples were run on EMD Millipore TLC Silica gel 60 F254 plates and were visualized by UV or by staining with standard $KMnO_4$. IR spectra were obtained on a PerkinElmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. Melting points were obtained on a Fisher-Johns Melting Point Apparatus. High-resolution mass spectra (HRMS) were recorded on a JEOL AccuTOF JMS-T1000LV mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source.

B. Optimization Details

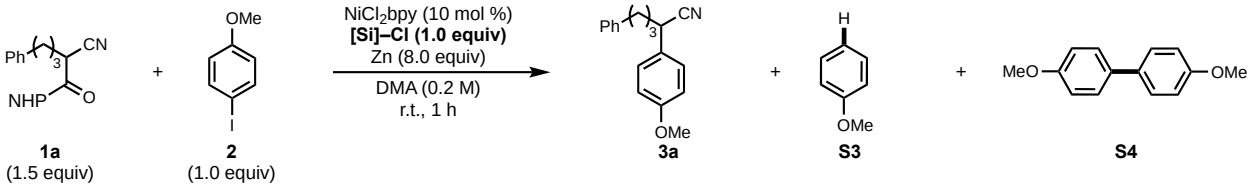
Procedure for optimization reactions on a 0.1 mmol scale: An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. NHP ester (0.15 mmol, 1.5 equiv), 4-iodoanisole (23 mg, 0.20 mmol, 1.0 equiv), Zn dust (52 mg, 0.80 mmol, 8.0 equiv), and $NiCl_2$bpy (2.9 mg, 0.010 mmol, 10 mol %) were added on the bench top. The tube was sealed with a septum and electrical tape and evacuated and backfilled with N_2 (x3). A solution of TMSCl (36 μL, 0.30 mmol, 3.0 equiv) in DMA (0.5 mL, 0.2 M) was then added to the tube containing the solids in one portion and the reaction mixture was stirred vigorously[4] at room temperature (23–25 °C). After 60 min, the reaction was exposed to air, *n*-Dodecane (23 μL, 0.1 mmol, 1.0 equiv) was added as an internal standard and the reaction mixture was diluted with EtOAc, quenched with 1M HCl, and extracted with EtOAc (x2). The mixture was passed directly over a short plug of silica gel before an aliquot of the crude filtered solution was taken for GC-MS analysis.

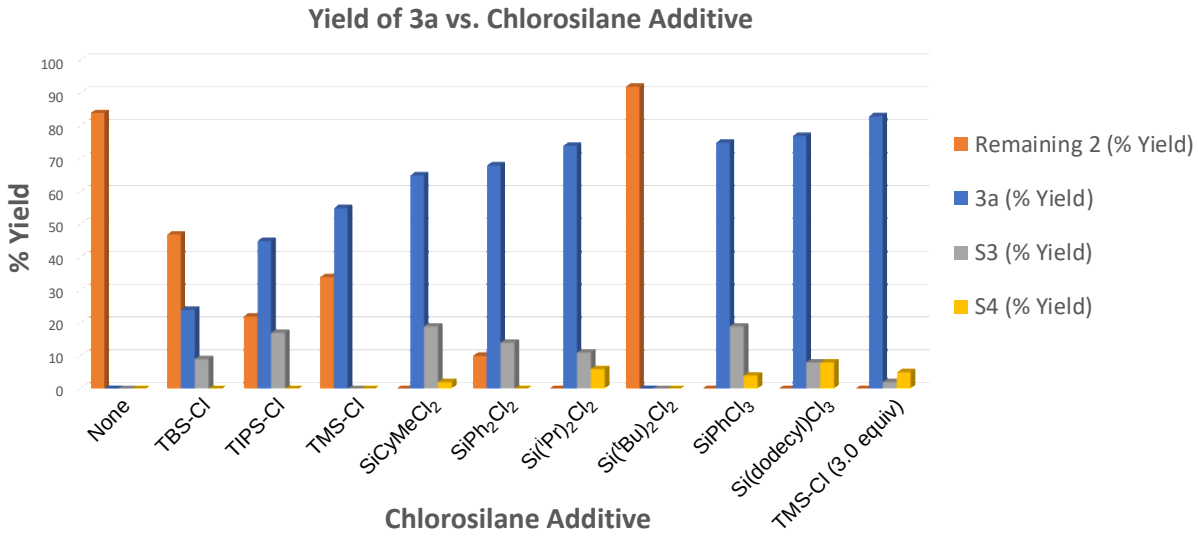
Note: For reactions that were monitored by ^{1}H NMR, 1,3,5-trimethoxybenzene (17 mg, 0.10 mmol, 1.0 equiv) was added at the beginning of the reaction with the other solids. After the

workup, the crude mixture was concentrated under reduced pressure and an aliquot was taken for ^{1}H NMR analysis.

C. Optimization of Reaction Parameters

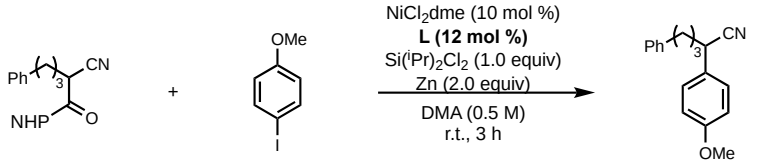
Figure S1. Evaluation of chlorosilane additives[a]





[a] yield determined by GC-MS using dodecane as an internal standard

Figure S2. Evaluation of ligand[a]



1a (1.5 equiv) + **2** (1.0 equiv) → **3a**

Entry	Ligand	**3a** (% Yield)	Remaining **2** (% Yield)
1	bpy	53	19
2	L2	0	57
3	L3	0	59
4	L4	0	96
5	L5	49	49
6	L6	26	51
7	L7	33	39
8	L8	35	67
9	L9	0	100
10	L10	48	45
11	L11	0	99

[a]yield determined by GC-MS using dodecane as an internal standard. The remaining mass balance of ArI **2** consists of **S3** and/or **S4**.

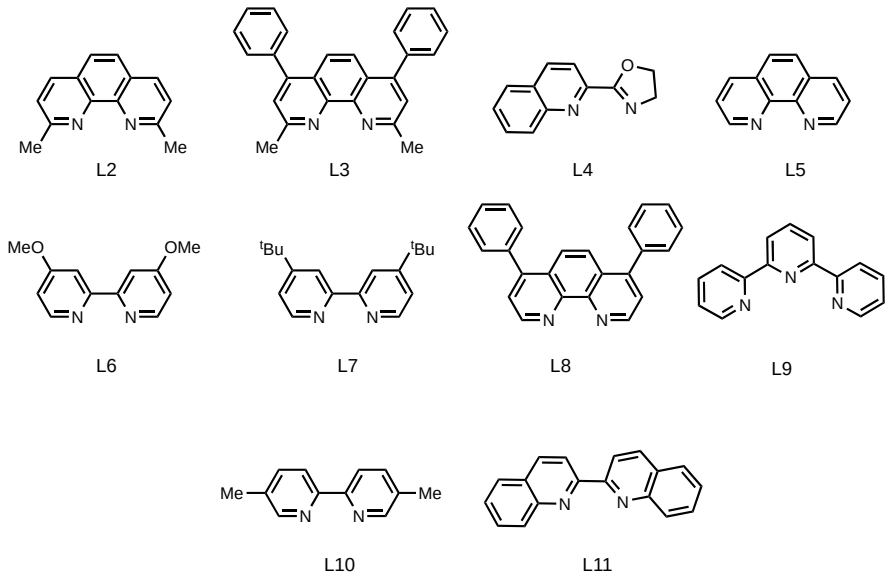
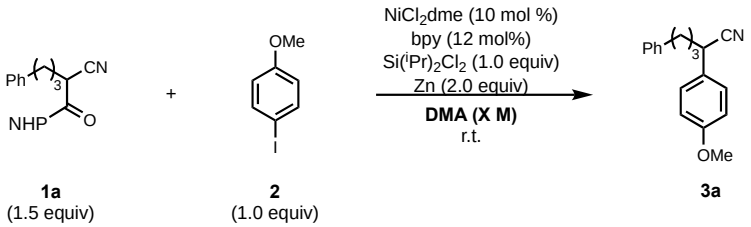


Figure S3. Evaluation of solvent concentration[a]

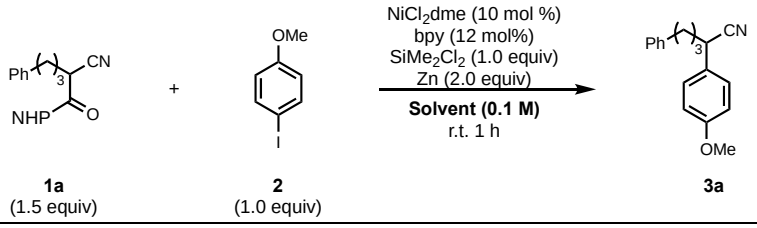


1a (1.5 equiv) + **2** (1.0 equiv) → **3a**

Entry	Concentration (M)	% yield (**3a**)
1	0.05	18
2	0.1	35
3	0.2	61
4	0.5	60

[a]yield determined by GC-MS using dodecane as an internal standard

Figure S4. Evaluation of reaction solvent[a]

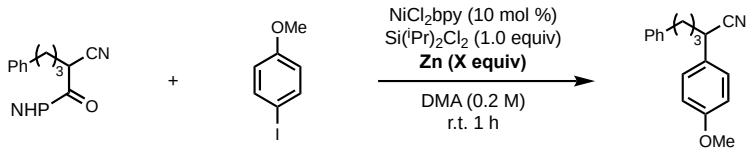


1a (1.5 equiv) + **2** (1.0 equiv) → **3a**

Entry	Solvent	**3a** (% Yield)
1	DMA	45
2	ACN	0
3	Benzene	0
4	DMF	0
5	1,4-dioxane	0
6	$PhCF_3$	0
7	PhMe	0
8	MeOH	0
9	DME	0
10	NMP	27
11	DMSO	0
12	DCM	0
13	THF	2

[a]yield determined by GC-MS using dodecane as an internal standard

Figure S5. Evaluation of Zn equivalents[a]



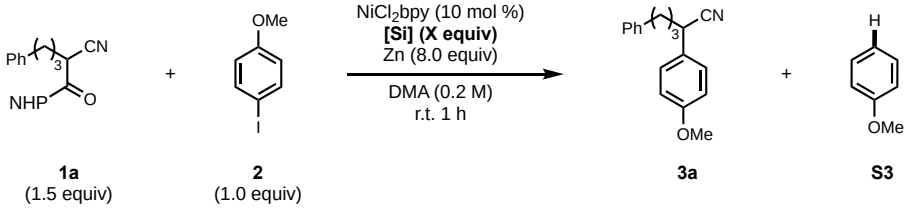
1a (1.5 equiv) **2** (1.0 equiv) **3a**

Entry	Zn (equiv)	**3a** (% Yield)	Remaining **2** (% Yield)
1	2	53	17
2	4	65	0
3	6	70	0
4	8	79	0
5	10	80	0

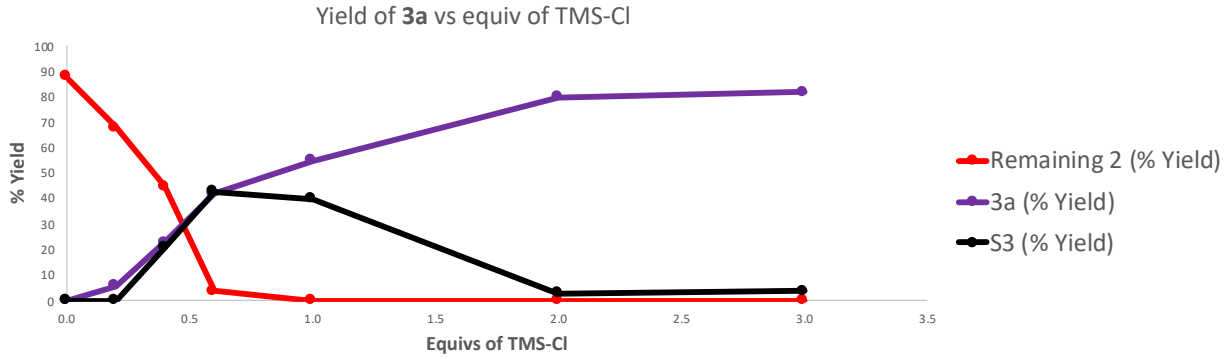
[a]yield determined by GC-MS using dodecane as an internal standard

D. Mechanistic Studies

Figure S6. Product distribution as a function of number of equivalents of TMSCl[a]

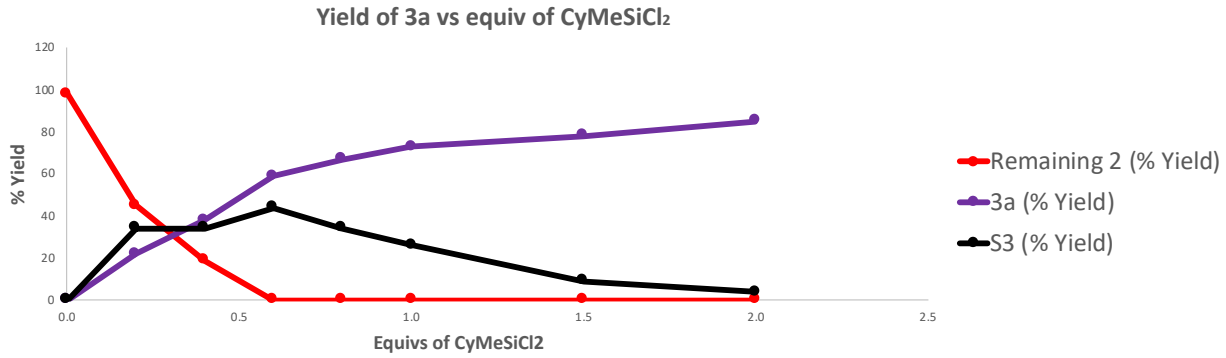


1a (1.5 equiv) **2** (1.0 equiv) **3a** **S3**



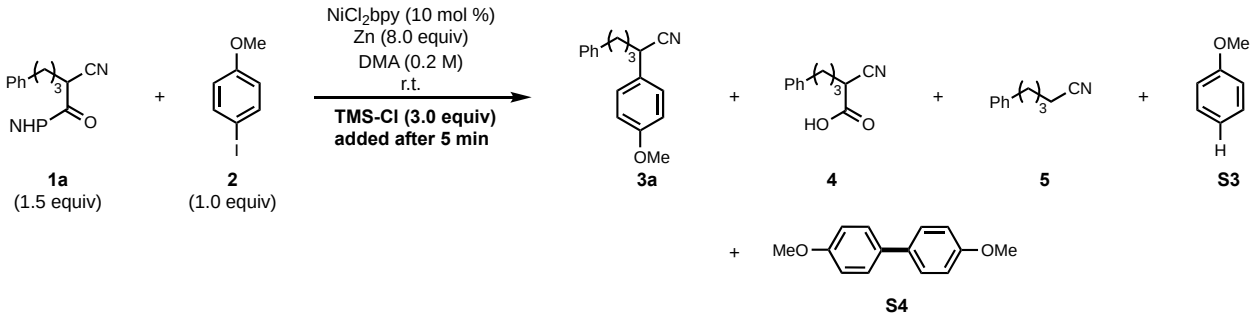
[a]yield determined by GC-MS using dodecane as an internal standard

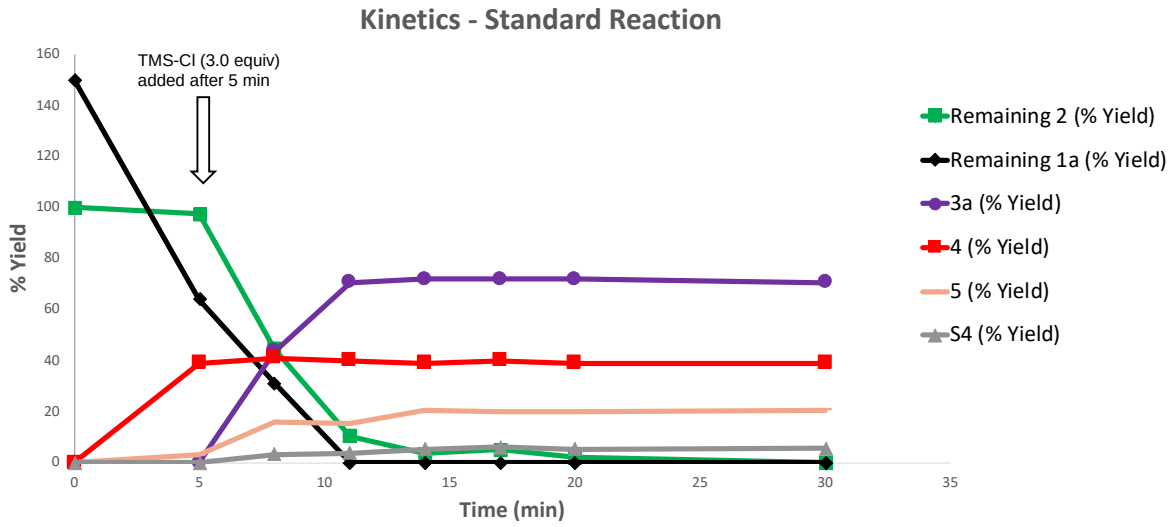
Figure S7: Product distribution as a function of number of equivalents of CyMeSiCl2[a]



[a]yield determined by GC-MS using dodecane as an internal standard

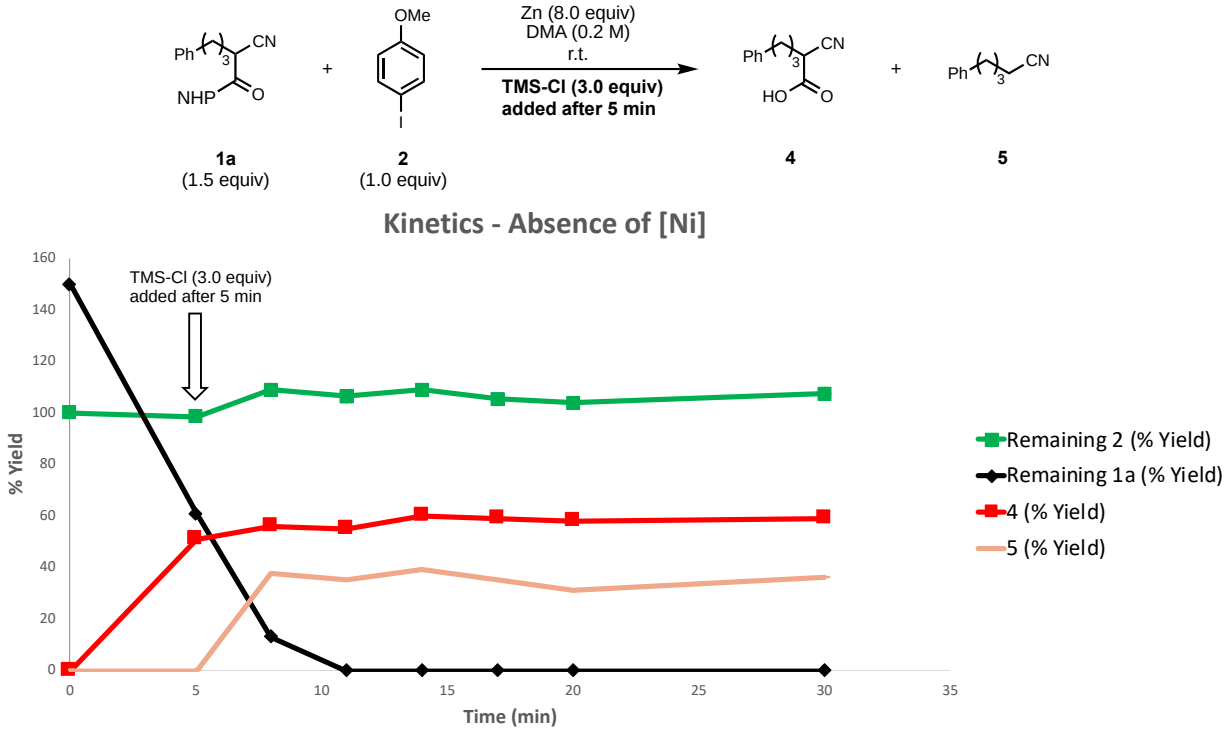
Figure S8. Reaction kinetics under standard conditions, with addition of TMSCl after 5 minutes[a]





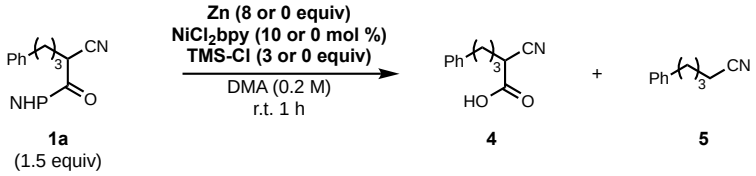
[a]Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard

Figure S9. Reaction kinetics in the absence of $NiCl_2$bpy, with addition of TMSCl after 5 minutes[a]



[a]Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard

Figure S10. Evaluation of the stability of **1a** in the presence of various reaction components[a]



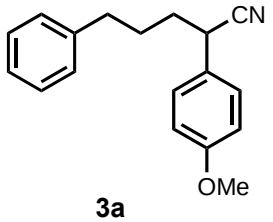
Entry	$NiCl_2$bpy (10 mol %)	TMSCl (3 equiv)	Zn (8 equiv)	**Remaining 1a**	**4**	**5**	NHP mass balance
1	yes	yes	no	137	16	0	153
2	yes	no	yes	71	76	6	153
3	no	yes	yes	0	75	43	118
4	no	yes (0.5 equiv)	yes	0	80	32	112
5	no	no	yes	117	36	0	153
6	no	yes	no	124	18	0	142
7	yes	no	no	118	30	0	148
8	yes	yes	yes	0	32	62	94

[a]yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. The mass balance of the NHP ester component may be lower due to loss of **4** in the aqueous layer during work up of the aliquots.

E. Reductive Arylation of NHP Esters: General Procedure 1

Representative procedure for a 0.2 mmol scale reaction: An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. NHP ester (0.30 mmol, 1.5 equiv), aryl iodide (0.20 mmol, 1.0 equiv), Zn dust (0.10 g, 1.6 mmol, 8.0 equiv), and $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv) were added to the tube while open to air. The tube was sealed with a septum and electrical tape and evacuated and backfilled with N_2 (x3). A solution of TMSCl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M) was then added in one portion and the solution was stirred vigorously[4] at room temperature (23–25 °C). After 60 min, the reaction was exposed to air, diluted with EtOAc, quenched with 1M HCl, and extracted with EtOAc (x2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel to afford the desired product.

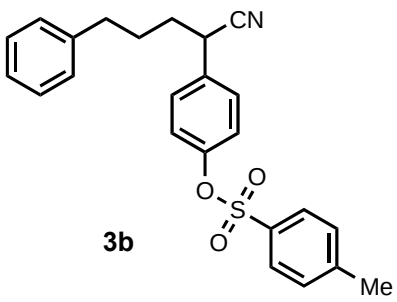
Product Characterization



3a

(*R*)-2-(4-methoxyphenyl)-5-phenylpentanenitrile (**3a**) was prepared according to **general procedure 1** but was run on a 0.5 mmol scale. The mixture was purified by column chromatography on silica gel (slow gradient 0–20% EtOAc/hexanes) to afford a mixture of desired product and reduced NHP **5**, which was removed by heating the sample at 120 °C under high vacuum (1 mbar) for 20 minutes to afford 92 mg (70% yield) of the desired compound as a clear oil.

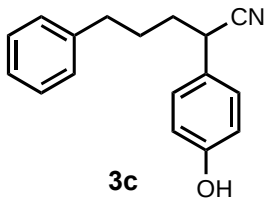
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.30–7.27 (m, 2H), 7.23–7.18 (m, 3H), 7.16–7.13 (m, 2H), 6.91–6.87 (m, 2H), 3.81 (s, 3H), 3.73 (dd, *J* = 8.3, 6.0 Hz, 1H), 2.65 (t, *J* = 7.2 Hz, 2H), 1.97–1.74 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 159.4, 141.3, 128.6, 128.5, 127.9, 126.2, 121.2, 114.5, 55.5, 36.6, 35.4, 35.2, 28.7 ppm; $\mathbf{R_f}$ = 0.32 (100% PhMe; $KMnO_4$, UV); **HRMS** *m/z* (DART): calcd for $C_{18}H_{20}NO$ (M+H) 266.1539 found 266.1541; $\mathbf{I_R}$ **(neat):** 2930, 2860, 2240, 1735, 1512, 1249, 1030, 830, 699 cm^{-1}.



3b

4-(1-cyano-4-phenylbutyl)phenyl 4-methylbenzenesulfonate (**3b**) was synthesized according to **general procedure 1**, and was purified by column chromatography on silica gel (very slow gradient of 0–20% EtOAc/hexanes) to afford 48 mg (59% yield) of the desired product as a white solid.

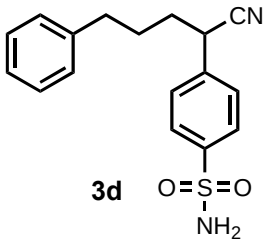
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.72–7.68 (m, 2H), 7.32–7.26 (m, 4H), 7.23–7.18 (m, 3H), 7.14–7.11 (m, 2H), 7.00–6.97 (m, 2H), 3.74 (dd, *J* = 8.4, 5.7 Hz, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.95–1.70 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 149.4, 145.7, 141.1, 134.8, 132.3, 130.0, 128.7, 128.7, 128.6, 128.5, 126.3, 123.2, 120.4, 36.9, 35.2, 35.2, 28.6, 21.9 ppm; **R_f:** 0.36 (20% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{24}H_{27}N_2O_3S$ ($M+NH_4$) 423.1737; found 423.1741; **IR (neat):** 3077, 3030, 2936, 2240, 1596, 1500, 1458, 1373, 1175 cm^{-1}; **Melting Point:** 83–85 °C.



3c

2-(4-hydroxyphenyl)-5-phenylpentanenitrile (**3c**)[5] was prepared according to **general procedure 1**, and was purified by two rounds of column chromatography on silica gel. 1st column: slow gradient 0–20% EtOAc/Hexanes, product was contaminated with phthalimide **S2**. Purified further by column chromatography on silica gel. 2nd column: gradient 0–20% EtOAc/PhMe), afforded 22 mg (43% yield) of the desired product as a yellow oil.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.30–7.25 (m, 2H), 7.22–7.13 (m, 5H), 6.84–6.89 (m, 2H), 3.71 (dd, *J* = 8.3, 5.8 Hz, 1H), 2.65 (t, *J* = 7.2 Hz, 2H), 1.97–1.70 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 155.6, 141.3, 128.7, 128.6, 128.5, 127.9, 126.2, 121.2, 116.0, 36.6, 35.4, 35.2, 28.7 ppm; **R_f:** 0.57 (20% EtOAc/PhMe; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{17}H_{21}N_2O$ ($M+NH_4$) 269.1648; found 269.1647; **IR (neat):** 3373, 3026, 2927, 2861, 2244, 1614, 1597, 1514, 1452, 1218, 1174, 689 cm^{-1}.

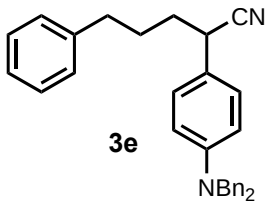


3d

4-(1-cyano-4-phenylbutyl)benzenesulfonamide (**3d**) was prepared according to **general procedure 1** and was purified by column chromatography on silica gel (slow gradient 0–40% EtOAc/Hexanes). The product was stripped of residual DMA by sonicating in DCM:Hexanes and left under high-vac for 24 hours to afford 47 mg (75% yield) of a white solid.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.93 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.31–7.27 (m, 2H), 7.22–7.18 (m, 1H), 7.16–7.12 (m, 2H), 5.01 (br s, 2H), 3.86 (dd, *J* = 8.4, 5.8

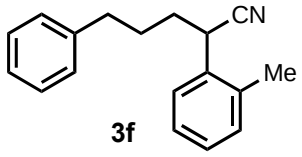
Hz, 1H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.01–1.74 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 142.0, 140.9, 140.9, 128.7, 128.5, 128.2, 127.5, 126.4, 119.9, 37.3, 35.1, 35.1, 28.6 ppm; **R_f:** 0.34 (40% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{17}H_{22}N_3O_2S$ (M+NH_4) 332.1427; found 332.1429; **IR (neat):** 3364, 3263, 3027, 2925, 2861, 2241, 1600, 1325, 1156, 750, 697 cm^{-1}; **Melting Point:** 94–96 °C.



3e

2-(4-(dibenzylamino)phenyl)-5-phenylpentanenitrile (**3e**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (gradient 0–75% PhMe/Hexanes) to afford a mixture of desired product and reduced NHP **5** which was removed by heating the sample at 120 °C under high vacuum (1 mbar) for 20 minutes to afford 49 mg (57% yield) of the desired product as a tan solid.

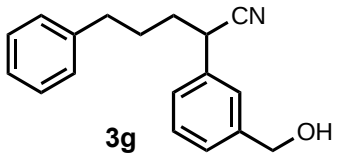
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.35–7.31 (m, 4H), 7.29–7.26 (m, 3H), 7.26–7.22 (m, 5H), 7.20–717 (m, 1H), 7.15–7.13 (m, 2H), 7.08–7.04 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 4.65 (s, 4H), 3.64 (dd, *J* = 8.5, 5.6 Hz, 1H), 2.64 (t, *J* = 7.1 Hz, 2H), 1.95–1.73 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 148.8, 141.3, 138.2, 128.7, 128.4, 128.4, 128.1, 127.0, 126.6, 126.0, 123.5, 121.4, 112.7, 54.3, 36.3, 35.2, 35.1, 28.6 ppm; **R_f:** 0.34 (40% PhMe/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{31}H_{31}N_2$ (M+H) 431.2482; found 431.2473; **IR (neat):** 3059, 3022, 2949, 2933, 2862, 2239, 1951, 1614, 1603, 1521, 1449, 1239, 727, 694 cm^{-1}; **Melting Point:** 86–87 °C.



3f

5-phenyl-2-(*o*-tolyl)pentanenitrile (**3f**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–10% EtOAc/Hexanes) to afford 23 mg (46% yield) of the desired product as a light brown oil.

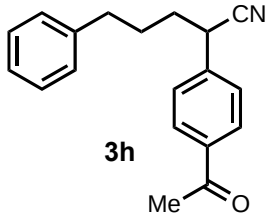
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.42–7.39 (m, 1H), 7.30–7.27 (m, 2H), 7.24–7.21 (m, 2H), 7.20–7.15 (m, 4H), 3.93 (dd, *J* = 8.8, 5.4 Hz, 1H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.98–1.76 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 141.2, 135.0, 134.3, 131.1, 128.6, 128.6, 128.5, 128.2, 127.6, 127.0, 126.2, 35.2, 34.2, 33.9, 28.9, 19.2 ppm; **R_f:** 0.56 (10% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{18}H_{20}N$ (M+H) 250.1590; found 250.1597; **IR (neat):** 3026, 2928, 2860, 2239, 1603, 1493, 1454, 748, 698 cm^{-1}.



3g

2-(3-(hydroxymethyl)phenyl)-5-phenylpentanenitrile (**3g**): An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. NHP ester (104 mg, 0.300 mmol, 1.50 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), and $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv) were added to the tube while open to air. The tube was sealed with a septum and electrical tape, and evacuated and backfilled with N_2 (x3). 3-Iodobenzyl alcohol (25 μL, 0.200 mmol, 1.00 equiv) was added via microsyringe, followed by a solution of TMSCl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M) in one portion. The reaction mixture was stirred vigorously at room temperature (23–25 °C). After 60 min, TBAF (0.5 mL of 1.0 M solution in THF, 0.5 mmol, 2.5 equiv) was added and the mixture was stirred for 20 minutes. The reaction was then exposed to air, diluted with EtOAc, quenched with 1M HCl, and extracted with EtOAc (x2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (slow gradient of 0–20% EtOAc/Hexanes) to afford 28 mg (53% yield) of the desired product as a brown oil.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.38–7.34 (m, 1H), 7.33–7.27 (m, 4H), 7.24–7.18 (m, 2H), 7.16–7.13 (m, 2H), 4.71 (s, 2H), 3.78 (dd, *J* = 8.4, 5.9 Hz, 1H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.01–1.71 (m, 5H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 142.0, 141.3, 136.2, 129.4, 128.6, 128.5, 126.7, 126.6, 126.2, 125.8, 120.8, 65.0, 37.4, 35.3, 35.2, 28.7 ppm; **R_f:** 0.24 (20% EtOAc:Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{18}H_{23}N_2O$ (M+NH_4) 283.1805; found 283.1809; **IR (neat):** 3411, 3026, 2928, 2861, 2240, 1126, 1603, 1495, 1452, 1029, 699 cm^{-1}.

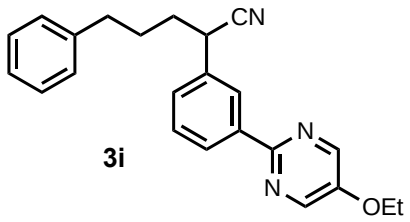


3h

2-(4-acetylphenyl)-5-phenylpentanenitrile (**3h**) was prepared according to **general procedure 1**, and was purified by column chromatography on silica gel (very slow gradient 0–20% EtOAc/Hexanes) to afford 29 mg (53% yield) of the desired product as a clear oil.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.98–7.94 (m, 2H), 7.42–7.38 (m, 2H), 7.30–7.25 (m, 2H), 7.21–7.18 (m, 1H), 7.15–7.12 (m, 2H), 3.85 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.60 (s, 3H), 2.01–1.75 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 197.3, 140.9, 140.8, 136.8, 129.1, 128.5, 128.3, 127.5, 126.2, 120.0, 37.2, 35.0, 35.0, 28.5, 26.7 ppm; **R_f:** 0.30

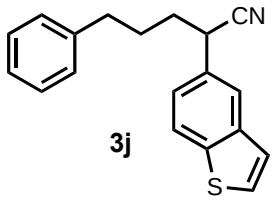
(20% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{19}H_{20}NO$ (M+H) 278.1539; found 278.1549; **IR (neat):** 3027, 2927, 2861, 2242, 1736, 1682, 1607, 1358, 1266, 699 cm^{-1}.



3i

2-(3-(5-ethoxypyrimidin-2-yl)phenyl)-5-phenylpentanenitrile (**3i**) was prepared according to **general procedure 1**, and was purified by column chromatography on silica gel (slow gradient 0–20% EtOAc/Hexanes) to afford 66 mg (92% yield) of the desired product as a clear oil which solidified over time to a white solid.

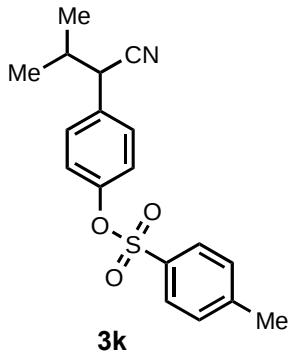
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 8.46 (s, 2H), 8.33–8.30 (m, 2H), 7.48 (tt, *J* = 7.7, 0.6 Hz, 1H), 7.41–7.38 (m, 1H), 7.29–7.24 (m, 2H), 7.20–7.14 (m, 3H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.88 (dd, *J* = 8.5, 6.1 Hz, 1H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.07–1.75 (m, 4H), 1.49 (t, *J* = 7.0 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 156.8, 151.6, 143.8, 141.2, 138.3, 136.2, 129.4, 128.4, 128.4, 128.4, 127.2, 126.4, 126.0, 120.7, 64.6, 37.4, 35.3, 35.1, 28.7, 14.7 ppm; **R_f:** 0.4 (20% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{23}H_{24}N_3O$ (M+H) 358.1914; found 358.1912; **IR (neat):** 3026, 2978, 2918, 2850, 2237, 1746, 1547, 1431, 1275, 698 cm^{-1}; **Melting Point:** 79–80 °C.



3j

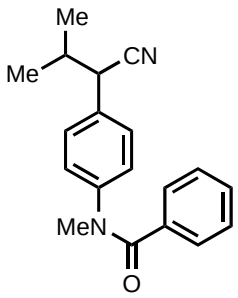
2-(benzo[*b*]thiophen-5-yl)-5-phenylpentanenitrile (**3j**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (very slow gradient 0–20% EtOAc/hexanes) to afford a mixture of desired product and reduced NHP **5** which was removed by heating the sample at 120 °C under high vacuum (1 mbar) for 20 minutes to afford 41 mg (70% yield) of the desired product as a clear oil.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.87 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.78 (d, *J* = 1.7 Hz, 1H), 7.50 (dd, *J* = 5.5, 0.5 Hz, 1H), 7.33 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.30–7.24 (m, 3H), 7.22–7.18 (m, 1H), 7.17–7.13 (m, 2H), 3.91 (dd, *J* = 8.3, 6.3 Hz, 1H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.07–1.77 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 141.1, 140.0, 139.4, 131.9, 128.5, 128.4, 127.8, 126.1, 123.7, 123.3, 123.2, 122.3, 120.9, 37.3, 35.5, 35.1, 28.6 ppm; **R_f:** 0.53 (20 EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{19}H_{21}N_2S$ ($M+NH_4$) 309.1420; found 309.1418; **IR (neat):** 3026, 2926, 2859, 2239, 1602, 1453, 1422, 748, 697 cm^{-1}.



3k

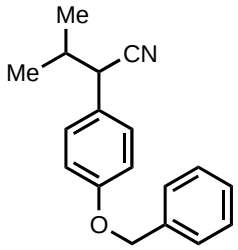
4-(1-cyano-2-methylpropyl)phenyl 4-methylbenzenesulfonate (**3k**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (very slow gradient 0–20% EtOAc/hexanes) to afford 36 mg (54% yield) of the desired product as a clear oil. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.68 (d, *J* = 8.4 Hz, 2H), 7.32–7.29 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.00–6.96 (m, 2H), 3.63 (d, *J* = 6.2 Hz, 1H), 2.44 (s, 3H), 2.12–2.03 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 149.3, 145.7, 134.0, 132.2, 129.9, 129.2, 128.6, 122.9, 199.5, 44.5, 33.8, 21.8, 20.8, 18.7 ppm; **R_f:** 0.33 (20% EtOAc/hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{18}H_{23}N_2O_3S$ (M+NH_4) 347.1424; found 347.1430; **IR (neat):** 3021, 2968, 2248, 1597, 1503, 1373, 1178, 1156, 749 cm^{-1}.



3l

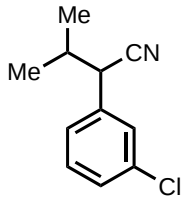
N-(4-(1-cyano-2-methylpropyl)phenyl)-*N*-methylbenzamide (**3l**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (very slow gradient 0–30% EtOAc/Hexanes) to afford 42 mg (72% yield) of the desired product as a white solid.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.29–7.23 (m, 3H), 7.19–7.12 (m, 4H), 7.06–7.02 (m, 2H), 3.58 (d, *J* = 6.3 Hz, 1H), 3.50 (s, 3H), 2.05 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 170.8, 144.8, 135.8, 133.2, 130.0, 128.9, 128.7, 127.9, 127.4, 119.6, 44.7, 38.5, 33.9, 20.8, 18.8 ppm; **R_f:** 0.12 (20% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{19}H_{21}N_2O$ (M+H) 293.16484; found 293.16528; **IR (neat):** 2965, 2880, 2238, 1640, 1608, 1577, 1511, 1361, 1104, 704 cm^{-1}; **Melting Point:** 60–65 °C.



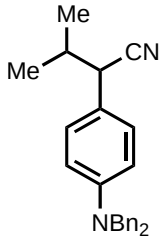
3m

2-(4-(benzyloxy)phenyl)-3-methylbutanenitrile (**3m**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–20% EtOAc/Hexanes) to afford 34 mg (65% yield) of the desired product as a clear oil.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.45–7.42 (m, 2H), 7.41–7.38 (m, 2H), 7.34–7.32 (m, 1H), 7.23–7.20 (m, 2H), 6.99–6.95 (m, 2H), 5.07 (s, 2H), 3.60 (d, *J* = 6.4 Hz, 1H), 2.09 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 158.5, 136.7, 129.0, 128.6, 128.1, 127.5, 127.2, 120.1, 115.1, 70.1, 44.4, 33.8, 20.7, 18.9 ppm; **R_f:** 0.58 (20% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{18}H_{20}NO$ (M+H) 266.1539; found 266.1535; **IR (neat):** 2965, 2231, 1609, 1512, 1240, 1014, 748 cm^{-1}.



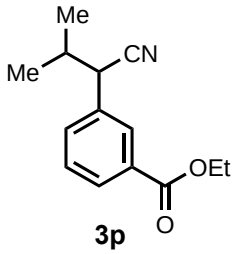
3n

2-(3-chlorophenyl)-3-methylbutanenitrile (**3n**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (gradient 0–15% EtOAc/hexanes) to afford 19 mg (49% yield) of the desired product as a yellow oil.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.32–7.30 (m, 3H), 7.22–7.18 (m, 1H), 3.64 (d, *J* = 6.2 Hz, 1H), 2.17–2.07 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm;
^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ_C 136.9, 134.8, 130.1, 128.3, 128.0, 126.0, 119.2, 44.8, 33.8, 20.8, 18.7 ppm; **R_f:** 0.43 (10% EtOAc/Hexanes; $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{11}H_{13}NCl$ (M+H) 194.0731; found 194.0734; **IR (neat):** 2964, 2921, 2850, 2249, 1597, 1575, 1466, 1430 cm^{-1}.



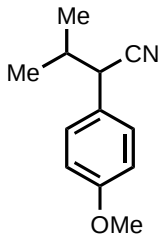
3o

2-(4-(dibenzylamino)phenyl)-3-methylbutanenitrile (**3o**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (gradient 0–75% PhMe/Hexanes) to afford 39 mg (55% yield) of the desired product as a yellow oil.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.36–7.32 (m, 4H), 7.29–7.22 (m, 6H), 7.09–7.05 (m, 2H), 6.74–6.70 (m, 2H), 4.66 (s, 4H), 3.52 (d, *J* = 6.4 Hz, 1H), 2.01–1.99 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 148.9, 138.4, 128.9, 128.8, 127.1, 126.7, 122.7, 120.6, 112.5, 54.4, 44.3, 33.8, 20.8, 19.1 ppm; **R_f:** 0.12 (40% PhMe/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{25}H_{27}N_2$ (M+H) 355.2169; found 355.2165; **IR (neat):** 3028, 2963, 2929, 2871, 2236, 1614, 1519, 1451, 1358, 1230 cm^{-1}



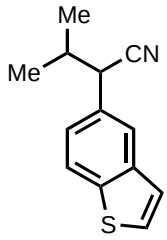
3p

ethyl 3-(1-cyano-2-methylpropyl)benzoate (**3p**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–25% EtOAc/Hexanes) to afford 16 mg (34% yield) of the desired product as a clear oil.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 8.01 (ddd, *J* = 7.7, 1.4, 1.4 Hz, 1H), 7.96–7.94 (m, 1H), 7.53 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.46 (tt, *J* = 7.8, 1.2 Hz, 1H), 4.43–4.34 (m, 2H), 3.72 (d, *J* = 6.3 Hz, 1H), 2.19–2.13 (m, 1H), 1.43–1.39 (m, 3H), 1.07 (dd, *J* = 6.7, 1.5 Hz, 3H), 1.04 (dd, *J* = 6.7, 1.6 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 166.1, 135.5, 132.3, 131.4, 129.4, 129.1, 129.0, 119.5, 61.4, 45.1, 33.9, 20.9, 18.9, 14.5 ppm; **R_f:** 0.33 (10% EtOAc:Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{14}H_{21}N_2O_2$ (M+NH_4) 249.1598; found 249.1598; **IR (neat):** 2966, 2932, 2239, 1716, 1282, 1188, 1106, 1022, 747 cm^{-1}



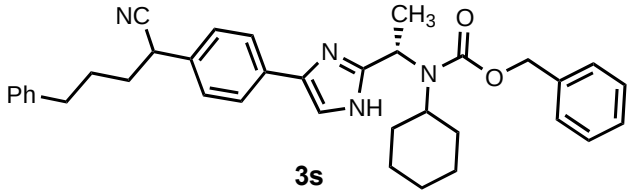
3q

2-(4-methoxyphenyl)-3-methylbutanenitrile (**3q**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–10% EtOAc/Hexanes) to afford 27 mg (72% yield) of the desired product as a clear oil.
Analytical data is consistent with that reported in the literature[6]: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.21 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.60 (J = 6.4 Hz, 1H), 2.13–2.02 (m, 1H), 1.04–1.02 (m, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 159.4, 129.1, 127.1, 120.3, 114.3, 55.5, 44.5, 34.0, 20.8, 19.0 ppm; **R_f:** 0.43 (10% EtOAc/Hexanes; UV, $KMnO_4$) **IR (neat):** 2964, 2933, 2838, 2237, 1612, 1512, 1464, 1249, 1180, 1033, 833 cm^{-1};



3r

2-(benzo[*b*]thiophen-5-yl)-3-methylbutanenitrile (**3r**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (very slow gradient 0–20% EtOAc/hexanes) to afford 24 mg (55% yield) of the desired product as a clear oil. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.88 (ddd, *J* = 8.3, 0.8, 0.8 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 5.4, 0.5 Hz, 1H), 7.34 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.27–7.24 (m, 1H), 3.79 (d, *J* = 6.3 Hz, 1H), 2.24–2.14 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 140.0, 139.4, 131.3, 127.8, 124.0, 123.9, 123.0, 123.0, 120.2, 45.3, 34.1, 21.0, 19.0 ppm; **R_f:** 0.63 (20% EtOAc/hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{13}H_{17}N_2S$ ($M+NH_4$) 233.1107; found 233.1106; **IR (neat):** 3018, 2964, 2928, 2238, 1464, 1439, 1215, 1051, 752 cm^{-1}

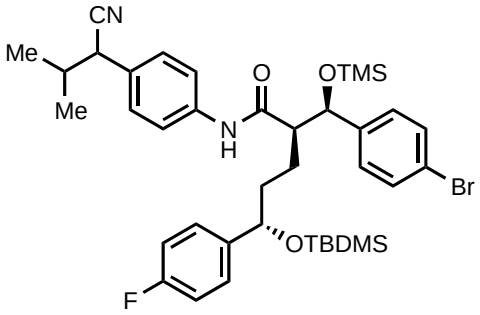


3s

benzyl ((*S*)-1-(4-(4-((*R*)-1-cyano-4-phenylbutyl)phenyl)-1*H*-imidazol-2-yl)ethyl)(cyclohexyl)carbamate (**3s**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (1st: gradient 0–40% EtOAc/hexanes. 2nd: gradient -0–40% EtOAc/hexanes) to afford 32 mg (29% yield) of the desired product as a brown solid. The compound exists as a complex mixture of rotamers.

Analytical data:

^{1}H NMR (600 MHz, dmso-*d6*, 333 K) δ_H 12.07–11.70 (m, 1H), 7.78–7.12 (m, 15H), 5.23–4.94 (m, 3H), 4.22–4.15 (m 1H), 3.52–3.28 (m, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.95–1.79 (m, 3H), 1.78–1.65 (m, 4H), 1.64–1.42 (m, 7H), 1.29–1.19 (m, 1H), 1.12–0.92 (m, 2H). **^{13}C NMR** (125 MHz, dmso-*d6*, 298 K) δ_C 168.1, 155.0, 154.3, 148.5, 148.0, 145.2, 141.5, 138.8, 136.9, 134.7, 134.3, 133.5, 132.7, 131.7, 130.5, 130.0, 129.9 128.3, 128.2, 127.7, 127.4, 126.0, 125.8, 125.2, 124.7, 124.2, 122.4, 121.5, 121.4, 113.2, 91.3, 65.9, 55.8, 55.2, 48.7, 48.2, 35.3, 34.3, 31.5, 30.5, 29.6, 28.5, 25.9, 25.0, 18.1, 17.3; **R_f:** 0.55 (40% EtOAc/Hexanes; UV, $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{13}H_{17}N_2S$ (M+H) 561.3224; found 561.3218; **IR (neat):** 3294, 2930, 2855, 2245, 1668, 1451, 1293, 1245, 1153, 697 cm^{-1}; **Melting Point:** 62–65 °C.

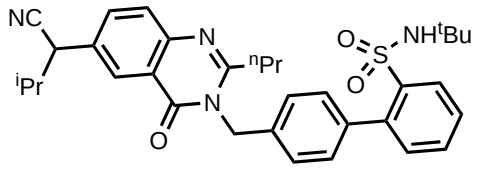


3t

(2*R*,5*S*)-2-((*R*)-(4-bromophenyl)((trimethylsilyl)oxy)methyl)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-(4-(1-cyano-2-methylpropyl)phenyl)-5-(4-fluorophenyl)pentanamide (**3t**)**:** An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. NHP ester (109 mg, 0.400 mmol, 2.00 equiv), (2*R*,5*S*)-2-((*R*)-(4-bromophenyl)(hydroxy)methyl)-5-((*tert*-butyldimethylsilyl)oxy)-5-(4-fluorophenyl)-*N*-(4-iodophenyl)pentanamide (143 mg, 0.200 mmol, 1.00 equiv), Zn dust (0.10 g, 1.6 mmol, 8.0 equiv), and $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv) was added on the bench top. The tube was sealed with a septum and electrical tape and evacuated and backfilled with N_2 (x3). A solution of TMSCl (0.10 mL, 0.80 mmol, 4.0 equiv) in DMA (1.0 mL, 0.2 M) was then added to the tube containing the solids in one portion and the mixture was stirred vigorously at room temperature (23–25 °C). After 60 min, the reaction was exposed to air, diluted with EtOAc, quenched with sat. NH_4Cl, and extracted with EtOAc (x2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (slow gradient 0–20% EtOAc) to afford the desired product (44 mg, 30% yield) as a clear solid (1:1 ratio of diastereomers as determined by ^{1}H NMR).

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.55 (d, *J* = 11.8 Hz, 1H), 7.37–7.33 (m, 2H), 7.29–7.26 (m, 2H), 7.22–7.18 (m, 2H), 7.17–7.11 (m, 4H), 6.97–6.91 (m, 2H), 4.78 (d, *J* = 6.9 Hz,

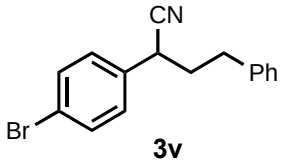
1H), 4.61 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.60–3.57 (m, 1H), 2.43 (dddt, *J* = 8.6, 5.4, 3.6, 1.8 Hz, 1H), 2.09–2.05 (m, 1H), 1.96–1.88 (m, 1H), 1.74–1.56 (m, 3H), 1.04–0.98 (m, 6H), 0.87 (s, 9H), 0.01 (m, 12H), -0.18 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 171.2, 171.2, 161.9 (d, J_{CF} = 244 Hz), 141.6 (d, J_{CF} = 4.8 Hz), 141.5, 141.5, 141.4, 141.4, 137.4, 137.4, 134.3, 131.4, 130.6, 128.5, 128.2, 127.4, 127.4 (d, J_{CF} = 7.9 Hz), 121.6, 121.6, 120.2, 120.1, 119.9, 115.0 (d, J_{CF} = 21.3 Hz), 75.8, 75.8, 74.8, 57.4, 57.4, 44.6, 39.0, 33.8, 29.8, 26.0, 25.3, 25.3, 20.8, 20.8, 18.9, 18.3, 0.1, -4.5, -4.8 ppm; **R_f:** 0.55 (20% EtOAc/hexanes; $KMnO_4$, UV); **HRMS** *m/z* (ESI): calcd for $C_{38}H_{52}BrFN_2NaO_3Si_2$ (M+Na) 761.2576; found 761.2582; **IR (neat):** 3337, 2930, 2856, 2245, 1663, 1603, 1513, 1251 cm^{-1}; **Melting Point:** 60–61 °C.



3u

N-(*tert*-butyl)-4'-((6-(1-cyano-2-methylpropyl)-4-oxo-2-propylquinazolin-3(4*H*)-yl)methyl)-[1,1'-biphenyl]-2-sulfonamide (**3u**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (gradient 0–50% EtOAc/hexanes) to afford 68 mg (60% yield) of the desired product as a white solid.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 8.20 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.76–7.69 (m, 2H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.51–7.46 (m, 3H), 7.29–7.26 (m, 3H), 5.46 (s, 2H), 3.80 (d, *J* = 6.4 Hz, 1H), 3.50 (br s, 1H), 2.77–2.73 (m, 2H), 2.22 (m, 1H), 1.91–1.81 (m, 2H), 1.08 (d, *J* = 6.7 Hz, 6H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.98 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 162.3, 157.6, 147.2, 142.2, 139.3, 139.2, 136.4, 133.9, 133.6, 132.4, 132.0, 130.6, 128.4, 128.1, 128.1, 126.5, 126.4, 120.6, 119.5, 54.6, 46.5, 45.0, 37.3, 34.1, 29.9, 20.9, 20.7, 19.1, 14.0 ppm; **R_f:** 0.57 (50 EtOAc/hexanes; $KMnO_4$, UV); **HRMS** *m/z* (DART): calcd for $C_{33}H_{39}N_4O_3S$ (M+H) 571.2737; found 571.2730; **IR (neat):** 3294, 2970, 2944, 2880, 2245, 1674, 1598, 1467, 1307, 1147, 776 cm^{-1}; **Melting Point:** 205–206 °C.

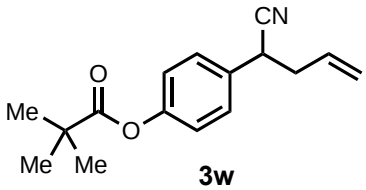


3v

2-(4-bromophenyl)-4-phenylbutanenitrile (**3v**) was prepared according to **general procedure 1**. The mixture as purified by column chromatography on silica gel (slow gradient 0–10% EtOAc/Hexanes) to afford 29 mg (48% yield) of the desired product as a clear oil.

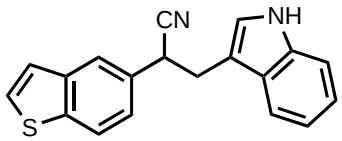
Analytical data: **^{1}H NMR** (500 MHz $CDCl_3$, 298 K): δ_H 7.59–7.56 (m, 2H), 7.40–7.36 (m, 2H), 7.33–7.28 (m, 1H), 7.27–7.24 (m, 4H), 3.77 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.92–2.82 (m, 2H), 2.39–2.27 (m, 1H), 2.25–2.16 (m, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 139.5, 134.6, 132.3, 129.0, 128.7, 128.4, 126.6, 122.2, 120.1, 37.2, 36.0, 32.9 ppm; **R_f:** 0.45 (10% EtOAc/Hexanes; $KMnO_4$);

HRMS *m/z* (DART): calcd for $C_{16}H_{18}N_2Br$ (M+NH_4) 317.0648; found 317.0655**; IR (neat):** 3092, 3069, 2927, 2861, 2239, 1486, 1454, 1070, 1010 cm^{-1}.



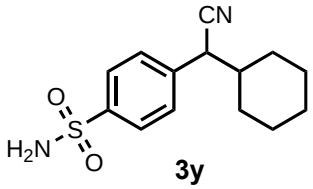
3w

4-(1-cyanobut-3-en-1-yl)phenyl pivalate (**3w**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–10% EtOAc/Hexanes) to afford 30 mg (57% yield) of the desired product as a clear oil.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.36–7.33 (m, 2H), 7.10–7.07 (m, 2H), 5.79 (ddt, *J* = 17.0, 9.8, 7.0 Hz, 1H), 5.22–5.19 (m, 1H), 5.19–5.16 (m, 1H), 3.86 (dd, *J* = 8.0, 6.4 Hz, 1H), 2.68–2.57 (m, 2H), 1.36 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 177.1, 151.0, 132.6, 132.5, 128.5, 122.3, 120.2, 119.7, 40.0, 39.3, 37.1, 27.2 ppm; **R_f:** 0.3 (10% EtOAc/Hexanes; $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{16}H_{20}NO_2$ (M+H) 258.1489; found 258.1509; **IR (neat):** 2977, 2928, 2242, 1749, 1508, 1203, 1108, 894 cm^{-1}.



3x

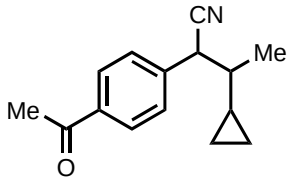
2-(benzo[*b*]thiophen-5-yl)-3-(1*H*-indol-3-yl)propanenitrile (**3x**) was prepared according to **general procedure 1**. The mixture was purified by successive rounds of column chromatography on silica gel (1st: slow gradient 0–30% EtOAc/Hexanes; 2nd: slow gradient 80–100% PhMe/Hexanes) to afford 36 mg (60% yield) of the desired product as a white solid.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 8.05 (br s, 1H), 7.87 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (d, *J* = 5.4, Hz, 1H), 7.39 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.32 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 4.24 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.46 (ddd, *J* = 14.5, 8.5, 0.7 Hz, 1H), 3.37 (ddd, *J* = 14.5, 6.2, 0.8 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 140.0, 139.5, 136.2, 132.1, 127.7, 126.9, 123.7, 123.5, 123.3, 123.1, 122.5, 122.4, 121.3, 119.8, 118.2, 111.4, 111.0, 39.1, 32.8 ppm; **R_f:** 0.23 (PhMe; UV $KMnO_4$); **HRMS** *m/z* (DART): calcd for $C_{19}H_{14}N_2S$ (M+H) 303.0951; found 303.0950; **IR (neat):** 3336, 3058, 2922, 2850, 2246, 1437, 1263, 1235, 736 cm^{-1}; **Melting Point:** 135–138 °C.



3y

4-(cyano(cyclohexyl)methyl)benzenesulfonamide (**3y**) was prepared according to **general procedure 1**. The mixture was purified by successive rounds of column chromatography on silica gel (1st: gradient 0–40% EtOAc/Hexanes; 2nd: slow gradient 20–40% EtOAc/Hexanes) to afford 44 mg (79% yield) of the desired product as a white solid.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.93 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 5.20 (s, 2H), 3.73 (d, *J* = 6.3 Hz, 1H), 1.81–1.73 (m, 5H), 1.69–1.64 (m, 2H), 1.26–1.11 (m, 4H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 141.9, 139.9, 128.4, 127.1, 119.3, 44.2, 42.9, 31.3, 29.5, 25.9, 25.8, 25.8 ppm; **R_f:** 0.27 (40 EtOAc/Hexanes; UV, $KMnO_4$)**; HRMS** *m/z* (DART): calcd for $C_{14}H_{19}N_2O_2S$ (M+H) 279.1162; found 279.1164**; IR (neat):** 3338, 3251, 2929, 2857, 2238, 1599, 1557, 1458, 1322, 1152, 708 cm^{-1}; **Melting Point:** 128–132 °C.

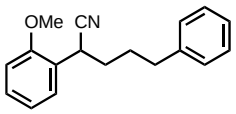


3z

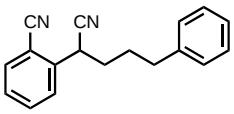
2-(4-acetylphenyl)-3-cyclopropylbutanenitrile (**3z**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (gradient 0–20% EtOAc/hexanes) to afford 30 mg (65% yield) of the desired product as a yellow oil as an inseparable mixture of diastereomers (4:1 by ^{1}H NMR; H_M proton signal for major diastereomer, H_m proton signal for minor diastereomer)

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.96 (d, *J* = 8.3 Hz, $2H_M$, $2H_m$), 7.45 (d, *J* = 8.4 Hz, $2H_m$), 7.41 (d, *J* = 8.4 Hz, $2H_M$), 4.06 (d, *J* = 4.9 Hz, $1H_M$), 3.91 (d, *J* = 5.6 Hz, $1H_m$), 2.62 (s, $3H_m$), 2.61 (s, $3H_M$), 1.36–1.31 (m, $1H_m$), 1.22–1.14 (m, $1H_M$), 1.11 (d, *J* = 6.8 Hz, $3H_m$), 1.05 (d, *J* = 6.7 Hz, $3H_M$), 0.9–0.8 (m, $1H_m$, $1H_M$), 0.60–0.50 (m, $2H_m$, $2H_M$), 0.20–0.11 (m, $2H_m$, $2H_M$) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 197.3, 139.9, 136.7, 128.8, 128.1, 119.1, 44.8, 44.1, 44.0, 43.8, 26.6, 17.9, 16.4, 15.8, 14.8, 5.4, 5.0, 4.3, 3.2 ppm; **R_f:** (0.48 20% EtOAc/hexanes; $KMnO_4$, UV); **HRMS** *m/z* (DART): calcd for $C_{15}H_{18}NO$ (M+H) 228.1383; found 228.1380; **IR (neat):** 3181, 3060, 2239, 1772, 1724, 1683, 1605, 1267, 712 cm^{-1}.

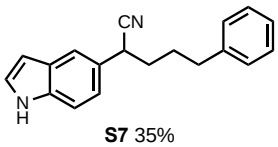
Figure S11: Less tolerated substrates:



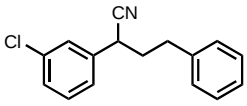
S5 27%



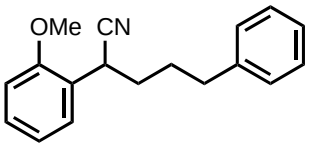
S6 17%



S7 35%



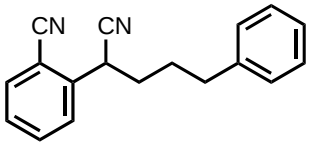
S8 55%



S5

2-(2-methoxyphenyl)-5-phenylpentanenitrile (**S5**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (very slow gradient 0–15% EtOAc/Hexanes) to afford a mixture of desired product and reduced NHP **5** which was removed by heating the sample at 120 °C under high vacuum (1 mbar) for 20 minutes to afford 14 mg (27% yield) of the desired product as a clear oil.

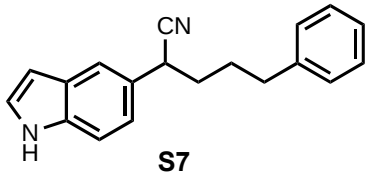
Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.38 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.31–7.26 (m, 3H), 7.21–7.14 (m, 3H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.22–4.18 (m, 1H), 3.83 (s, 3H), 2.65 (ddd, *J* = 8.0, 6.6, 2.3 Hz, 2H), 1.94–1.73 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 156.0, 141.4, 129.3, 128.4, 128.4, 128.3, 125.9, 124.2, 121.2, 120.9, 110.8, 55.4, 35.1, 33.1, 31.2, 28.7 ppm; **R_f:** 0.63 (10% EtOAc/Hexanes; UV, $KMnO_4$); **IR (neat):** 3026, 2935, 2860, 2240, 1600, 1493, 1454, 1438, 1247, 1026, 750, 699 cm^{-1}.



S6

2-(1-cyano-4-phenylbutyl)benzonitrile (**S6**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–25% EtOAc/Hexanes) to afford 9 mg (17% yield) of the desired product as a clear oil.

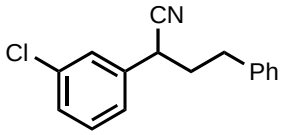
Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.69 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.67–7.64 (m, 2H), 7.46 (ddd, *J* = 7.7, 5.3, 3.4 Hz, 1H), 7.30–7.26 (m, 2H), 7.22–7.18 (m, 1H), 7.18–7.15 (m, 2H), 4.27–4.23 (m, 1H), 2.75–2.64 (m, 2H), 2.03–2.81 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 140.9, 139.6, 133.9, 133.5, 128.9, 128.7, 128.5, 128.4, 126.3, 119.4, 116.8, 111.8, 36.1, 35.1, 35.1, 28.7 ppm; **R_f:** 0.24 (10% EtOAc:Hexanes; UV, $KMnO_4$).



S7

2-(1*H*-indol-5-yl)-5-phenylpentanenitrile (**S7**) was prepared according to **general procedure 1**. The mixture was purified by successive rounds of column chromatography on silica gel (1st: slow gradient 0–30% EtOAc/Hexanes; 2nd: 100% PhMe) to afford 19 mg (35% yield) of the desired product as a clear oil.

Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.27 (br s, 1H), 7.59 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.38 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.31–7.26 (m, 2H), 7.24 (dd, *J* = 3.2, 2.4 Hz, 1H), 7.22–7.18 (m, 1H), 7.17–7.15 (m, 2H), 7.10 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.55 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H), 3.87 (dd, *J* = 8.3, 6.4 Hz, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.06–1.75 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 141.4, 135.3, 128.4, 128.4, 128.2, 127.1, 126.0, 125.3, 121.7, 121.1, 119.5, 111.7, 102.6, 37.4, 35.8, 35.2, 28.7 ppm; **R_f:** 0.26 (100% PhMe; UV, $KMnO_4$); **IR (neat):** 3425, 3019, 2245, 1496, 1454, 1343, 1215, 747 cm^{-1}.



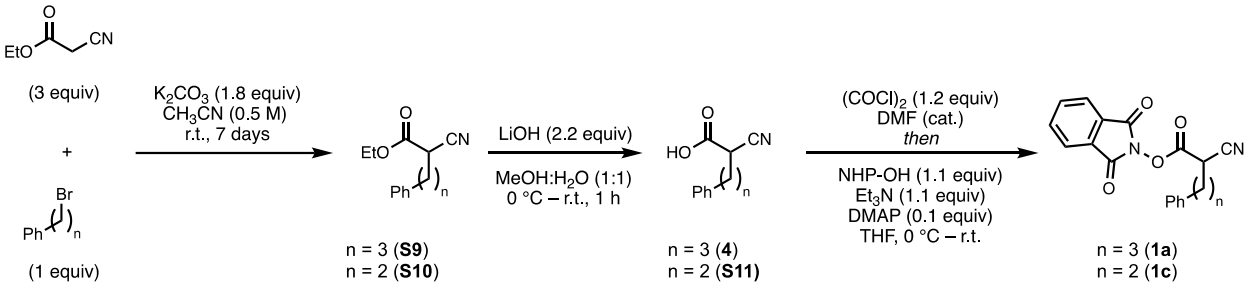
S8

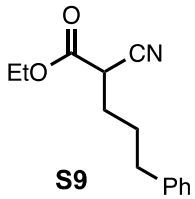
2-(3-chlorophenyl)-4-phenylbutanenitrile (**S8**) was prepared according to **general procedure 1**. The mixture was purified by column chromatography on silica gel (slow gradient 0–10% EtOAc/Hexanes) to afford 28 mg (55% yield) of the desired product as a clear oil.

Analytical data**: ^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.30–7.24 (m, 5H), 7.22–7.12 (m, 4H), 3.66 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.85–2.70 (m, 2H), 2.27–2.03 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 139.4, 137.5, 135.0, 130.4, 128.7, 128.4, 128.4, 127.5, 126.6, 125.4, 119.9, 37.2, 36.2, 32.9 ppm; **R_f:** 0.58 (10% EtOAc/Hexanes; $KMnO_4$).

F. Preparation of NHP Ester Starting Materials

Figure S12: Preparation of **1a** and **1c**

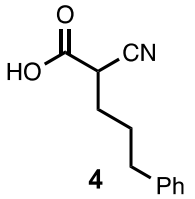




S9

ethyl 2-cyano-5-phenylpentanoate (**S9**)**:** Ethylcyanoacetate (31.9 mL, 300 mmol, 3.00 equiv) was added to a suspension of K_2CO_3 (24.9 g, 180 mmol, 1.80 equiv) in acetonitrile (200 mL) followed by 1-bromo-3-phenylpropane (7.6 mL, 50 mmol, 0.5 equiv). After near complete consumption of the alkyl bromide (determined by ^{1}H NMR, approx. 3 days), another portion of 1-bromo-3-phenylpropane (7.6 mL, 50 mmol, 0.5 equiv) was added. Upon complete consumption of the alkyl bromide (approx. 3 days), the reaction mixture was poured in 1M HCl, and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The excess ethylcyanoacetate was distilled off at 120 °C at a pressure of 1 mbar before the material was further purified by column chromatography on silica gel (slow gradient 0–20% EtOAc in hexanes) to afford 21 g (92% yield) of **S9** as a clear oil which was contaminated with approx. 7% of the byproduct resulting from double alkylation.

Analytical data consistent with that reported in the literature:[7] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.32–7.16 (m, 5H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.49 (m, 1H), 2.69 (t, *J* = 7.4 Hz, 2H), 1.97 (m, 2H), 1.86 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 166.2, 140.9, 128.7, 128.5, 126.3, 116.6, 62.9, 37.6, 35.1, 29.4, 28.5, 14.1 ppm.

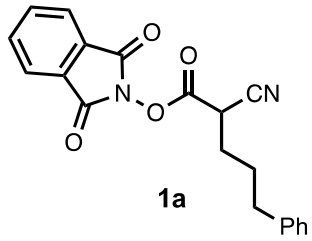


4

2-cyano-5-phenylpentanoic acid (**4**)**: S9** (12.9 g, 55.7 mmol, 1.00 equiv) was dissolved in MeOH (55 mL) and water (55 mL) and cooled to 0 °C. LiOH (2.93 g, 112 mmol, 2.20 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon completion (as determined by TLC, approx. 1 hr), the reaction mixture was quenched with 1M HCl, and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield 9.7 g (86% yield) of **S10** as white solid which was of sufficient purity for use in the next step.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.79 (br s, 1H), 7.38–7.18 (m, 5H), 3.61 (dd, *J* = 7.2, 6.4 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.06–1.81 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 171.3, 140.7, 128.7, 128.5, 126.4, 115.8, 37.5, 35.0, 29.4, 28.4 ppm; **IR (neat):** 2934, 2888, 2539, 2253, 1717, 1600, 1494, 1454, 1421, 1282, 1243, 748, 697 cm^{-1}.

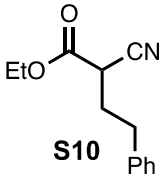
General Procedure 2: Synthesis of N-hydroxyphthalimide esters



1a

1,3-dioxoisoindolin-2-yl 2-cyano-5-phenylpentanoate (**1a**)**: 4** (5.0 g, 25 mmol, 1.0 equiv) was dissolved in DCM (30 mL), and $(COCl)_2$ (2.5 mL, 30 mmol, 1.2 equiv) was added dropwise. 2-4 drops of DMF were then added and the mixture was left to stir at room temperature for 2 hours. Once bubbling had ceased (approx. 2 hr), the reaction mixture was then concentrated under reduced pressure, and the yellow oily residue was dissolved in THF (30 mL) and cooled to 0 °C. N-hydroxyphthalimide (4.4 g, 27 mmol, 1.1 equiv), and DMAP[8] (0.31 g, 2.5 mmol, 0.10 equiv) were added, followed by dropwise addition of NEt_3 (3.8 mL, 27 mmol, 1.1 equiv). The reaction mixture was warmed slowly to room temperature and stirred for 2 hours before being quenched with 1M HCl and extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over MgSO4, and concentrated under reduced pressure. The crude yellow solid was suspended in $CHCl_3$ and sonicated for 2 minutes before being passed through a plug of celite (eluting with $CHCl_3$) to remove excess N-hydroxyphthalimide and concentrated under reduced pressure. The crude material was then passed through a short pad of silica gel eluting with dichloromethane (200–300 mL), followed by 1.5% MeOH in DCM (100 mL)[9] and concentrated under reduced pressure. The oily residue was then dissolved in a minimal amount of EtOAc (~15 mL) before hexanes (~500 mL) was added and stirred vigorously overnight which crashed out the desired product. The solid was then collected by filtration and dried under vacuum to afford 4.9 g (59% yield) of **1a** as a white solid. The purity of this compound can be increased by hot recrystallization using hexanes and EtOAc if desired.

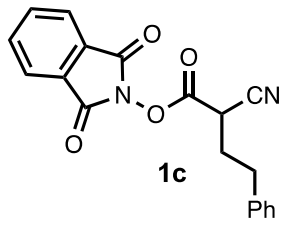
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.34–7.28 (m, 2H), 7.24–7.19 (m, 3H), 3.92 (t, *J* = 6.7 Hz, 1H), 2.76 (t, *J* = 7.4 Hz, 2H), 2.19 (dt, *J* = 8.9, 6.4 Hz, 2H) 2.03 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 163.4, 161.2, 140.6, 135.3, 128.8, 128.8, 128.5, 126.5, 122.4, 114.4, 35.5, 35.0, 30.0, 28.1 ppm; $\mathbf{R}_f$ = 0.9 (2% MeOH/CH_2Cl_2; $KMnO_4$, UV); **IR (neat):** 2961, 2258, 1811, 1788, 1738, 1709, 1464, 1358, 695 cm^{-1}; **Melting point**: 72–75 °C.



S10

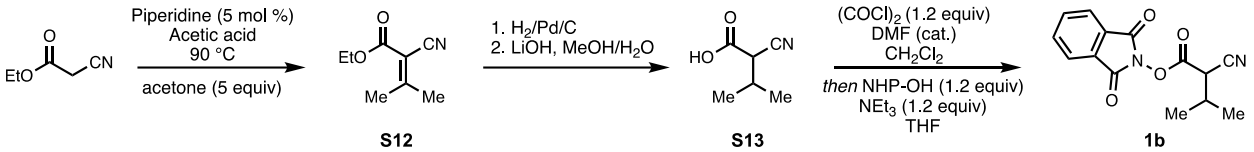
Ethyl 2-cyano-4-phenylbutanoate (**S10**): Ethylcyanoacetate (32 mL, 0.30 mol, 3.0 equiv) was added to a suspension of K_2CO_3 (24.9 g, 180 mmol, 1.80 equiv) in acetonitrile (200 mL) followed by a dropwise addition of (2-bromoethyl)benzene (6.9 mL, 50 mmol, 0.5 equiv). After near complete consumption of the alkyl bromide (as determined by ^{1}H NMR, approx. 3 days), another half equivalent of (2-bromoethyl)benzene (6.9 mL, 50 mmol, 0.5 equiv)) was added. Upon complete consumption of the alkyl bromide (approx. 4 days), the reaction mixture was poured

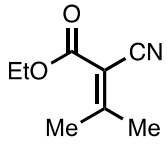
over 1M HCl, and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The excess ethylcyanoacetate was distilled off at 120 °C at a pressure of 1 mmbar before the material was further purified by column chromatography on silica gel (slow gradient 0–20% EtOAc in hexanes) to afford 12 g (54% yield) of **S10** as a clear oil.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 5.87–5.21 (m, 1H), 5.33–5.18 (m, 2H), 4.26 (q, *J* = 7.1 2H), 3.55 (dd, *J* = 7.5, 6.1 Hz, 1H), 2.76–2.61 (m, 2H), 1.31 (t, *J* = 7.1, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 165.5, 131.3, 120.0, 116.0, 62.8, 37.4, 33.8, 13.9 ppm;



1,3-dioxoisoindolin-2-yl 2-cyano-4-phenylbutanoate (**1c**): **S10** (5.0 g, 23 mmol, 1.0 equiv) was dissolved in MeOH (23 mL) and water (23 mL), and the mixture was cooled to 0 °C. LiOH (1.2 g, 51 mmol, 2.2 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon completion (as determined by TLC, approx. 1 hr), the reaction mixture was quenched with 1 M HCl, and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$ and concentrated under reduced pressure to afford 3.6 g (82% yield) of **S11** as a yellow solid which was used directly in the next step according to **general procedure 2**, using **S11** (7.6 g, 40 mmol, 1.0 equiv), CH_2Cl_2 (48 mL), $(COCl)_2$ (4.1 mL, 48 mmol, 1.2 equiv), and DMF (3 drops) followed by THF (80 mL), N-hydroxyphthalimide (7.2 g, 44 mmol, 1.1 equiv), DMAP (0.49 g, 4.0 mmol, 0.10 equiv), and NEt_3 (6.1 mL, 44 mmol, 1.1 equiv). The crude brown solid was suspended in $CHCl_3$, sonicated for 2 minutes before being passed through a plug of celite (eluting with $CHCl_3$) to remove excess N-hydroxyphthalimide, and finally concentrated under reduced pressure. The crude material was then passed through a short pad of silica gel eluting with dichloromethane (200–300 mL), followed by 1.5% MeOH in DCM (100 mL).**Error! Bookmark not defined.** The material was concentrated under reduced pressure to afford 5.5 g (41% yield) of **1c** as an off-white solid.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.93–7.91 (m, 2H), 7.86–7.82 (m, 2H), 7.37–7.26 (m, 5H), 3.86 (d, *J* = 7.1 Hz, 1H), 3.04 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.94 (dt, *J* = 13.8, 8.1 Hz, 1H) 2.51–2.45 (m, 2H) ppm; **^{13}C NMR (**100 MHz, $CDCl_3$, 298 K): δ_C 163.3, 161.0, 138.3, 135.1, 128.9, 128.6, 128.5, 127.0, 124.3, 114.1, 34.6, 32.3, 32.1 ppm; **IR (neat):** 2917, 2262, 1810, 1786, 1739, 1458, 1185, 1114, 875, 693 cm^{-1}; **Melting Point**: 100–102 °C.

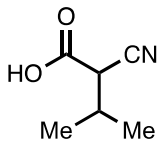
Figure S13: Preparation of **1b**





S12

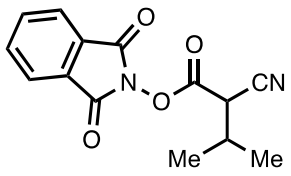
ethyl 2-cyano-3-methylbut-2-enoate (**S12**)**:** Ethylcyanoacetate (5.3 mL, 50 mmol, 1.0 equiv), acetone (18 mL, 0.25 mol, 5.0 equiv), glacial acetic acid (6.3 mL), and piperidine (0.21 mL, 2.5 mmol, 0.050 equiv) were added to a round bottom flask. The flask was sealed with a rubber septum before being submerged in a pre-heated oil bath at 90 °C overnight. Upon completion, the reaction was diluted with EtOAc, and the organic layers were washed with sat. $NaHCO_3$ (x2), brine (x1), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (slow gradient of 10–14% EtOAc in hexanes) to afford 4.8 g (62% yield) of **S12** which eventually solidified to a pale solid.
Analytical data consistent with that reported in the literature:[10] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 4.27 (q, *J* = 7.1 Hz, 2H), 2.40 (d, *J* = 0.6 Hz, 3H), 2.30 (d, *J* = 0.6 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 173.7, 162.0, 115.8, 105.3, 61.8, 27.5, 22.9, 14.2 ppm; $\mathbf{R_f}$ = 0.52 (20% EtOAc:Hexanes; UV, $KMnO_4$).



S13

2-cyano-3-methylbutanoic acid (**S13**)**:** A solution of **S12**(4.8 g, 31 mmol, 1.0 equiv) in EtOAc was added to a flask containing Pd/C (0.5 g, 10% w/w) and the flask was evacuated and backfilled with nitrogen 3 times before ensuring that all of the Pd/C particles were suspended in the solution by adding EtOAc down the side of the flask. 100 mL of MeOH was then added slowly down the side of the flask under a positive pressure of N_2. The flask was then evacuated and backfilled with hydrogen 3 times and hydrogen gas was bubbled through the solution until full conversion of the starting material (as determined by TLC, approx. 2 hours). The solution was then passed over celite, ensuring the filter cake was never dry, and concentrated under reduced pressure. The crude material was dissolved in MeOH (30 mL) and H_2O (30 mL). The mixture was

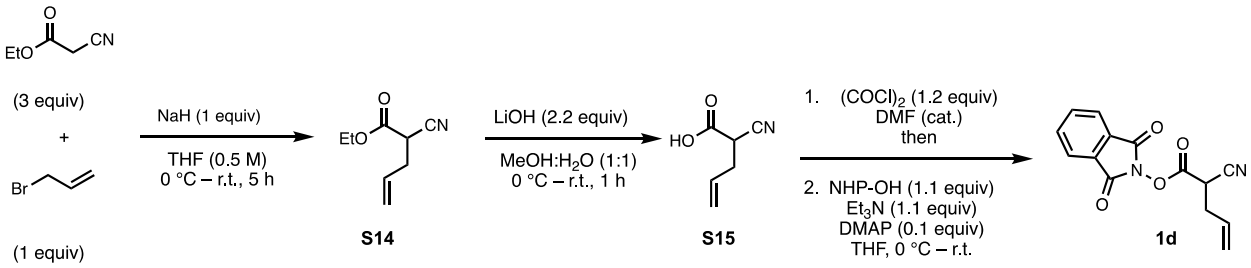
cooled to 0 °C and LiOH (1.6 g, 66 mmol, 2.2 equiv) was added. The reaction was allowed to warm slowly to room temperature and stirred for 2 hours before being poured into 1 M HCl and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1) and concentrated under reduced pressure to afford 3.9 g (98% over 2 steps) of **S13** as a white solid. Analytical data consistent with that reported in the literature.[11] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.82 (br s, 1H), 3.50 (d, *J* = 5.1 Hz, 1H), 2.52–2.41 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 171.3, 114.8, 45.4, 30.2, 20.9, 18.9.

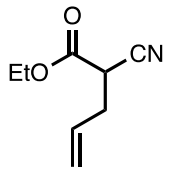


1b

1,3-dioxoisoindolin-2-yl 2-cyano-3-methylbutanoate (**1b**) was prepared according to the general procedure 1 using **S13** (3.9 g, 30 mmol, 1.0 equiv), $(COCl)_2$ (3.0 mL, 36 mmol, 1.2 equiv), DMF (2-3 drops), and DCM (40 mL), followed by THF (40 mL), N-hydroxyphthalimide (5.4 g, 33 mmol, 1.1 equiv), and NEt_3 (4.6 g, 33 mmol, 1.1 equiv) to afford 6.2 g (76% yield) of **1b** as a white solid. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.94–7.89 (m, 2H), 7.85–7.80 (m, 2H), 3.82 (d, *J* = 5.0 Hz, 1H), 2.70–2.58 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 163.0, 161.1, 135.1, 128.6, 124.2, 113.4, 43.1, 31.1, 20.6, 18.7 ppm; **IR (neat):** 2980, 2925, 2254, 1816, 1784, 1708, 1463, 1184, 1134, 972, 693 cm^{-1}; **Melting Point**: 87–89 °C.

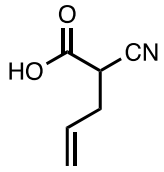
Figure S14. Preparation of **1d**





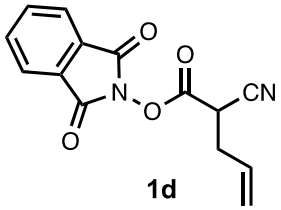
S14

Ethyl 2-cyanopent-4-enoate (**S14**): To a flask containing sodium hydride (2.0 g, 50 mmol, 1.0 equiv) was added THF (100 mL) and the mixture was cooled to 0 °C in an ice bath. Ethylcyanoacetate (16 mL, 150 mmol, 3.0 equiv) was added dropwise and the mixture was stirred at this temperature for 30 minutes before allyl bromide (4.3 mL, 50 mmol, 1.0 equiv) was added. Upon reaction completion (as determined by TLC, approx. 5 h) the reaction was quenched with water and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (gradient 0–20% EtOAc/hexanes) to afford 5.30 g (69% yield) of **S14** as a yellow solid.
Analytical data is consistent with that reported in the literature.[12] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 5.87–5.76 (m, 1H), 5.31–5.18 (m, 2H), 4.31–4.22 (m, 2H), 3.55 (dd, *J* = 7.5, 6.1 Hz, 1H), 2.71–2.65 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 165.5, 131.3, 120.0, 116.0, 62.8, 37.4, 33.8, 13.9 ppm.



S15

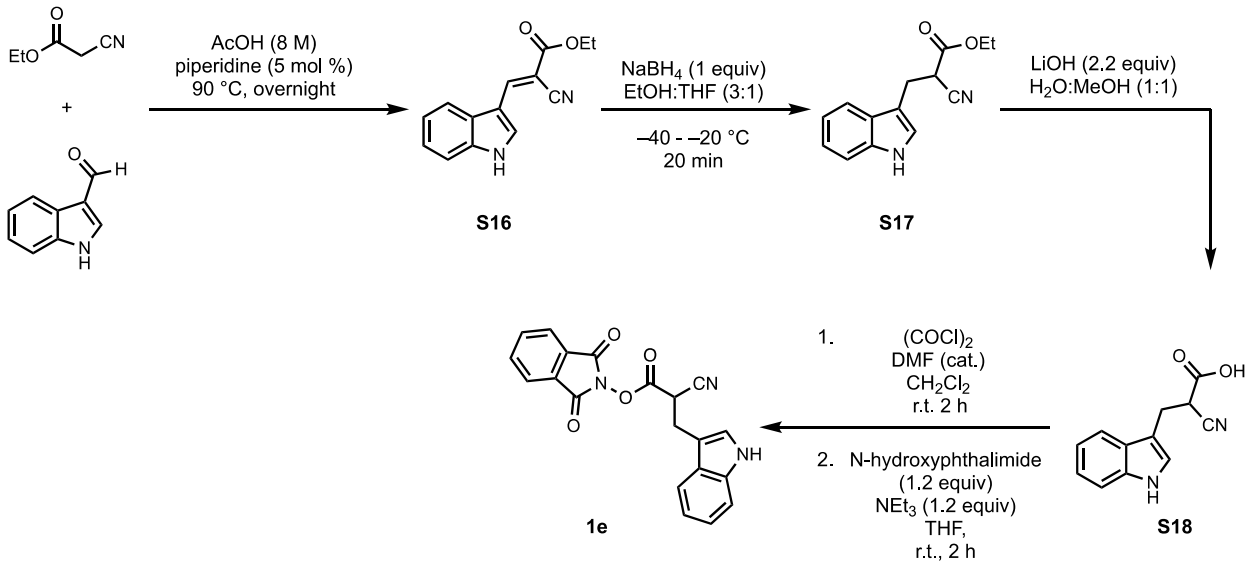
2-Cyanopent-4-enoic acid (**S15**): **S14** (2.1 g, 14 mmol, 1.0 equiv) was dissolved in MeOH (14 mL) and water (14 mL) and cooled to 0 °C. LiOH (0.72 g, 30 mmol, 2.2 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon reaction completion (as determined by TLC, approx. 1 hr), the reaction mixture was quenched with 1 M HCl, and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford 1.4 g (82% yield) of **S15** as a white solid.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 5.84 (ddt, *J* = 17.0, 10.1, 7.0, 1.1 Hz, 1H), 5.39–5.19 (m, 2H), 3.66 (dd, *J* = 7.5, 6.0 Hz, 1H), 2.82–2.64 (m, 2H) ppm. **^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 170.2, 130.8, 120.5, 115.3, 37.4, 33.6 ppm.

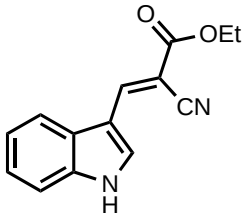


1d

1,3-dioxoisoindolin-2-yl 2-cyanopent-4-enoate (**1d**) was prepared according to **general procedure 2** using **S15** (3.6 g, 28 mmol, 1.0 equiv), CH_2Cl_2 (35 mL), $(COCl)_2$ (3.0 mL, 35 mmol, 1.2 equiv), and DMF (3 drops) followed by THF (60 mL), N-hydroxyphthalimide (5.2 g, 32 mmol, 1.1 equiv), DMAP (0.35 g, 2.9 mmol, 0.10 equiv), and NEt_3 (4.5 mL, 32 mmol, 1.1 equiv) to afford 4.3 g (55% yield) of **1d** as a white solid.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.99–7.78 (m, 4H), 5.94 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.51–5.34 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 1H), 2.98–2.83 (m, 2H) ppm.**^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 162.6, 160.9, 135.0, 129.8, 128.5, 124.2, 121.5, 113.8, 35.5, 34.1 ppm. **IR (neat):** 3102, 2258, 1816, 1789, 1735, 1352, 1116, 1082, 872, 695 cm^{-1}; **Melting Point**: 65–66 °C.

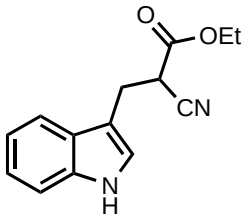
Figure S15. Preparation of **1e**





S16

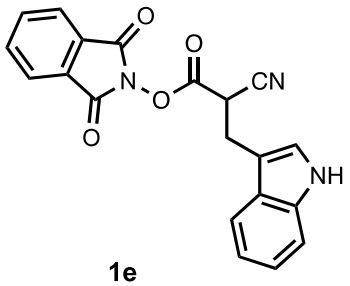
ethyl (*E*)-2-cyano-3-(1*H*-indol-3-yl)acrylate (**S16**): To a round bottom flask were added ethylcyanoacetate (2.1 mL, 20 mmol, 1.0 equiv), indole-3-carboxaldehyde (2.9 g, 20 mmol, 1.0 equiv), glacial acetic acid (2.5 mL, 8 M), and piperidine (0.10 mL, 1.0 mmol, 5.0 mol %). The flask was sealed with a rubber septum and submerged in a pre-heated oil bath at 90 °C. Upon completion, the reaction was diluted with EtOAc, and washed with sat. $NaHCO_3$ (x1), and brine (x1). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by hot recrystallization in EtOH to afford 3.0 g (63% yield) of **S16** as a yellow solid.
Analytical data consistent with that reported in the literature.[13] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 9.32 (br s, 1H), 8.66 (dd, *J* = 3.3, 0.7 Hz, 1H), 8.63 (d, *J* = 0.6 Hz, 1H), 7.86–7.81 (m, 1H), 7.52–7.46 (m, 1H), 7.37–7.29 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 163.8, 146.5, 135.6, 130.6, 127.4, 124.2, 122.6, 118.3, 118.1, 112.2, 111.3, 95.0, 62.0, 14.3 ppm;



S17

ethyl 2-cyano-3-(1*H*-indol-3-yl)propanoate (**S17**): A solution of **S16** (2.9 g, 12 mmol, 1.0 equiv) in EtOH (36 mL) and THF (25 mL) was cooled to –40 °C before $NaBH_4$ (0.46 g, 12 mmol, 1.0 equiv) was added in one portion. The reaction was allowed to warm to –20 °C over the course of approximately 20 minutes before being quenched with sat. NH_4Cl and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (gradient 0–50% EtOAc/hexanes) to afford 1.6 g (56% yield) of **S17** as a yellow solid.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.17 (br s, 1H), 7.59 (ddt, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.38 (J = 8.2, 1.0 Hz, 1H), 7.25–7.19 (m, 2H), 7.15 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.49 (ddd, *J* = 14.6, 5.6, 0.8 Hz, 1H), 3.40 (ddd, *J* = 14.6, 8.3, 0.7 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 166.1, 136.3,

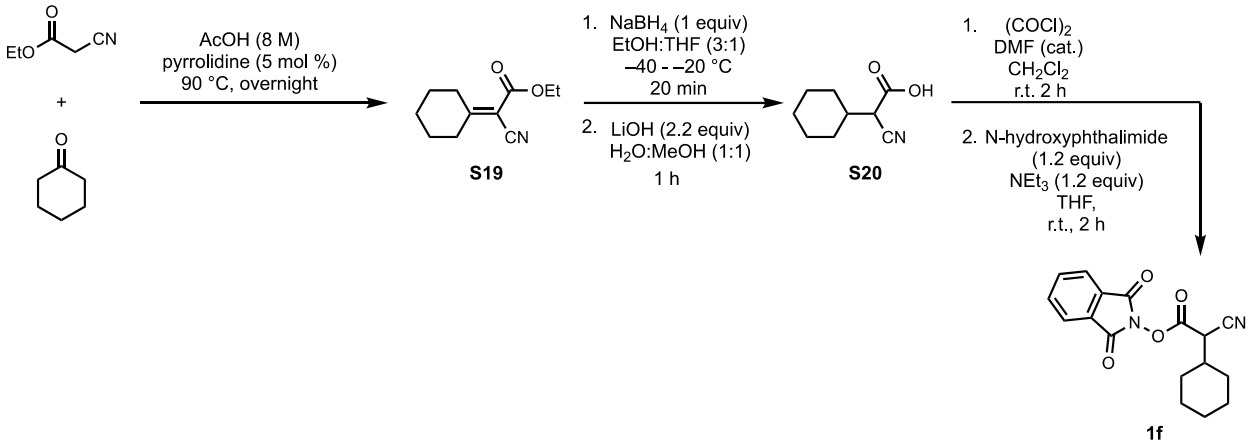
126.8, 123.5, 122.6, 120.0, 118.3, 117.0, 111.6, 110.0, 63.0, 39.4, 26.3, 14.0 ppm; **R_f:** 0.71 (50% EtOAc/Hexanes; $KMnO_4$, UV).

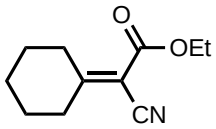


1e

1,3-dioxoisoindolin-2-yl 2-cyano-3-(1*H*-indol-3-yl)propanoate (**1e**): **S17** (1.6 g, 6.5 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of MeOH:H_2O (14 mL), and cooled to 0 °C before LiOH (0.34 g, 14 mmol, 2.2 equiv) was added. The reaction was warmed to room temperature and stirred for 1 hour before 1M HCl was added and the mixture was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford 1.3 g (91% yield) of **S18** as a red solid which was used directly in the next step according to general procedure 2 using **S18** (1.1 g, 5.0 mmol, 1.0 equiv), $(COCl)_2$ (0.51 mL, 6.0 mmol, 1.2 equiv), DMF (2 drops), and CH_2Cl_2 (15 mL), followed by N-hydroxyphthalimide (0.98 g, 6.0 mmol, 1.2 equiv), NEt_3 (0.84 mL, 6.0 mmol, 1.2 equiv), and THF (15 mL, 0.30 M). The crude material was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2) to afford 1.4 g (79% yield) of **1e** as a yellow solid.
Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 8.22 (br, s, 1H), 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.65 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.41 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.25 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.19 (J = 8.0, 7.0, 1.0 Hz, 1H), 4.21 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.73 (ddd, *J* = 14.6, 5.7, 0.8 Hz, 1H), 3.60 (ddd, *J* = 14.7, 8.3, 0.7 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 163.1, 161.1, 136.2, 135.1, 128.6, 126.4, 124.3, 124.0, 122.7, 120.1, 118.0, 114.6, 111.5, 108.6, 37.1, 27.0 ppm; **R_f:** 0.81 (2% MeOH/CH_2Cl_2; $KMnO_4$, UV); **IR (neat):** 3425, 3414, 2267, 1817, 1788, 1741, 1456, 1186, 1102 cm^{-1}; **Melting Point:** 135–138 °C.

Figure S16. Preparation of **1f**

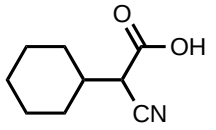




S19

ethyl 2-cyano-2-cyclohexylideneacetate (**S19**): To a round bottom flask were added ethylcyanoacetate (3.2 mL, 30 mmol, 1.0 equiv), cyclohexanone (3.7 mL, 36 mmol, 1.2 equiv), glacial acetic acid (4 mL, 8 M), and pyrrolidine (0.25 mL, 3 mmol, 10 mol %). The flask was sealed with a rubber septum and submerged in a pre-heated oil bath at 90 °C. Upon completion, the reaction was diluted with EtOAc, and washed with sat. $NaHCO_3$ (x1), and brine (x1). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (gradient 0–30% EtOAc/hexanes) to afford 3.6 g (62% yield) of **S19** as a clear oil.

Analytical data consistent with that reported in the literature.[14] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 4.26 (q, *J* = 7.1 Hz, 2H), 2.99–2.94 (m, 2H), 2.69–2.63 (m, 2H), 1.83–1.61 (m, 6H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 180.1, 162.1, 115.7, 102.2, 61.8, 37.0, 31.7, 28.7, 28.4, 25.8, 14.2 ppm; **R_f:** 0.6 (20%EtOAc/hexanes; $KMnO_4$, UV)

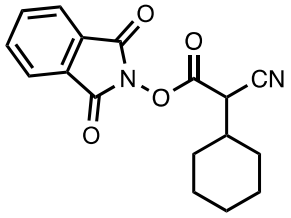


S20

2-cyano-2-cyclohexylacetic acid (**S20**): A solution of **S19** (3.2 g, 16 mmol, 1.0 equiv) in EtOH (40 mL) and THF (15 mL) was cooled to –40 °C before $NaBH_4$ (0.62 g, 16 mmol, 1.0 equiv) was added in one portion. The reaction was allowed to warm to –20 °C over the course of approximately 20 minutes before sat. NH_4Cl was added and extracted with EtOAc (x3). The combined organic layers

were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was then dissolved in a 1:1 mixture of MeOH:H_2O (14 mL), and cooled to 0 °C before LiOH (0.85 g, 36 mmol, 2.2 equiv) was added. The reaction was warmed to room temperature and stirred for 1 hour before 1 M HCl was added and the solution was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford 2.3 g (82% yield over 2 steps) of **S20** as a white solid.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 9.94 (br s, 1H), 3.46 (d, *J* = 5.4 Hz, 1H), 2.11–2.03 (m, 1H), 1.89–1.66 (m, 5H), 1.39–1.15 (m, 5H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 171.7, 115.2, 44.8, 38.9, 31.3, 29.4, 25.9, 25.7, 25.5 ppm;

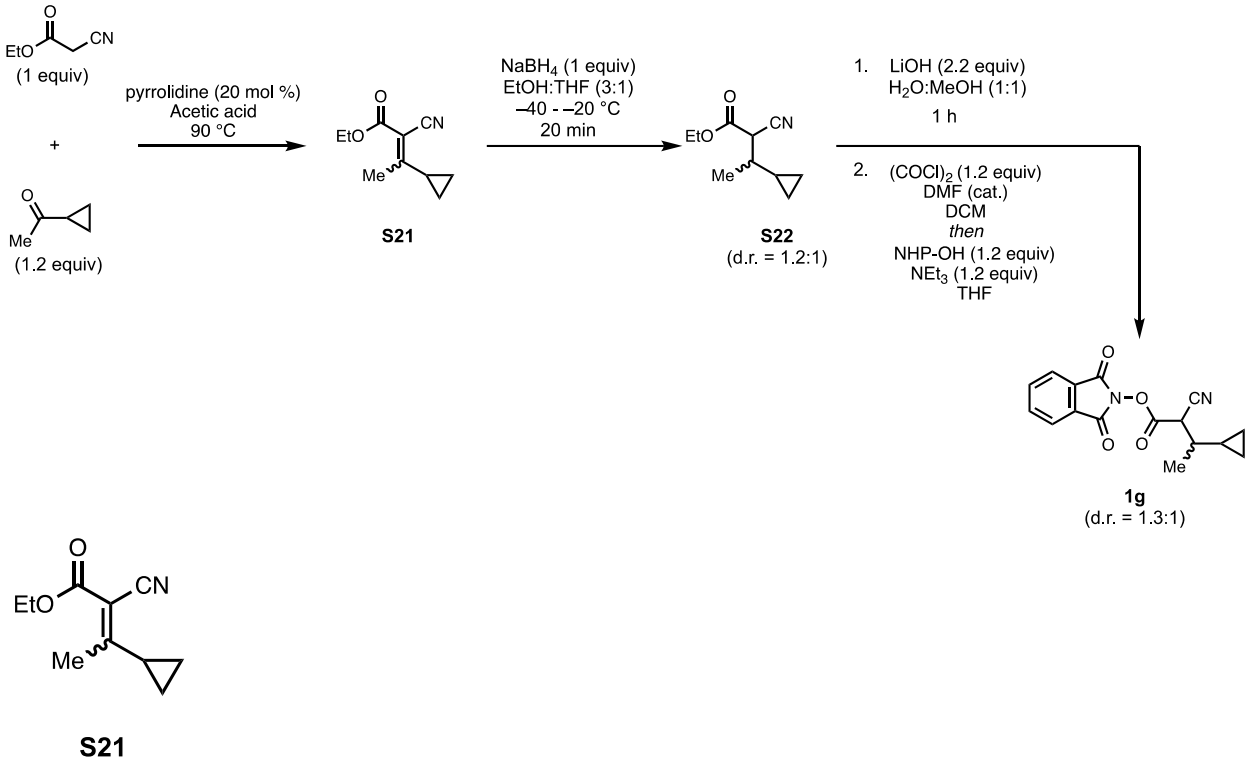


1f

1,3-dioxoisoindolin-2-yl 2-cyano-2-cyclohexylacetate (**1f**) was prepared according to **general procedure 2** using **S20** (2.3 g, 16 mmol, 1.0 equiv), $(COCl)_2$ (1.7 mL, 20 mmol, 1.2 equiv), DMF (3 drops), and CH_2Cl_2 (50 mL), followed by N-hydroxyphthalimide (3.2 g, 20 mmol, 1.2 equiv), NEt_3 (2.7 mL, 20 mmol, 1.2 equiv), and THF (15 mL, 0.3 M). The crude material was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2). The oily residue was then dissolved in a minimal amount of EtOAc (~2 mL) before hexanes (~100 mL) was added and stirred vigorously overnight which crashed out the desired product. The solid was then collected by filtration and dried under vacuum to afford 2.1 g (41% yield) of **1f** as a white solid.

Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K) δ_H 7.93–7.89 (m, 2H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.80 (d, *J* = 5.4 Hz, 1H), 2.26 (tddd, *J* = 8.8, 7.0, 4.3, 2.6 Hz, 1H), 2.06–2.01 (m, 1H), 1.95–1.84 (m, 3H), 1.77–1.70 (m, 1H), 1.47–1.31 (m, 4H), 1.28–1.19 (m, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ_C 162.9, 161.2, 135.1, 128.6, 124.2, 113.7, 42.3, 39.7, 30.9, 29.2, 25.8, 25.6, 25.3 ppm; **R_f:** 0.8 (1% MeOH/CH_2Cl_2; $KMnO_4$); **IR (neat):** 2932, 2857, 2252, 1810, 1784, 1744, 1355, 1182, 1078, 693 cm^{-1}; **Melting Point:** 85–88 °C.

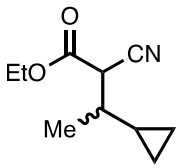
Figure S17. Preparation of **1g**



S21

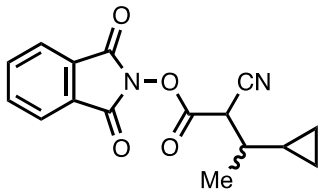
ethyl (*E*)-2-cyano-3-cyclopropylbut-2-enoate **S21**: Ethylcyanoacetate (2.1 mL, 20 mmol, 1.0 equiv), 1-cyclopropylethan-1-one (2.4 mL, 24 mmol, 1.2 equiv), glacial acetic acid (5 mL), and pyrrolodine (0.33 mL, 4.0 mmol, 0.20 equiv) were added to a round bottom flask. The flask was sealed with a rubber septum before being submerged in a pre-heated oil bath at 90 °C overnight. Upon completion, the reaction was diluted with EtOAc, and the organic layers were washed with sat. $NaHCO_3$ (x2), brine (x1), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (slow gradient of 0–20% EtOAc in hexanes) to afford 0.9 g (25% yield) of **S21** as a white semi-solid as a mixture of E:Z isomers (1.5:1 as determined by ^{1}H NMR; H_M proton signal for major isomer, H_m proton signal for minor isomer).

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 4.30–4.22 (m, $2H_M$, $2H_m$), 3.46 (tt, J = 8.3, 5.1 Hz, $1H_m$), 2.40 (tt, J = 8.1, 4.9 Hz, $1H_M$), 1.95 (s, $3H_M$), 1.86 (s, $3H_m$), 1.36–1.31 (m, $3H_M$, $3H_m$) 1.17–1.11 (m, $2H_M$, $2H_m$), 1.02–0.97 (m, $2H_M$, $2H_m$) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.4, 162.7, 162.1, 116.5, 104.1, 103.1, 61.5, 61.4, 20.3, 17.8, 16.2, 14.1, 14.1, 14.0, 10.4, 9.3 ppm; **R_f:** 0.51 (20% EtOAc/hexanes; $KMnO_4$, UV).



S22
(d.r. = 1.2:1)

ethyl 2-cyano-3-cyclopropylbutanoate (**S22**): A solution of **S21** (0.9 g, 5 mmol, 1 equiv) in EtOH (12 mL) and THF (4 mL) was cooled to –40 °C before $NaBH_4$ (0.2 g, 5 mmol, 1 equiv) was added in one portion. The reaction was allowed to warm to –20 °C over the course of approximately 20 minutes before being quenched with sat. NH_4Cl and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford 0.79 g (87% yield) of the crude material (1.2:1 ratio of diastereomers as determined by ^1H NMR; H_M proton signal for major diastereomer, H_m proton signal for minor diastereomer).
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 4.33–4.21 (m, $2H_M$, $2H_m$), 3.62 (d, *J* = 4.8 Hz, $1H_M$), 3.51 (d, *J* = 5.0 Hz, $1H_m$), 1.59–1.50 (m, $1H_m$), 1.47–1.39 (m, $1H_M$), 1.35–1.29 (m, $3H_M$, $3H_m$), 1.21 (d, *J* = 6.9 Hz, $3H_m$), 1.18 (d, *J* = 6.8 Hz, $3H_M$), 0.90–0.79 (m, $1H_M$, $1H_m$), 0.65–0.50 (m, $2H_M$, $2H_m$), 0.28–0.10 (m, $2H_M$, $2H_m$) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 166.0, 165.9, 115.8, 115.7, 62.6, 62.5, 44.8, 44.5, 40.7, 40.4, 18.6, 16.5, 16.1, 14.6, 14.0, 14.0, 4.9, 4.8, 4.6, 3.1 ppm; **R_f:** 0.64 (20% EtOAc/hexanes; $KMnO_4$).



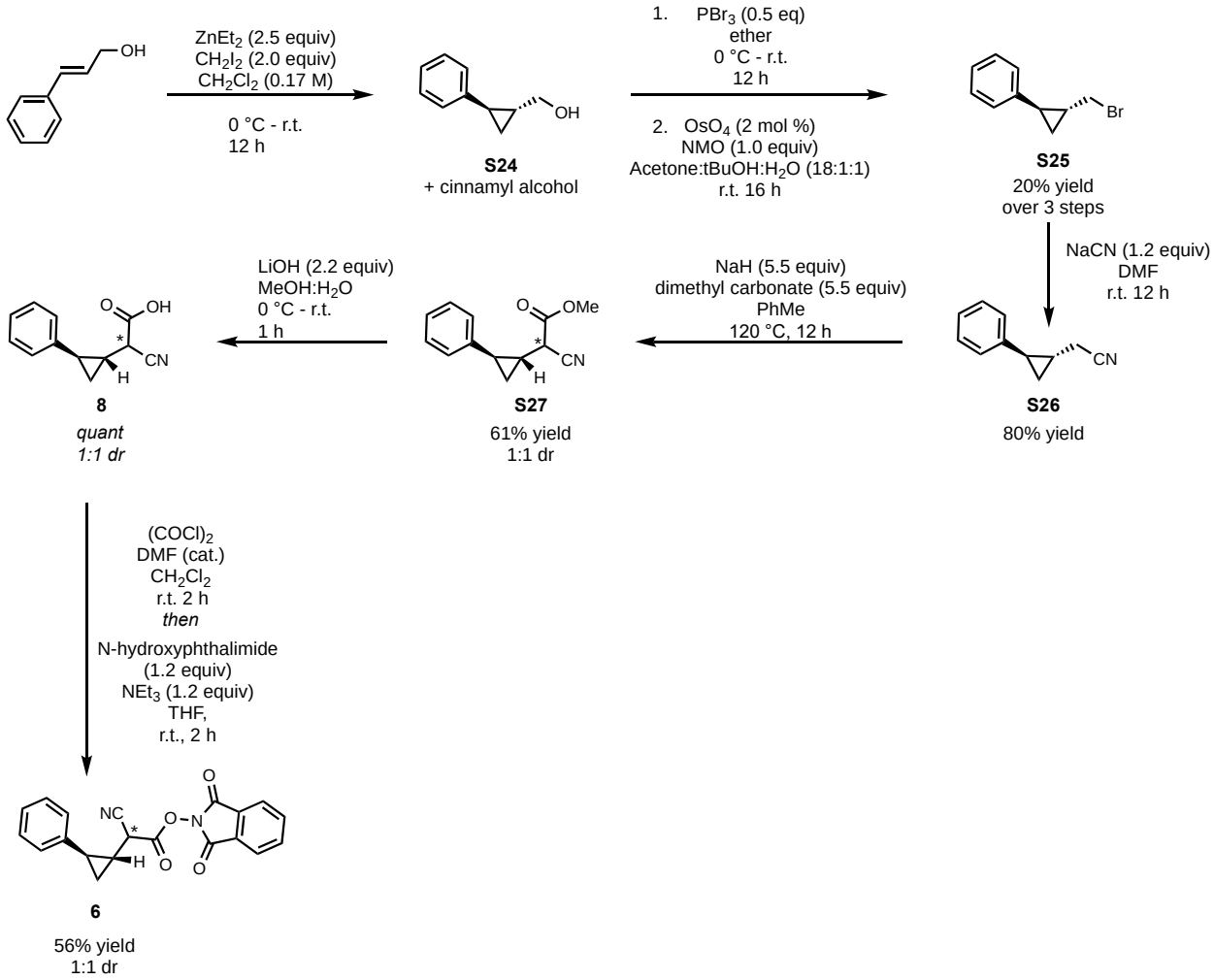
1g
(d.r. = 1.3:1)

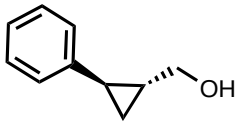
1,3-dioxoisoindolin-2-yl 2-cyano-3-cyclopropylbutanoate (**1g): S22** (0.77 g, 4.3 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of MeOH:H_2O (10 mL), and cooled to 0 °C before LiOH (0.22 g, 9.4 mmol, 2.2 equiv) was added. The reaction was warmed to room temperature and stirred for 1 hour before 1M HCl was added and extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford 0.65 g (98% yield) of **S23** as a thick clear oil which was used directly in the next step according to **general procedure 2** with **S23** (0.77 g, 4.3 mmol, 1.0 equiv), $(COCl)_2$ (0.43 mL, 5.0 mmol, 1.2 equiv), DMF (2 drops), and CH_2Cl_2 (15 mL), followed by N-hydroxyphthalimide (0.82 g, 5.0 mmol, 1.2 equiv), NEt_3 (0.70 mL, 5.0 mmol, 1.2 equiv), and THF (15 mL). The crude material was purified by column chromatography on silica gel (gradient 0–2% MeOH/CH_2Cl_2) and dried under high vacuum for 2 days to afford 1.1 g (87% yield) of **1g** as white solid (1.3:1 mixture of diastereomers

as determined by ^{1}H NMR; H_M proton signal for major diastereomer, H_m proton signal for minor diastereomer).

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.93–7.88 (m, $2H_M$, $2H_m$), 7.85–7.80 (m, $2H_M$, $2H_m$), 4.08 (d, *J* = 4.2 Hz, $1H_M$), 3.94 (d, *J* = 4.7 Hz, $1H_m$), 1.79–1.71 (m, $1H_m$), 1.68–1.62 (m, $1H_M$), 1.37 (d, *J* = 5.6 Hz, $3H_M$), 1.36 (d, *J* = 5.8 Hz, $3H_m$), 1.05–0.94 (m, $1H_M$, $1H_m$), 0.74–0.48 (m, $2H_M$, $2H_m$), 0.38–0.21 (m, $2H_M$, $2H_m$) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 163.1, 163.0, 161.3, 161.2, 135.2, 135.2, 128.8, 128.8, 124.4, 124.4, 114.0, 113.7, 42.5, 42.5, 41.9, 41.4, 18.4, 16.4, 16.3, 14.9, 5.3, 5.2, 4.9, 3.8 ppm; **R_f:** 9.9 (2% MeOH/CH_2Cl_2; $KMnO_4$, UV); **IR (neat):** 3015, 2971, 2922, 2269, 1814, 1779, 1739, 1608, 1467, 1184 cm^{-1}; **Melting Point:** 47 – 49 °C.

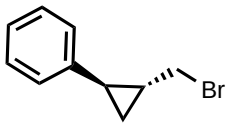
Figure S18. Preparation of Radical Clock Substrate **6**





S24

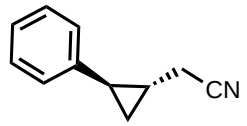
Rac-((1*R*,2*R*)-2-phenylcyclopropyl)methanol (**S24**) was prepared according to a literature procedure.[15] Cinnamyl alcohol (3.4 g, 25 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) and the mixture was cooled to 0 °C before $ZnEt_2$ (36 mL, 0.86 M solution in hexane, 31 mmol, 1.2 equiv) was added dropwise. In a separate flask, diiodomethane (4.0 mL, 50 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (100 mL) and the mixture was cooled to 0 °C before $ZnEt_2$ (36 mL, 0.86 M solution in hexane, 31 mmol, 1.2 equiv) was added dropwise. Both reaction vessels were stirred at 0 °C for 30 minutes before the contents of the reaction flask containing cinnamyl alcohol was transferred to the flask containing diiodomethane via cannula transfer. The reaction was stirred at 0 °C for 30 minutes and then allowed to warm slowly to room temperature over 16 hours. Sat. NH_4Cl was added, followed by 1 M HCl, and the mixture was extracted with CH_2Cl_2 (x2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield **S24** which contained residual inseparable cinnamyl alcohol.



S25

Rac-((1*R*,2*R*)-2-(bromomethyl)cyclopropyl)benzene (**S25**): Crude **S24** was dissolved in ether (50 mL), and the mixture was cooled to 0 °C before PBr_3 (1.2 mL, 12.5 mmol, 0.5 equiv) was added. The reaction was left to stir overnight before H_2O was added, and the solution was extracted with ether (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford **S25**. The crude residue was contaminated with cinnamyl bromide, so to facilitate purification, this crude material was dissolved in a 18:1:1 acetone:tBuOH:H_2O (130 mL combined) mixture, and OsO_4 (1.5 mL, 4.0% solution in H_2O, 0.02 equiv, 0.25 mmol) was added, followed by NMO (1.4 g, 12.3 mmol, 1.0 equiv). The reaction was left to stir overnight at room temperature before saturated $Na_2S_2O_3$ was added, and the mixture was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was passed over a plug of silica gel (eluting with hexanes), to afford 0.84 g (20% yield over 3 steps) of **S25** as a clear oil.

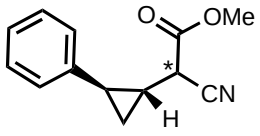
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.30–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.12–7.08 (m, 2H), 3.52 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.43 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.95 (ddd, *J* = 9.5, 5.7, 4.4 Hz, 1H), 1.66–1.56 (m, 1H), 1.22 (dt, *J* = 8.3, 5.5 Hz, 1H), 1.03 (dt, *J* = 8.9, 5.4 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 141.5, 128.5, 126.2, 126.1, 38.4, 26.4, 25.7, 18.0 ppm; $\mathbf{R_f}$ 0.8 (Hexanes; $KMnO_4$).



S26

Rac-2-((1*S*,2*R*)-2-phenylcyclopropyl)acetonitrile (**S26**): **S25** (0.84 g, 4.0 mmol, 1.0 equiv) was dissolved in DMF (10 mL), and NaCN (0.24 g, 4.8 mmol, 1.2 equiv) was added(caution)[16]. The reaction was left to stir overnight at room temperature before sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc:Hexanes) to afford 0.5 g (80% yield) of **S26** as a clear oil.

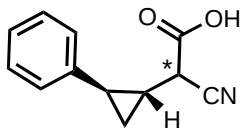
Analytical data consistent with that reported in the literature.[15] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.34–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.13–7.10 (m, 2H), 2.68–2.53 (m, 2H), 1.96 (ddd, *J* = 9.5, 5.5, 4.4 Hz, 1H), 1.44–1.35 (m, 1H), 1.14 (dt, *J* = 8.4, 5.6 Hz, 1H), 1.06 (dt, *J* = 9.0, 5.5 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 141.1, 128.5, 126.2, 126.0, 118.2, 22.9, 21.5, 17.6, 14.9 ppm; **R_f:** 0.3 (10% EtOAc/Hexanes; $KMnO_4$).



S27

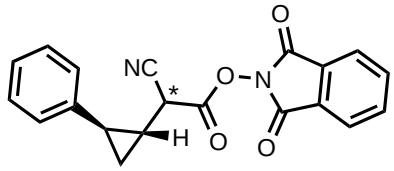
Rac-methyl 2-cyano-2-((1*R*,2*R*)-2-phenylcyclopropyl)acetate (**S27**) was prepared according to a modified literature procedure[17]: To a solution of **S26** (0.5 g, 3.2 mmol, 1.0 equiv) in PhMe (10 mL) was added dimethylcarbonate (0.59 mL, 7.0 mmol, 2.2 equiv) and NaH (0.28 g, 7.0 mmol, 2.2 equiv). The mixture was heated at reflux at 120 °C for 4 hours, before additional dimethylcarbonate (0.89 mL, 11 mmol, 3.3 equiv) and NaH (0.42 g, 11 mmol, 3.3 equiv) were added based on incomplete conversion (as determined by TLC). The reaction mixture was left to stir further overnight. Saturated NH_4Cl was added dropwise at 0 °C, and the mixture was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (slow gradient of 0–40% EtOAc:Hexanes) to afford 0.42 g (61% yield) of **S27** as a yellow oil as a 1:1 mixture of diastereomers (as determined by ^{1}H NMR). Integrations refer to both diastereomers with overlapping signals.

Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.24–7.18 (m, 4H), 7.16–7.10 (m, 2H), 7.07–7.01 (m, 4H), 3.79–3.77 (m, 6H), 3.45–3.40 (m, 2H), 2.10–2.03 (m, 2H), 1.62–1.54 (m, 2H), 1.15–1.09 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 166.1, 140.2, 140.1, 128.7, 128.6, 126.6, 126.6, 126.4, 115.1, 115.1, 53.8, 53.8, 41.1, 41.0, 22.6, 21.6, 21.0, 20.7, 13.7, 13.2 ppm; **R_f:** 0.38 (20% EtOAc/Hexanes; $KMnO_4$).



8

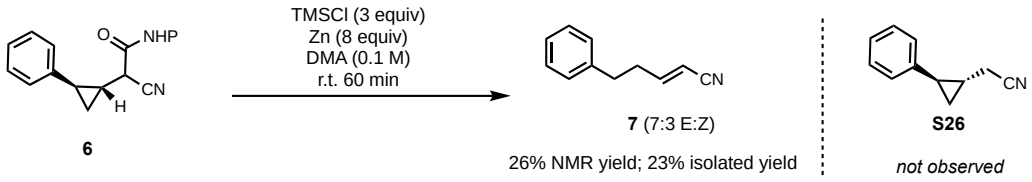
Rac-2-cyano-2-((1*R*,2*R*)-2-phenylcyclopropyl)acetic acid (**8**): **S27** (1.1 g, 5.1 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of MeOH:H_2O (14 mL), and cooled to 0 °C before LiOH (0.24 g, 10 mmol, 2.2 equiv) was added. The reaction was warmed to room temperature and stirred for 45 min before 1 M HCl was added and the mixture was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure to afford 1.0 g (*quant.*) of **8** as a yellow oil as a 1:1 mixture of diastereomers (as determined by ^{1}H NMR). Integrations refer to both diastereomers with overlapping signals.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.32–7.26 (m, 4H), 7.23–7.18 (m, 2H), 7.15–7.19 (m, 4H), 3.58–3.53 (m, 2H), 2.21–2.13 (m, 2H), 1.72–1.64 (m, 2H), 1.28–1.20 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 170.3, 170.3, 140.0, 139.9, 128.7, 128.7, 126.7, 126.6, 126.4, 114.6, 114.5, 41.2, 41.1, 22.8, 21.7, 20.9, 20.6, 13.8, 13.2 ppm.



6

Rac-1,3-dioxoisoindolin-2-yl 2-cyano-2-((1*R*,2*R*)-2-phenylcyclopropyl)acetate (**6**) was prepared according to general procedure 2 using **8** (1.0 g, 5.0 mmol, 1.0 equiv), $(COCl)_2$ (0.51 mL, 6.0 mmol, 1.2 equiv), DMF (2 drops), and CH_2Cl_2 (15 mL, 0.30 M) followed by N-hydroxyphthalimide (0.98 g, 6.0 mmol, 1.2 equiv), NEt_3 (0.84 mL, 6.0 mmol, 1.2 equiv), and THF (15 mL, 0.3 M). The crude material was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2) to afford 0.98 g (56% yield) of **6** as a thick oil and as a 1:1 mixture of diastereomers (as determined by ^{1}H NMR). Integrations refer to both diastereomers with overlapping signals.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.95–7.89 (m, 4H), 7.85–7.81 (m, 4H), 7.33–7.28 (m, 4H), 7.25–7.16 (m, 6H), 3.97 (d, *J* = 7.1 Hz, 1H), 3.89 (d, *J* = 7.5 Hz, 1H), 2.37–2.28 (m, 2H), 1.88–1.78 (m, 2H), 1.38–1.31 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 162.8, 162.7, 161.1, 139.5, 139.4, 135.3, 128.8, 128.7, 128.7, 126.9, 126.8, 126.7, 113.4, 113.2, 39.0, 39.0, 23.0, 22.3, 20.8, 20.7, 13.8, 13.1 ppm; **R_f:** 0.8 (2%MeOH/CH_2Cl_2; $KMnO_4$); **IR (neat):** 3030, 2261, 1820, 1790, 1741, 1467, 1353, 1185, 1079, 972, 692 cm^{-1}.

Figure S19: Radical Clock Experiment:

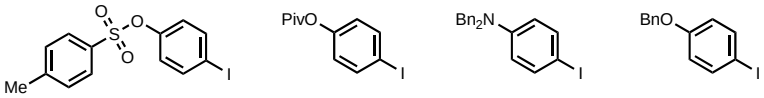


(*E*)-5-phenylpent-2-enenitrile **7**: An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. **6** (0.11 g, 0.31 mmol, 1.0 equiv) and Zn (0.16 g, 2.5 mmol, 8.0 equiv) were added on the bench top. The tube was sealed with a septum and electrical tape and evacuated and backfilled with N_2 (x3). A solution of TMSCl (0.12 mL, 0.93 mmol, 3.0 equiv) in DMA (0.3.1 mL, 0.1 M) was then added to the tube in one portion and the mixture was stirred vigorously at room temperature (23–25 °C). After 60 min, the reaction was exposed to air, diluted with EtOAc, quenched with 1 M HCl, extracted with EtOAc (x2), passed directly over a short plug of silica gel, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (gradient 0–10% EtOAc:Hex) to afford 11 mg of **7** as a slightly yellow oil as a 7:3 mixture of isomers.
Analytical data is consistent with that reported in the literature.[18] H_M proton signal for major isomer (E), H_m proton signal for minor isomer (Z).

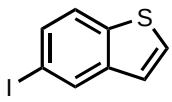
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.33–7.14 (m, $5H_m$, $5H_M$), 6.72 (dt, *J* = 16.3, 7.0 Hz, $1H_M$), 6.52–6.44 (m, $1H_m$), 5.35–5.29 (m, $1H_m$, $1H_M$), 2.81–2.74 (m, $2H_m$, $2H_M$), 2.60–2.51 (m, $2H_m$, $2H_M$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 154.7, 153.8, 139.8, 139.8, 128.6, 128.6, 128.4, 128.3, 126.5, 126.4, 117.3, 100.5, 100.4, 39.4, 34.3, 33.9, 33.2 ppm; **R_f:** 0.22 (10% EtOAc/hexanes; $KMnO_4$, UV).

G. Preparation of Aryl Iodide Starting Materials

The following aryl iodides were prepared according to literature procedures: **S28**[19], **S29**[20], **S30**[21], **S31**.[22]



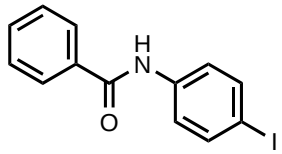
S28 **S29** **S30** **S31**



S32

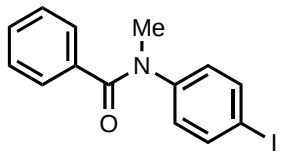
5-iodobenzo[*b*]thiophene (**S32**) was prepared according to a literature procedure.[23]
A round bottom flask was charged with 5-bromobenzo[*b*]thiophene (1.1 g, 5.0 mmol, 1.0 equiv), CuI (95 mg, 0.50 mmol, 10 mol %) and NaI (1.5 g, 10 mmol, 2.0 equiv), and was then evacuated and backfilled with N_2 (x3) and sealed with a rubber septum and electrical tape. Then, dimethylethylenediamine (0.11 mL, 1.0 mmol, 20 mol %) was added followed by dioxane (5 mL,

1 M) and was then submerged in a pre-heated oil bath at 110 °C overnight. Upon completion, the reaction was quenched with NH_4Cl (sat.) and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was sonicated in hexanes for 2 minutes and collected by filtration to afford 1.2 g (91% yield) **S32** as a brown solid.
Analytical data consistent with that reported in the literature.[24] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.18 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.63 (dt, *J* = 8.5, 0.7 Hz, 1H), 7.60 (ddd, *J* = 8.5, 1.6, 0.5 Hz, 1H), 7.43 (dd, *J* = 5.5, 0.5 Hz, 1H), 7.25 (dd, *J* = 5.4, 0.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 141.9, 139.2, 132.8, 132.6, 127.8, 124.2, 123.0 ppm.



S33

N-(4-iodophenyl)benzamide (**S33**): 4-iodoaniline (2.2 g, 10 mmol, 1.0 equiv) was dissolved in THF (10 mL, 1 M) and the mixture was cooled to 0 °C before NEt_3 (1.7 mL, 12 mmol, 1.2 equiv) was added followed by benzoyl chloride (1.4 mL, 12 mmol, 1.2 equiv). The reaction was allowed to stir for 30 minutes before H_2O (30 mL) was added. The solid was filtered and washed with EtOAc (10 mL) to afford 2.6 g (81% yield) of **S33** as a purple solid which was used directly in the next step.



S34

N-(4-iodophenyl)-*N*-methylbenzamide (**S34**): A round bottom flask was charged with NaH (0.18 g, 4.5 mmol, 1.5 equiv) and cooled to 0 °C before DMF (6 mL, 0.5 M) was added. **S33** (0.97 g, 3.0 mmol, 1.0 equiv) was then added in one portion and the mixture was left to stir at the same temperature for 30 minutes. Then, iodomethane (0.28 mL, 4.5 mmol, 1.5 equiv) was added dropwise and the mixture was left to stir for 1 hour. Upon completion, the reaction was quenched with NH_4Cl (sat.) and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (gradient 0–20% EtOAc/hexanes) to afford 0.87 g (87% yield) of **S34** as a white solid.
Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.57–7.50 (m, 2H), 7.30–7.26 (m, 3H), 7.24–7.17 (m, 2H), 6.81–6.76 (m, 2H), 3.47 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 170.7, 144.9, 138.4, 135.7, 130.1, 128.8, 128.8, 128.1, 91.2, 38.4 ppm; **IR (neat):** (neat): 1633, 1565, 1578, 1483, 1446, 1419,1360 cm^{-1}.

H. References

[1] DMA purchased from other vendors generally resulted in decreased yields (by ~10–20%).
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[4] Care was taken that the stir-rate wasn't too high such that the concentrated solution didn't splatter on the sides of the reaction tube. For 1 mL total volume (0.2 mmol scale reaction), a stir-rate of ~700 rpm was optimal.
[5] Initially after work up the product exists as the TMS-protected phenol, however, the free phenol was obtained after purification on silica gel.
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[8] The reaction also proceeded in the absence of DMAP
[9] In general the R_f of NHP esters on TLC were 0.6–0.8 in a solvent system of CH_2Cl_2 (streaky), and 0.8–0.95 in a solvent system of 1.5% MeOH/CH_2Cl_2.
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[16] NaCN is toxic and should be handled exclusively in a well-ventilated fumehood and kept away from all sources of acid. The reaction should be treated as if unreacted NaCN is present and the aqueous work-up solution should be disposed of in a separate container.
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