Ni-catalyzed Electrochemical Decarboxylative C–C couplings in Batch and Continuous Flow

Hui Li,† Christopher P. Breen,†‡ Hyowon Seo,‡ Timothy F. Jamison,*‡ Yuan-Qing Fang,*† Matthew M. Bio,*†

† *Snapdragon Chemistry, Inc., Cambridge, Massachusetts 02470, United States*
‡ *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 United States*

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I. General Information

General Methods

Reactions were monitored by either offline HPLC or thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254). Visualization was achieved with shortwave UV light or iodine stain. Flash column chromatography was performed using either SiliaFlash M60 from SiliCycle, or a Biotage Isolera automated flash chromatography system equipped with SNAP KP-Sil or Ultra-Sil columns (silica gel, average particle size 50 μm and 25 μm spherical respectively). ^{1}H-NMR spectra were recorded on either a Varian 500 MHz spectrometer, a Jeol 500 MHz spectrometer, or a Bruker 400 MHz spectrometer with calibration of spectra to $CHCl_3$ (7.26 ppm). ^{13}C-NMR spectra were recorded either at 126 MHz on a Varian 500 MHz spectrometer, at 126 MHz on a Jeol 500 MHz spectrometer, or at 101 MHz on a Bruker 500 MHz spectrometer at ambient temperature with chemical shifts expressed in ppm using solvent as the internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F-NMR spectra were recorded on either a Varian 300 MHz at 282 MHz, or a Bruker 500 MHz spectrometer at 376 MHz spectrometer with chemical shifts reported in ppm and referenced to α,α,α-trifluorotoluene (-63.7 ppm) added as an internal standard. Chemical shift values (δ) are expressed in ppm downfield relative to internal standard (tetramethylsilane at 0 ppm). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br s (broad singlet). Coupling constants are reported in hertz (Hz). Fourier-Transform infrared spectroscopy (FT-IR) data recorded on either a JASCO FT/IRM4100 Fourier Transform Infrared Spectrometer or an Agilent Cary 630 spectrometer equipped with an attenuated total response (ATR) accessory. High resolution mass spectra were acquired from the Mass Spectrometry Laboratory at the Massachusetts Institute of Technology.

Chemicals

Nickel(II) bromide dimethoxyethane adduct ($NiBr_2$·dme) was purchased from Strem Chemicals (min 97%). 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbbpy) was purchased from Sigma-Aldrich. Other reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar, TCI America, Oakwood Chemical, and AK Scientific. Products were used as received without further purification.

Electrochemical Reactors, Power Supply, Electrode Materials

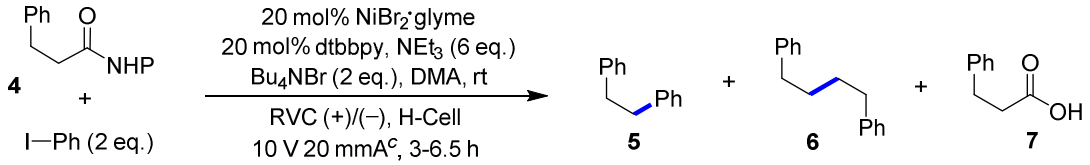
Electrochemical H-cells were purchased from Pine Research (catalog # RRPG060). A Programmable DC power supply was purchased from BK Precision (Model 9202). Reticulated vitreous carbon (RVC) foam was purchased from KR Reynolds (100 ppi) and cut as needed. Stainless steel wires were purchased from Home Depot.

Continuous-flow electrochemical reactions were performed in a C-Flow LAB 1x1 electrochemical cell (material of cell frame is PEEK), which was purchased from C-Tech Innovation Ltd.. Flow reactors utilized high-purity PFA tubing (1/8″ or 1/16″ OD) from Cole-Parmer Instrument Company. Harvard Apparatus PhD Ultra syringe pumps were used to pump reagents and solutions.

II. ***Experimental Procedures and Analytical Data***

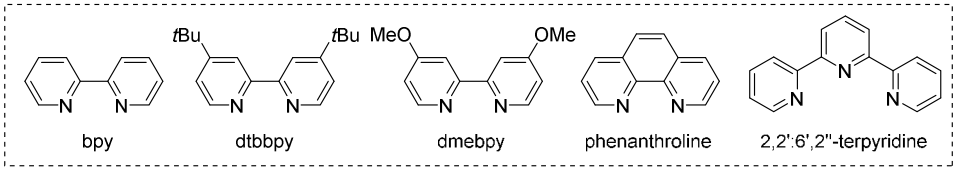
Section 1.

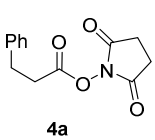
Table S1. Complete Table of Reaction Optimization



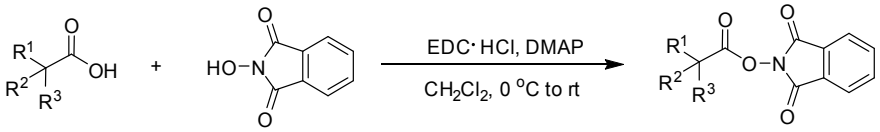
Entry	Deviation from above	Yield (%), 5	Yield (%), 6	Yield (%), 7
1	none	54	11	22
2	undivided cell	6	39	18
3	nickel foam cathode	41	23	21
4	DMF instead of DMA	49	20	21
5	CH_3CN instead of DMA	48	26	19
6	bpy instead of dtbbpy	47	23	24
7	dmebpy instead of dtbbpy	49	14	25
8	Phenanthroline or 2,2':6',2"-terpyridine instead of dtbbpy[d]	—[e]	—	—
9	30 mol% Ni^{II}/dtbbpy	67	9	18
10	30 mol% Ni^{II}/dtbbpy, Bu_4NClO_4	65	10	15
11	30 mol% Ni^{II}/dtbbpy, Bu_4NPF_6	74	6	14
12	no electricity	0	0	0
13	no $NiBr_2$·glyme	0	44	38
14	30 mol% Ni^{II}/dtbbpy, Bu_4NPF_6, DIPEA instead of NEt_3	73	8	14
15	30 mol% Ni^{II}/dtbbpy, Bu_4NPF_6, 60 °C	27	21	40
16	30 mol% Ni^{II}/dtbbpy, Bu_4NPF_6, 0 °C	60	16	20
17	ester **4a** instead of **4**	0	0	< 5

[a] Reactions were carried out in 2 mmol scale. [b] Yield determined by calibrated HPLC assay. [c] Maximum potential and current output set at 10 V and 20 mmA, respectively. [d] Phenanthroline or 2,2':6',2"-terpyridine forms insoluable precipitate with $NiBr_2$·glyme in DMAc or DMF. [e] Not determined





Section 2. General procedure for preparation of NHP Esters (Procedure A)



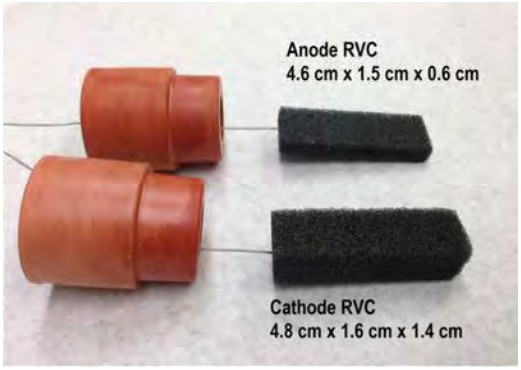
To a CH_2Cl_2 solution of alkyl carboxylic acid (1 equiv., ~0.3 M), *N*-hydroxyphathalimide (1 equiv.) and DMAP (1.3 equiv.) at 0 °C was added EDC·HCl (1.2 equiv.) portionwise. Ice-water bath was removed and the reaction mixture was stirred at room temperature until the full consumption of starting carboxylic acid as determined by HPLC or TLC analysis (typically about 2 hours). The reaction was quenched with 1N HCl and diluted with CH_2Cl_2. The CH_2Cl_2 layer was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue then underwent silica gel column chromatography to provide the corresponding NHP esters.

Section 3. Reaction setup, general procedure for electrocatalytic arylations in an H-cell

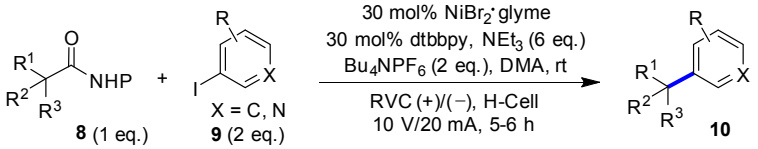
Reaction Setup

Figure S1. Overall setup for batch electrochemical coupling performed in an H-cell

Figure S2. Cathode and Anode RVC dimensions



General procedure for electrocatalytic arylations in an H-cell (Procedure B)



$NiBr_2$·dme (0.6 mmol) and dtbbpy (0.6 mmol) were dissolved in *N*-*N*-dimethylacetamide (DMA) (6 mL) and stirred at 60 °C until a green homogeneous solution was obtained (generally within 1 h). The solution was then cooled to room temperature.

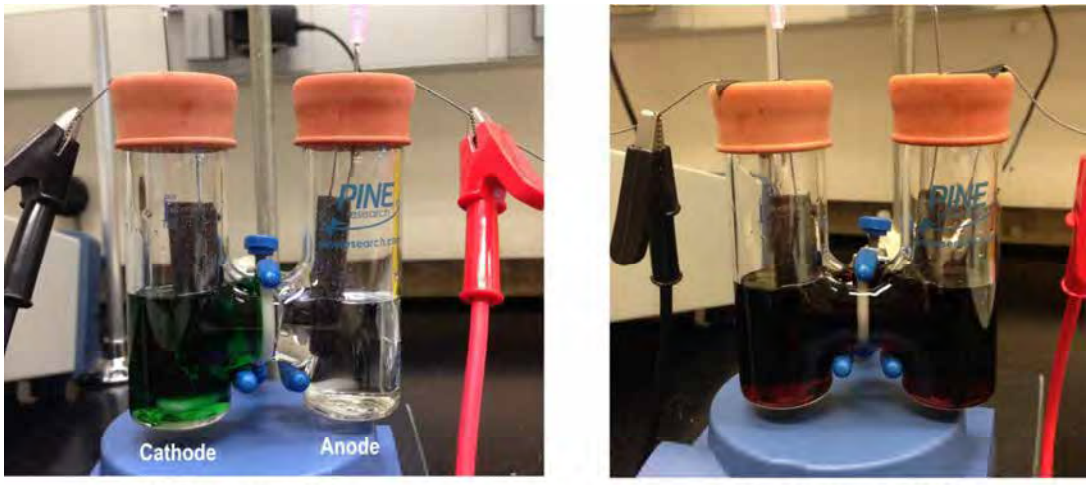
To the cathode chamber of an H-cell was added NHP ester **8** (2 mmol)[1], aryl halide 9 (4 mmol), Bu_4NPF_6 (1.55 g, 4 mmol), the above freshly prepared $NiBr_2$·dme/dtbbpy solution and DMA (~11 mL, so that the total volume of solution in cathode side is about 18 mL).

To the anode chamber of an H-cell was added triethylamine (1.67 mL, 12 mmol), Bu_4NPF_6 (1.55 g, 4 mmol) and DMA (~16 mL, so that the total volume of solution in anode side is about 18 mL).

Part of the RVC cathode and anode were submerged into the reaction mixtures (Figure S3-A). Generally about 4.5-5 cm^3 of *cathode* RVC foam was submerged.[2] The cathode solution was purged with nitrogen for about 5 min. The reaction mixture was then electrolyzed at 10 V/20 mA (maximum potential and current, respectively) at room temperature until full consumption of starting NHP ester **8** as determined by HPLC analysis. Color changes were observed for both cathode and anode mixtures, which turned deep-brown at the end of reaction (Figure S3-B).

The cathodic reaction mixture was transferred into a separatory funnel and diluted with ethyl acetate (40 mL). The mixture was washed with brine/H_2O (v/v = 1:1, 15 mL) three times. The ethyl acetate layer was separated, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue then underwent silica gel column chromatography to provide the corresponding arylated products.

Figure S3. Close-up of H-cell



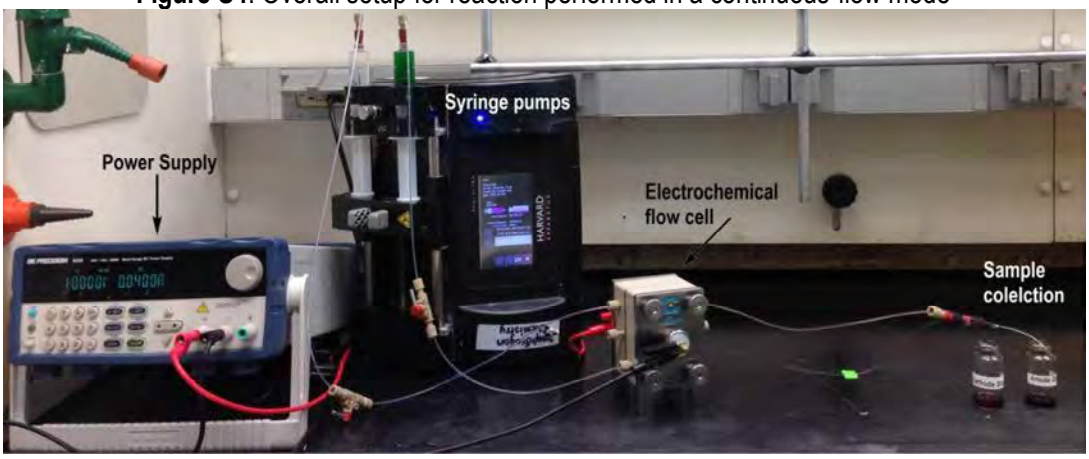
(A) Before Electrolysis (B) After Electrolysis (for ~5 h)

[1] All reactions were performed on 2-mmol scale.
[2] It is important to make sure that the stainless steel wire used to hang the RVC not be in contact with reaction mixture.

Section 4. Reaction setup, procedure and table of optimization for continuous-flow electro-catalytic arylations

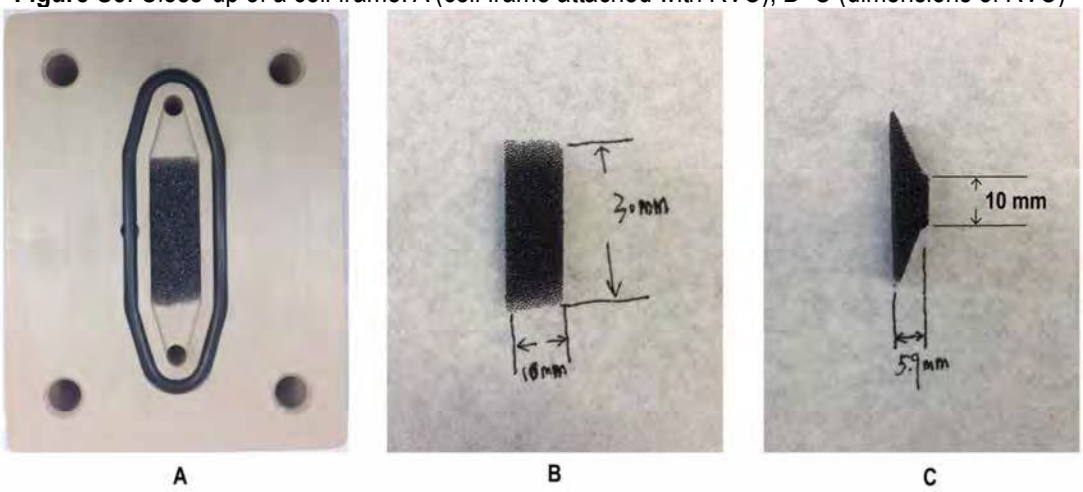
Reaction setup

Figure S4. Overall setup for reaction performed in a continuous-flow mode



As shown in Figure S5-A, RVC carbon foams (100 ppi) were attached to the anode and cathode graphite plates of C-flow® cell frames so as to increase the surface area of both electrodes. Figure S5-B and S5-C show the dimension of the carbon foam, which is ~1 cm^3. The internal wet volume of cathode or anode cell frame is about 0.5 mL.

Figure S5. Close-up of a cell frame: A (cell frame attached with RVC), B+C (dimensions of RVC)



General procedure for flow experiments (Procedure C)

Preparation of cathode solution: NHP ester **4** (2 mmol), iodobenzene (4 mmol), Bu_4NBP_6 (1.55 g, 4 mmol), freshly prepared $NiBr_2$·dme/dtbbpy (0.6 mmol) solution in DMA (see Procedure B for preparation), then diluted with DMA to 20 mL. The solution was then loaded into a 24-mL syringe.

Preparation of anode solution: triethylamine (1.67 mL, 12 mmol), Bu_4NBP_6 (1.55 g, 4 mmol), then diluted with DMA to 20 mL. The solution was then loaded into a 24-mL syringe.

The electrochemical flow cell shown in Figure S4 was conditioned by having 10 mL of Bu_4NPF_6/DMA (0.2 M) flowed through it so as to wet electrodes and nafion membrane. After connecting the flow cell with the power supply, the cathode and anode solutions were delivered by a Harvard syringe pump at the same flow rate into the flow cell. Reaction streams flowing out of the cathode and anode cell frames were collected in scintillation vials. When a flow condition has changed, we waited for about 5 residence time before collecting a sample for HPLC assay so that the sample collected is representative of the steady state reaction.

Table of optimization for continuous-flow electro-catalytic arylations

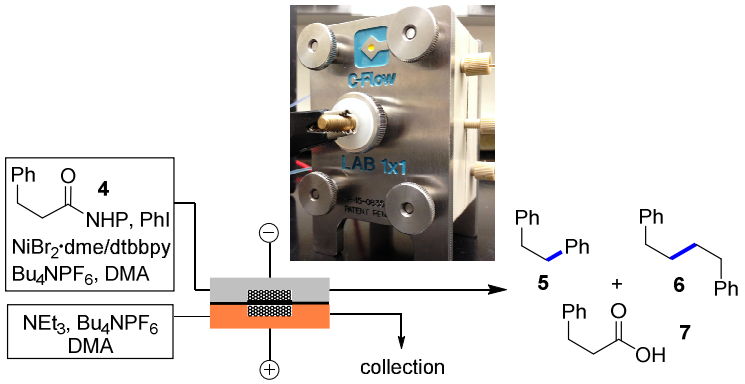


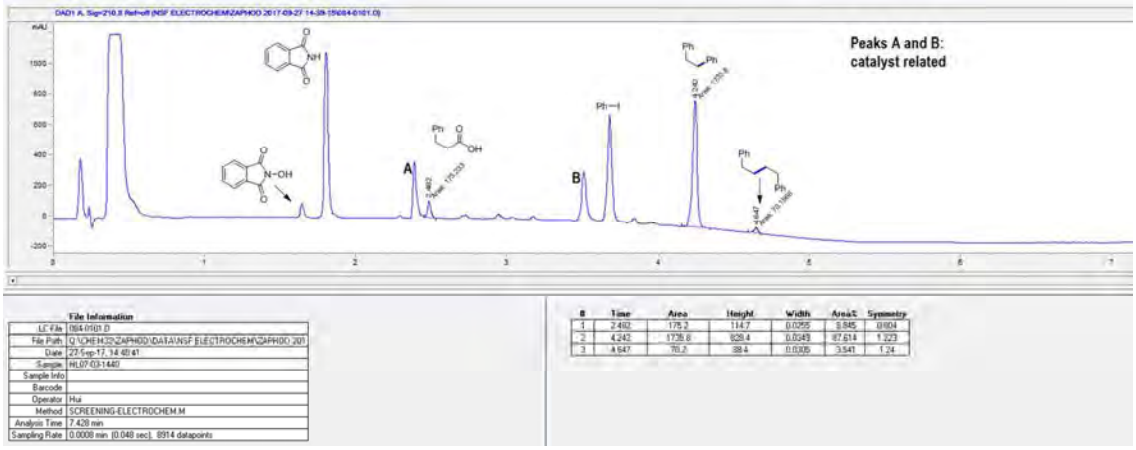
Table S2. Flow rate and current density studies[a]

entry	*j* (mA/cm³)[b]	flow rate (μL/min)	t_R (min)[c]	yield (%)[d]			mass balance (%)	selectivity (**5** : **6**)
				5	**6**	**7**		
1	38.1	100	5.0	44	39	8	91	1.1
2	38.1	110	4.5	52	34	8	94	1.5
3	38.1	130	3.8	54	33	8	95	1.6
4	38.1	140	3.6	52	29	7	88	1.8
5	38.1	160	3.1	49	22	9	80	2.2
6	29.2	83	6.0	47	32	7	86	1.5
7	29.2	100	5.0	58	23	8	89	2.5
8	29.2	110	4.2	61	19	8	88	3.2
9	29.2	120	3.9	62	17	10	89	3.7
10	29.2	130	3.8	57	14	10	81	4.1
11	13.7	50	10	70	12	9	91	5.8
12	13.7	60	8.3	81	7	8	96	11.6
13	13.7	70	7.1	74	6	10	90	12.3

[a] Cathode stream: 4 (0.1 M), PhI (2 eq.) $NiBr_2$·dme/dtbbpy (30 mol%), Bu_4NPF_6 (0.2 M); anode stream: NEt_3 (6 eq.), Bu_4NPF_6 (0.2 M). [b] *j* = current density, mA per cubic centimeter of RVC carbon foam (100

ppi). [c] Internal wet volume of anode or cathode flow cell is 0.5 mL. [d] Yield determined by calibrated HPLC assay.

Representative HPLC chromatogram of reaction mixture in flow (Table S2, entry 12)



Section 5. Cyclic voltammetry studies

Cyclic voltammetry studies were conducted with an Autolab PGSTAT101 potentiostat/galvanostat as shown in Figure S6. The electrochemical cell (catalog # AKCELL1) and electrodes were purchased from Pine Research. A glassy carbon disc (catalog # AFE1XFP030GCR) was used as the working electrode and Pt wire (catalog # AFCTR5) as the counter electrode. Redox potentials are reported versus a Ag/AgCl reference electrode (catalog # RREF0021). To the electrochemical cell was added the compound of interest (0.05 mmol), Bu_4NClO_4 (1.71 g, 5 mmol) and CH_3CN (50 mL). The mixture was sparged with nitrogen for 5 min before cyclic voltammetry measurements.

Figure S6. Cyclic voltammetry study with Autolab PGSTAT101

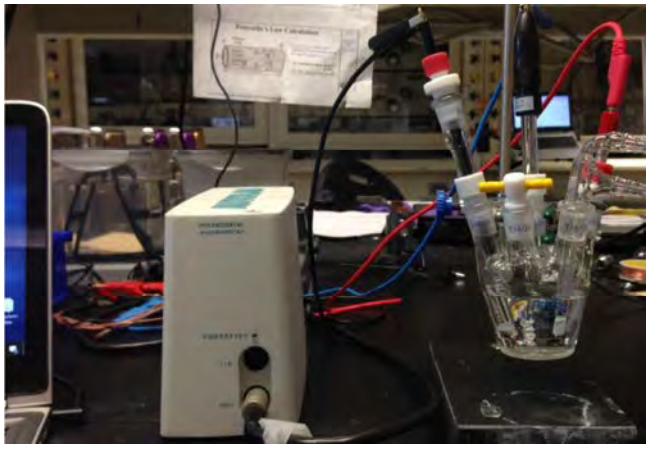


Figure S7. CV of NHP ester **4**

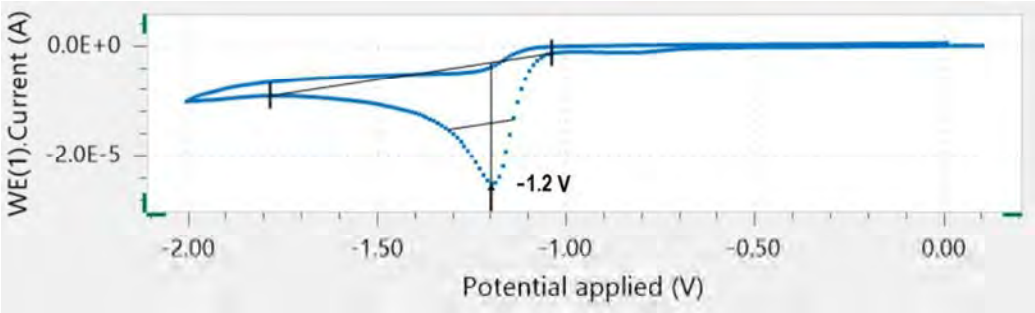


Figure S8. CV of iodobenzene

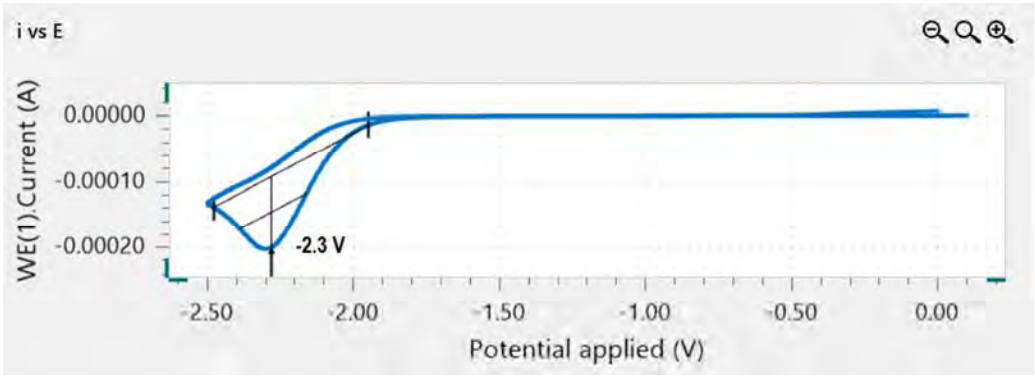
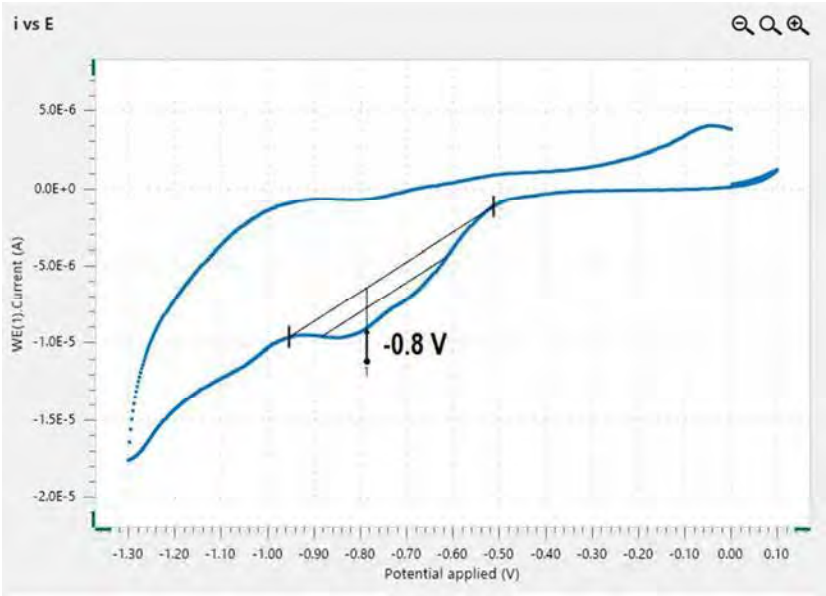
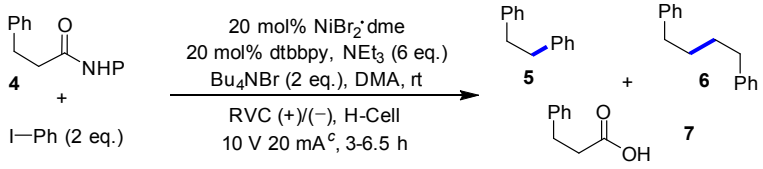


Figure S9. CV of $NiBr_2$/dtbbpy complex



Section 6. Reaction kinetics study



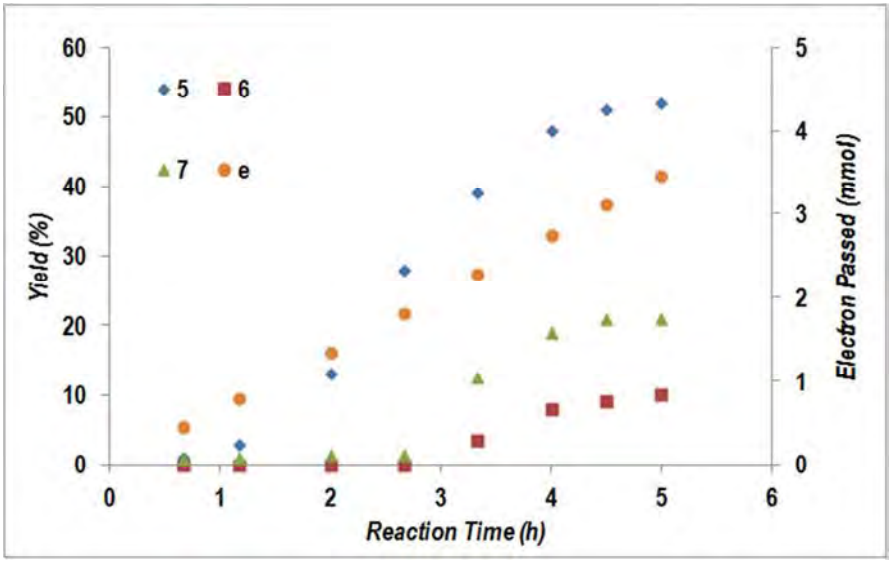
Kinetic study was performed on the reaction between NHP ester **4** and iodobenzene. To the cathode chamber of an H-cell was added NHP ester **4** (2 mmol), iodobenzene (4 mmol), Bu_4NBr (1.29 g, 4 mmol), freshly prepared $NiBr_2$·dme/dtbbpy solution (0.4 mmol, see Procedure B for preparation) and DMA (~11 mL, so that the total volume of solution in cathode side is about 18 mL). To the anode chamber of an H-cell was added triethylamine (1.67 mL, 12 mmol), Bu_4NBr (1.29 g, 4 mmol) and DMA (~16 mL, so that the total volume of solution in anode side is about 18 mL). The cathode solution was purged with nitrogen for about 5 min. The reaction mixture was then electrolyzed at 10 V/20 mA (maximum potential and current, respectively) at room temperature.

Sampling was performed by accurately withdrawing 50 μL of cathode reaction mixture and diluted with 950 μL of CH_3CN (20x dilution), which was followed by calibrated HPLC assay. Table S3 and Figure S10 shows the yields of compounds **5**, **6**, **7**, as well as the amount of charge and electron passed through the system over time.

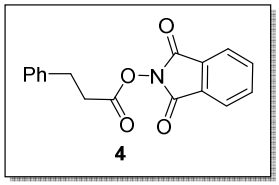
Table S3. Reaction yields, amount of charge and electron over time

entry	reaction time (h)	yield (%)			charge passed (C)	electron passed (mmol)
		5	**6**	**7**		
1	0.67	1	0	0.8	43.2	0.45
2	1.17	3	0	1	75.6	0.79
3	2.00	13	0	1.5	129.6	1.35
4	2.67	28	0	1.5	173.4	1.80
5	3.33	39	3.5	12.6	219.0	2.28
6	4.00	48	8	19	264.6	2.75
7	4.50	51	9	21	298.8	3.11
8	5.00	52	10	21	333.0	3.46

Figure S10. Kinetic profile of electro-catalytic coupling between **4** and iodobenzene



Section 7. Characterization data for NHP esters



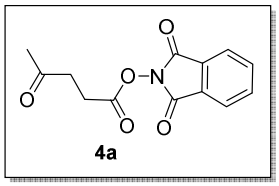
4

Procedure A was followed with hydrocinnamic acid (20 mmol) to yield 4.9607 g (84 %) of product as a white solid after flash chromatography (20% EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.22 (m, 3H), 3.10 (t, *J* = 7.8 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.01, 162.02, 139.31, 134.89, 129.04, 128.85, 128.43, 126.84, 124.11, 32.85, 30.68.

This data is in agreement with what has been previously reported for this compound.[3]



4a

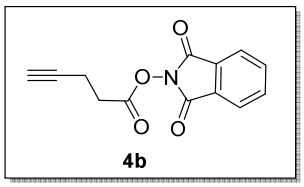
Procedure A was followed using levulinic acid (10 mmol) to yield 1.6313 g (62 %) of product as a colorless solid after flash chromatography (40 % EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.00 – 2.89 (m, 4H), 2.23 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 205.10, 169.30, 161.91, 134.92, 128.98, 124.14, 37.78, 29.83, 25.23.

IR neat (cm^{-1}) 1740, 1700, 1604, 1358, 1331, 1251, 1024, 1014, 877, 750.

HRMS: 262.0710 m/z $[M+H]^+$ calc'd for $C_{13}H_{11}NO_5$, 262.0701 m/z observed.



4b

Procedure A was followed with 4-pentynoic acid (10 mmol) to yield 2.2863 g (94 %) of product as a

[3] Lv, Y.; Sun, K.; Pu, W.; Mao, S.; Li, G.; Niu, J.; Chen, Q.; Wang, T. *RCS Adv.* **2016**, *6*, 93486-93490

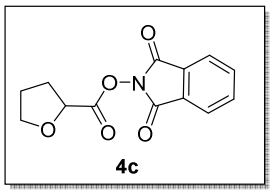
colorless solid after flash chromatography (20 % EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.66 (td, *J* = 7.5, 2.6 Hz, 2H), 2.07 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.09, 161.87, 134.97, 128.94, 124.15, 81.04, 70.18, 30.47, 14.29.

IR neat (cm^{-1}): 3278, 1784, 1738, 1467, 1413, 1373, 1356, 1184, 1132, 1078, 1037, 961, 864, 787, 692.

HRMS: 244.0604 m/z $[M+H]^+$ calc'd for $C_{13}H_9NO_4$, 244.0599 m/z observed.



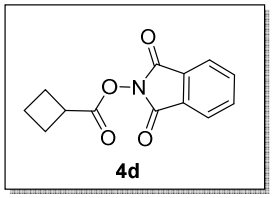
4c

Procedure A was followed with tetrahydro-2-furoic acid (10 mmol) to yield 1.7455 g (67 %) of product as a white solid after flash chromatography (20 % EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.88 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.10 (q, *J* = 7.5, 7.1 Hz, 1H), 4.01 (q, *J* = 7.5, 7.1 Hz, 1H), 2.50 – 2.34 (m, 2H), 2.07 (dtd, *J* = 41.4, 13.5, 13.0, 6.8 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.91, 161.85, 134.95, 129.03, 124.16, 75.09, 70.00, 31.03, 25.23.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[4]



4d

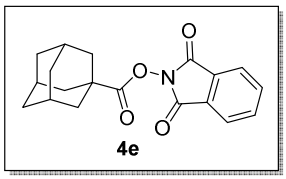
Procedure A was followed with cyclobutanecarboxylic acid (10 mmol) to yield 1.9012 g (78 %) of product as a white solid after flash chromatography (15-25% EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.52 (p, *J* = 8.4 Hz, 1H), 2.56 – 2.47 (m, 2H), 2.41 (dtd, *J* = 12.9, 8.7, 4.6 Hz, 2H), 2.17 – 2.00 (m, 2H).

[4] Cornella, J.; Edwards, J.T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P.S. *J. Am Chem. Soc.* **2016**, *138*, 2174-2177

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.53, 162.21, 134.84, 129.12, 124.05, 35.17, 25.52, 18.86.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[4]



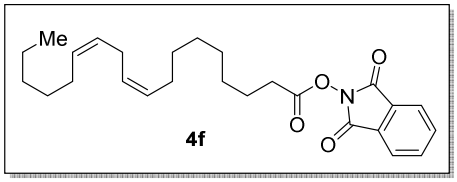
4e

Procedure A was followed with 1-adamantanecarboxylic acid (10 mmol) to yield 3.0681 g (94 %) of product as a white solid after flash chromatography (10-25 % EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 2.16 – 2.13 (m, 6H), 2.12 – 2.08 (m, 3H), 1.79 – 1.76 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.38, 162.28, 134.75, 129.19, 123.96, 40.62, 38.56, 36.31, 27.75.

This data is consistent with what has been previously reported for this compound.[5]



4f

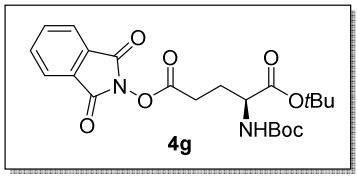
Procedure A was followed with linoleic acid (15.0 mmol) to yield 4.0474 g (63 %) of product as a colorless oil after flash chromatography (5 % EtOAc/hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.42 – 5.29 (m, 4H), 2.77 (t, *J* = 6.6 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.08 – 2.02 (m, 4H), 1.78 (p, *J* = 7.5 Hz, 2H), 1.48 – 1.41 (m, 2H), 1.39 – 1.26 (m, 13H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.76, 162.15, 134.86, 130.37, 130.16, 129.11, 128.22, 128.06, 124.08, 31.67, 31.14, 29.71, 29.50, 29.18, 28.95, 27.36, 27.33, 25.79, 24.81, 22.72, 14.22.

IR neat (cm^{-1}): 2918, 2851, 1826, 1789, 1739, 1610, 1466, 1404, 1374, 1281, 1249, 1217, 1185, 1141, 1069, 1048, 1020, 984, 861, 878, 854, 791, 721, 692

HRMS: 425.2566 m/z $[M+H]^{+}$ calc'd for $C_{26}H_{36}NO_4$, 425.2519 m/z observed.



4g

[5] Pratsch, G.; Lackner, G.L.; Overman, L.E. *J. Org. Chem.* **2015**, *80*, 6025-6036

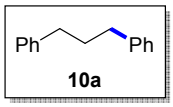
The procedure for making this compound was adapted from Weix and coworkers.[6] To an oven dried flask was added Boc-L-glutamic acid 1-*tert*-butyl ester (5.0 mmol, 1.00 eq.) and dissolved in 25 mL (0.2 M) of THF with magnetic stirring. *N*-hydroxyphthalimide (8.3 mmol, 1.66 eq.) was then added to the flask, followed by *N,N'*-diisopropylcarbodiimide (7.5 mmol, 1.50 eq.), and finally 4-(dimethylamino)pyridine (0.25 mmol, 0.0500 eq.). The reaction mixture was stirred at room temperature for 4 hours after which the reaction was judged to be complete by HPLC analysis. The heterogeneous reaction mixture was then filtered and condensed under negative pressure. The crude isolate was then purified by flash chromatography using EtOAc/hexanes to yield 1.4800 g (66 %) of the title compound as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.7, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.4, 2.5 Hz, 2H), 5.19 (d, *J* = 7.0 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.37 – 2.25 (m, 1H), 2.11 – 2.01 (m, 1H), 1.47 (d, *J* = 16.3 Hz, 18H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.94, 169.11, 161.95, 155.56, 134.92, 129.05, 124.13, 82.80, 80.17, 53.27, 28.45, 28.15, 27.56.

This data is consistent with what has been previously reported for this compound.[6]

Section 8. Characterization data for coupling products



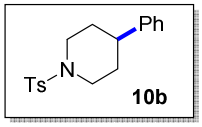
10a

Procedure B was followed with 1,3-dioxoisoindolin-2-yl 4-phenylbutanoate (618 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (100 % hexane) to give 263 mg of product as a colorless oil, with an isolated yield of 67%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.13 (m, 9H), 2.72 (t, *J* = 7.8 Hz, 4H), 2.12 – 1.93 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.38, 128.55, 128.42, 125.85, 35.56, 33.08.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[6]



10b

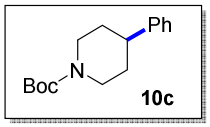
Procedure B was followed with 1,3-dioxoisoindolin-2-yl 1-tosylpiperidine-4-carboxylate (428.5 mg, 1 mmol) and iodobenzene (225 μL, 2 mmol). Purification was performed by silica gel column chromatography (10% EtOAc/hexane) to give 204 mg of product as a colorless solid, with an isolated yield of 63%.

[6] Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016−5019

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.18 (m, 1H), 7.17 – 7.10 (m, 2H), 3.93 (d, *J* = 11.7 Hz, 2H), 2.45 (s, 3H), 2.44 – 2.30 (m, 3H), 1.95 – 1.77 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.89, 143.47, 133.12, 129.61, 128.57, 127.76, 126.67, 126.57, 46.86, 41.83, 32.53, 21.53.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]

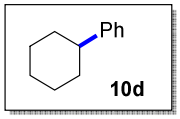


Procedure B was followed with 1,3-dioxoisoindolin-2-yl 1-Boc-piperidine-4-carboxylate (745 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (3-5% EtOAc/hexane) to give 318 mg of product as a colorless oil, with an isolated yield of 65%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 4.25 (s, 2H), 2.80 (t, *J* = 13.0 Hz, 2H), 2.70 – 2.54 (m, 1H), 1.82 (d, *J* = 13.1 Hz, 2H), 1.63 (dd, *J* = 12.5, 4.1 Hz, 2H), 1.49 (d, *J* = 1.7 Hz, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.88, 145.81, 128.53, 126.79, 126.36, 79.41, 44.43, 42.75, 33.23, 28.53.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]

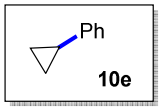


Procedure B was followed with 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (547 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (hexane) to give 198 mg of product as a colorless oil, with an isolated yield of 62%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.33 (m, 2H), 7.31 – 7.27 (m, 2H), 7.25 (m, 1H), 2.57 (d, *J* = 3.5 Hz, 1H), 2.01 – 1.87 (m, 4H), 1.83 (ddd, *J* = 12.8, 3.1, 1.5 Hz, 1H), 1.57 – 1.42 (m, 4H), 1.34 (dd, *J* = 12.6, 3.6 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.12, 128.31, 126.86, 125.81, 44.68, 34.54, 27.00, 26.26.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]



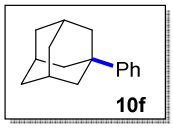
[7] Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132−11135

Procedure B was followed with 1,3-dioxoisoindolin-2-yl cyclopropanecarboxylate (462 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (hexane) to give 97 mg of product as a colorless oil, with an isolated yield of 41%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 – 7.10 (m, 2H), 1.95 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.01 (dd, *J* = 8.4, 2.1 Hz, 2H), 0.86 – 0.66 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.07, 128.38, 125.77, 125.47, 15.51, 9.31.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[8]



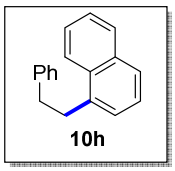
10f

Procedure B was followed with 1,3-dioxoisoindolin-2-yl cyclopropanecarboxylate (651 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (100 % hexanes) to give 97 mg of product as a colorless solid, with an isolated yield of 52%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 2.11 (m, 3H), 1.93 (d, *J* = 3.0 Hz, 6H), 1.84 – 1.74 (m, 6H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.5, 128.2, 125.6, 125.0, 43.3, 37.0, 36.3, 29.1

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]



10h

Procedure B was followed with 1,3-dioxoisoindolin-2-yl 3-phenylpropanoate (590 mg, 2.0 mmol) and 1-iodonaphthalene (584 μL, 4 mmol). Purification was performed by Biotage Ultra-Sil 50 g column (100% pentane) to give 219 mg of product as a colorless oil, with an isolated yield of 47 %.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.55 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H), 7.40 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.29 – 7.23 (m, 3H), 3.42 – 3.37 (m, 2H), 3.10 – 3.05 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.11, 137.90, 134.01, 131.88, 128.98, 128.55, 126.89, 126.14, 126.11, 126.00, 125.68, 125.60, 123.76, 37.22, 35.25.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[9]

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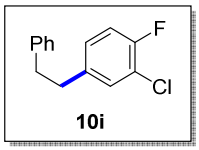
[8] Zhou, Y.; Uyeda, C. *Angew. Chem. Int. Ed*. **2016**, *55*, 3171-3175

[9] Shen, Z. L.; Goh, K. K. K.; Yang, Y. S.; Lai, Y. C.; Wong, C. H. A.; Cheong, H. L.; Loh, T. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 511-514



10i

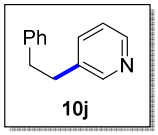
Procedure B was followed with 1,3-dioxoisoindolin-2-yl 3-phenylpropanoate (590 mg, 2 mmol) and 3-chloro-4-fluoroiodobenzene (510 μL, 4 mmol). Purification was performed by Biotage Ultra-Sil 50 g column (100% penatne) to give 245 mg of product as a clear oil, with an isolated yield of 50 %.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.19 (m, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 1H), 7.02 – 6.98 (m, 1H), 2.90 (s, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.65 (d, *J* = 246.4 Hz), 141.04, 138.72 (d, *J* = 4.1 Hz), 130.52, 128.55 (d, *J* = 2.0 Hz), 128.20 (d, *J* = 7.0 Hz), 126.28, 120.57 (d, *J* = 17.6 Hz), 116.37 (d, *J* = 20.8 Hz), 37.81 (d, *J* = 1.5 Hz), 36.96.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -120.77 – -120.98 (m).

IR Neat (cm^{-1}): 3028, 2928, 2859, 1602, 1497, 1453, 1406, 1245, 1059, 874, 812, 749, 696.
EI LRMS: 234.1 m/z [M]$^{+}$ calc'd for $C_{14}H_{12}ClF$, 234.1 m/z observed.



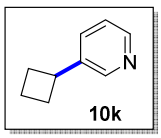
10j

Procedure B was followed with 1,3-dioxoisoindolin-2-yl 3-phenylpropanoate (590 mg, 2 mmol) and 3-iodopyridine (820 mg, 4 mmol). Purification was performed by silica gel column chromatography (40% EtOAc/hexane) to give 190 mg of product as a colorless oil, with an isolated yield of 52 %.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (dt, *J* = 6.4, 1.9 Hz, 2H), 7.50 – 7.39 (m, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.09 (m, 4H), 2.95 (s, 4H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.11, 147.63, 147.60, 140.93, 136.93, 136.07, 128.59, 128.58, 126.32, 123.39, 123.34, 37.59, 35.07

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]



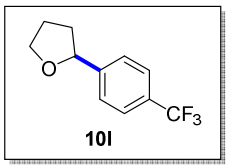
10k

Procedure B was followed with 1,3-dioxoisoindolin-2-yl cyclobutanecarboxylate (491 mg, 2.0 mmol) and 3-iodopyridine (820 mg, 4.0 mmol). Purification was performed by Biotage Ultra-Sil 25 g column (10 – 20% ethyl acetate/hexanes) to give 152 mg of product as a clear liquid, with 57 % isolated yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.41 (d, *J* = 4.6 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.54 (p, *J* = 8.6 Hz, 1H), 2.36 (q, *J* = 8.5 Hz, 2H), 2.19 – 2.09 (m, 2H), 2.04 (dt, *J* = 18.4, 9.6 Hz, 1H), 1.88 (q, *J* = 8.8 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.46, 147.26, 141.13, 133.74, 123.22, 37.86, 29.57, 18.56.
IR Neat (cm^{-1}): 2967, 2938, 2864, 1573, 1477, 1420, 1244, 1025, 995, 805, 711.

HRMS: 134.0964 m/z [M+H]$^+$ calc'd for $C_9H_{11}N$, 134.0964 m/z observed.



10l

Procedure B was followed with 1,3-dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate (522.4 mg, 2 mmol) and 4-iodobenzotrifluoride (1.09 g, 4 mmol). Purification was performed by Biotage Ultra-Sil 25 g column (3 – 15% ethyl acetate/hexanes) to give 226 mg of product as a clear oil, with an isolated yield of 52 %.

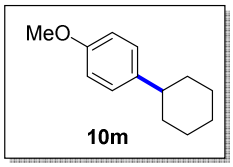
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.41 (m, 2H), 4.95 (t, *J* = 7.2 Hz, 1H), 4.11 (dt, *J* = 8.4, 6.8 Hz, 1H), 3.96 (dt, *J* = 8.3, 6.9 Hz, 1H), 2.37 (dq, *J* = 12.2, 6.7 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.77 (dq, *J* = 12.3, 7.7 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.1, 147.7, 125.7, 125.2 (q, *J* = 3.9 Hz) 68.9, 34.7, 25.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.4.

IR Neat (cm^{-1}): 2872, 1620, 1417, 1324, 1162, 1121, 1066, 1017, 823, 837.

HRMS: 217.0835 m/z [M+H]$^+$ calc'd for $C_{11}H_{11}F_3O$, 217.0846 m/z observed.



10m

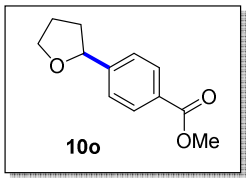
Procedure B was followed with 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (547 mg, 2 mmol) and 4-iodoanisole (936 mg, 4 mmol). Purification was performed by silica gel column chromatography (3-4% EtOAc/hexane) to give 152 mg of product as a colorless solid, with an isolated yield of 40%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.21 – 7.09 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 2.54 – 2.39 (m, 1H), 1.94 – 1.79 (m, 4H), 1.79 – 1.70 (m, 1H), 1.47 – 1.34 (m, 4H), 1.27 (tt, *J* = 12.8, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.78, 140.50, 127.75, 127.74, 113.78, 55.37, 43.83, 34.87, 27.11, 26.33.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[10]

[10] Liu, D.; Li, Y.; Liu, C.; Lei, A.; Qi, X.; Lan, Y. *Org. Lett.* **2016**, *17*, 6456-6459



10o

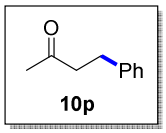
Procedure B was followed with 1,3-dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate (522.4 mg, 2 mmol) and methyl 4-iodobenzoate (1.05 g, 4 mmol). Purification was performed by Biotage Ultra-Sil 25 g column (3 – 15% ethyl acetate/hexanes) to give 242 mg of product as a colorless solid, with an isolated yield of 59 %.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 4.94 (t, *J* = 7.2 Hz, 1H), 4.11 (dt, *J* = 8.3, 6.8 Hz, 1H), 3.95 (dt, *J* = 8.3, 7.0 Hz, 1H), 3.90 (s, 3H), 2.36 (dq, *J* = 12.3, 6.7 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.77 (dq, *J* = 12.2, 7.6 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.0, 148.9, 129.6, 128.9, 125.4, 80.2, 68.8, 52.0, 34.7, 25.9.

IR Neat (cm^{-1}): 2953, 2869, 1718, 1811, 1576, 1435, 1414, 1377, 1275, 1175, 1109, 1062, 1018, 965, 922, 856, 765, 706.

HRMS: 207.1016 m/z [M+H]$^{+}$ calc'd for $C_{12}H_{14}O_3$, 207.1026 m/z observed.



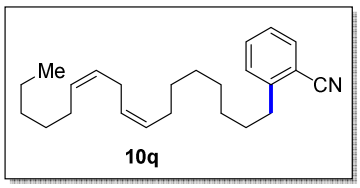
10p

Procedure B was followed with 1,3-dioxoisoindolin-2-yl 4-oxopentanoate (522 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (5% EtOAc/hexane) to give 225 mg of product as a colorless solid, with an isolated yield of 76%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (s, 2H), 7.23 – 7.15 (m, 3H), 2.90 (d, *J* = 7.8 Hz, 2H), 2.77 (d, *J* = 8.1 Hz, 2H), 2.14 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 207.92, 141.05, 128.34, 126.16, 45.20, 30.11, 29.79.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[11]



10q

Procedure B was followed with 1,3-dioxoisoindolin-2-yl (9Z,12Z)-octadeca-9,12-dienoate (1.374 g, 2 mmol) and 2-iodobenzonitirle (916 mg, 4 mmol). Purification was performed by Biotage Ultra-Sil 25 g column (3 – 15% EtOAc/hex) to give 235 mg of product as a colorless oil, with a yield of 35 %.

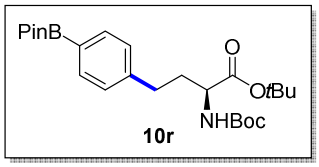
[11] Moteki, S.; Usui, A.; Zhang, T.; Solorio Alvarado, C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8657-8660

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.50 (td, *J* = 7.7, 1.5 Hz, 1H), 7.33 – 7.24 (m, 2H), 5.43 – 5.27 (m, 4H), 2.89 – 2.81 (m, 2H), 2.81 – 2.73 (m, 2H), 2.05 (q, *J* = 6.9 Hz, 4H), 1.76 – 1.62 (m, 2H), 1.45 – 1.23 (m, 14H), 0.94 – 0.83 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 132.7, 132.6, 130.2, 130.1, 129.4, 128.0, 127.9, 126.3, 118.2, 112.3, 34.6, 31.5, 30.9, 29.6, 29.3, 29.3, 29.2, 29.2, 27.2, 25.6, 22.6, 14.1.

IR Neat (cm^{-1}): 3011, 2927, 2857, 2252, 2141, 2100, 1998, 1958, 1600, 1486, 1465, 761, 725.

HRMS: 338.2842 m/z [M+H]$^{+}$ calc'd for $C_{24}H_{35}N$, 338.2841 m/z observed.



10r

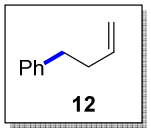
Procedure B was followed with 1-(tert-butyl) 5-(1,3-dioxoisoindolin-2-yl) (tert-butoxycarbonyl)-*L*-glutamate (897 mg, 2 mmol) and 4-iodophenylboronic acid pinacol ester (1.32 g, 4 mmol). Purification was performed by Biotage Ultra-Sil 25 g column (3 – 10% EtOAc/hexane) to give 360 mg of product as a colorless solid, with an isolated yield of 39%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.06 (d, *J* = 8.3 Hz, 0.5H), 4.24 (d, *J* = 7.2 Hz, 0.5H), 2.67 (qt, *J* = 13.7, 7.3 Hz, 2H), 2.13 – 2.04 (m, 1H), 1.95 – 1.82 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H), 1.33 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 155.3, 144.6, 135.0, 127.8, 83.7, 81.9, 79.7, 53.9, 34.7, 31.8, 28.3, 28.0, 24.8.

IR (neat, cm^{-1}) 2978, 2935, 2873, 1716, 1612, 1510, 1454, 1361, 1320, 1174, 1149, 1147, 1090, 1060, 1023, 963, 859, 827, 738, 659.

HRMS: 461.3058 m/z [M+H]$^{+}$ calc'd for $C25H40BNO_6$, 461.3065 m/z observed.



12

Procedure B was followed with 1,3-dioxoisoindolin-2-yl 2-cyclopropylacetate (490 mg, 2 mmol) and iodobenzene (450 μL, 4 mmol). Purification was performed by silica gel column chromatography (hexane) to give 121 mg of product as a colorless solid, with an isolated yield of 46%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 3H), 5.91 (ddtd, *J* = 16.9, 10.2, 6.6, 1.0 Hz, 1H), 5.13 – 5.06 (m, 1H), 5.06 – 4.99 (m, 1H), 2.81 – 2.71 (m, 2H), 2.42 (dtd, *J* = 9.2, 6.5, 1.4 Hz, 2H).
^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.00, 138.22, 128.56, 128.42, 125.94, 115.04, 35.66, 35.54.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[12]

[12] Liu, R.; Lu, Z.; Hu, X.; Li, J.; Yang, X. *Org. Lett.* **2015**, *17*, 1489-1492