Supporting Information for:

Development of a Scalable Negishi Cross-Coupling Process for the Preparation of 2-chloro-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)aniline

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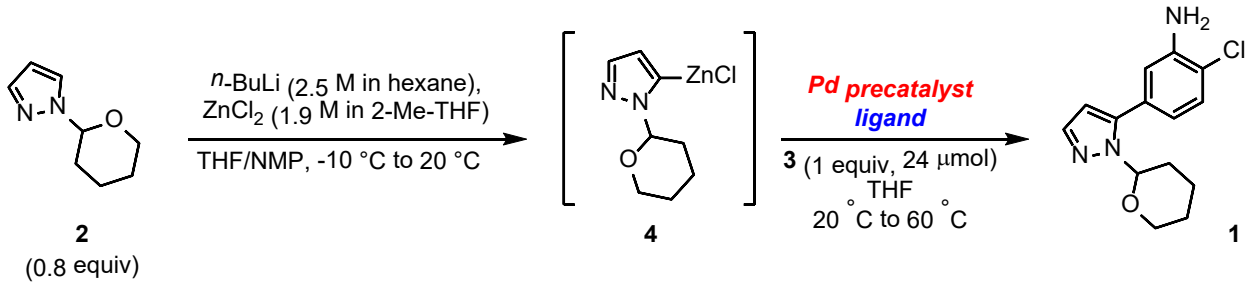
General Information

All operations were performed under a nitrogen atmosphere. Starting materials, reagents, and solvents were used as-received from commercial vendors. Standard benchtop techniques were employed for handling air and moisture sensitive reagents. Hexyllithium (2.3 M in hexane) and $ZnCl_2$ (1.9 M in 2-Me-THF) were purchased from Sigma-Aldrich. UPLCMS analysis was performed using a Waters Acquity BEH Shield RP-18 column (1.7 μm, 2.1 mm x 50 mm) with detection by UV at 220 nm and low resolution mass spectrometry detection (positive ion mode) with a Shimadzu LCMS-2020 mass spectrometer. HPLC analysis was performed using a Supelco Ascentis Express C-18 column (2.7 μm, 4.6 mm x 50 mm) with UV detection at 220 nm. High-resolution mass spectrometry (HRMS) was performed on an Agilent 6230B TOF mass spectrometer. NMR spectra were recorded on a Bruker AV-500 instrument, and are referenced to residual undeuterated solvents ($CDCl_3$: δ 7.26, DMSO-d_6: δ 2.50; CD_3CN: δ 1.94, MeOH-d_4: δ 3.31). Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant J (Hz), and integration. Reaction calorimetry was carried out using a Mettler-Toledo EasyMax 402 Calorimeter fitted with HFCal calorimetry hardware, an Aalborg XRF 17, and an Easy Control Box (ECB).

In situ FTIR Spectroscopy

ReactIR 45m with MCT Detector using HappGenzel Apodization; Probe: SiComp (Silicon) connected via AgX 6mm x 1.5m Fiber (Silver Halide); Sampling: 3000 to 650 cm^{-1} at 8 wavenumber resolution; AutoSelect; Gain: 1x;

High-Throughput Catalyst Screening



2 (0.8 equiv)

4

1

Generation of heteroaryl zinc species **4**

In a N_2-filled glovebox, charged **2** (300 mg, 1.95 mmol) and THF (3.0 mL) to a 20-mL scintillation vial under N_2 and cooled solution to -10 °C with agitation at 300 RPM. Added *n*-butyllithium (820 μL, 2.1 mmol, 2.5 M in hexanes) dropwise to the vial over 4 minutes and aged the resulting slurry for 10 minutes at -10 °C. Added $ZnCl_2$ dropwise to the vial over 4 minutes (1.1 mL, 2.1 mmol, 1.9 M in 2-Me-THF). Aged the slurry for 5 minutes at -10 °C and warmed to 20 °C. To facilitate uniform dosing of the arylzinc reagent to the screening plate, NMP (1.5 mL) was added to the vial at 20 °C.

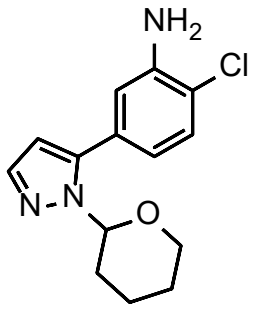
Screening Procedure

Pre-dosed phosphine ligand vials (2 μmol for monodentate ligands and 1 μmol for bidentate ligands) were added to a 96-well reaction plate. A solution of $Pd(allyl)Cl]_2$ (90 uL of a 0.005M solution in THF) was then added to each vial and the plate was aged at ambient temperature for 20 minutes. A solution of **3** in THF (60 μL of a 0.4M solution) was then added to each vial. The plate was concentrated to dryness using a Genevac and microstir bars were added to each vial. A solution of **4** (66 μL, from above) was added to each vial, followed by 34 μL THF to bring the total reaction volume to 100 μL. The plate was sealed under N_2 with a Teflon sheet, two black rubber mats, and a metal lid. The plate was removed from the glovebox and heated for 16 hours at 60 °C with orbital shaking at 300 RPM. After cooling to ambient temperature, the vials were diluted with 80:20 MeCN:water (400 μL). An aliquot (20 μL) was transferred to a 96-well filter plate and further diluted in 80:20 MeCN:water (650 μL). The samples were subjected to UPLCMS analysis.

Table S1. Ligand screening data with $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$

Pd precatalyst		Ligand		THF:NMP (3:1)	Stir	Temp	Time	1 (pdt)	THP-Pyrazole
Name	mol %	Name	L/M	M	RPM	°C	h	*AP*	*AP*
Pd(OAc)2	3.8%	PPh3	2.2	0.24	300	60	16.0	45.38%	8.13%
[(Allyl)PdCl]2	1.9%	PPh3	2.2	0.24	300	60	16.0	41.57%	10.09%
Pd(OAc)2	3.8%	P(fur)3	2.2	0.24	300	60	16.0	22.49%	13.20%
[(Allyl)PdCl]2	1.9%	P(fur)3	2.2	0.24	300	60	16.0	33.98%	11.40%
Pd(OAc)2	3.8%	PPh2(o-anis)	2.2	0.24	300	60	16.0	57.26%	5.81%
[(Allyl)PdCl]2	1.9%	PPh2(o-anis)	2.2	0.24	300	60	16.0	50.73%	8.00%
Pd(OAc)2	3.8%	P(p-CF3-Ph)3	2.2	0.24	300	60	16.0	32.83%	11.24%
[(Allyl)PdCl]2	1.9%	P(p-CF3-Ph)3	2.2	0.24	300	60	16.0	28.88%	12.74%
Pd(OAc)2	3.8%	P(o-Tol)3	2.2	0.24	300	60	16.0	48.51%	9.06%
[(Allyl)PdCl]2	1.9%	P(o-Tol)3	2.2	0.24	300	60	16.0	40.82%	9.86%
Pd(OAc)2	3.8%	PCy3 HBF4	2.2	0.24	300	60	16.0	41.77%	9.50%
[(Allyl)PdCl]2	1.9%	PCy3 HBF4	2.2	0.24	300	60	16.0	34.14%	12.22%
Pd(OAc)2	3.8%	PPh2Pyr	2.2	0.24	300	60	16.0	41.25%	9.26%
[(Allyl)PdCl]2	1.9%	PPh2Pyr	2.2	0.24	300	60	16.0	39.78%	9.66%
Pd(OAc)2	3.8%	PtBu3 HBF4	2.2	0.24	300	60	16.0	***80.92%***	2.78%
[(Allyl)PdCl]2	1.9%	PtBu3 HBF4	2.2	0.24	300	60	16.0	***81.30%***	4.04%
Pd(OAc)2	3.8%	PtBu2Me HBF4	2.2	0.24	300	60	16.0	35.57%	10.60%
[(Allyl)PdCl]2	1.9%	PtBu2Me HBF4	2.2	0.24	300	60	16.0	26.50%	13.05%
Pd(OAc)2	3.8%	A-caPhos	2.2	0.24	300	60	16.0	54.31%	7.30%
[(Allyl)PdCl]2	1.9%	A-caPhos	2.2	0.24	300	60	16.0	55.14%	7.80%
Pd(OAc)2	3.8%	A-taPhos	2.2	0.24	300	60	16.0	56.24%	9.28%
[(Allyl)PdCl]2	1.9%	A-taPhos	2.2	0.24	300	60	16.0	78.58%	4.29%
Pd(OAc)2	3.8%	CX-A	2.2	0.24	300	60	16.0	0.27%	15.12%
[(Allyl)PdCl]2	1.9%	CX-A	2.2	0.24	300	60	16.0	0.58%	16.44%
Pd(OAc)2	3.8%	CX-ABn	2.2	0.24	300	60	16.0	28.29%	12.73%
[(Allyl)PdCl]2	1.9%	CX-ABn	2.2	0.24	300	60	16.0	58.12%	7.46%
Pd(OAc)2	3.8%	X-Phos	2.2	0.24	300	60	16.0	***89.54%***	1.12%
[(Allyl)PdCl]2	1.9%	X-Phos	2.2	0.24	300	60	16.0	***86.91%***	2.69%
Pd(OAc)2	3.8%	RuPhos	2.2	0.24	300	60	16.0	78.52%	2.78%
[(Allyl)PdCl]2	1.9%	RuPhos	2.2	0.24	300	60	16.0	73.59%	4.86%
Pd(OAc)2	3.8%	S-Phos	2.2	0.24	300	60	16.0	63.43%	4.57%
[(Allyl)PdCl]2	1.9%	S-Phos	2.2	0.24	300	60	16.0	66.51%	4.21%
Pd(OAc)2	3.8%	JackiePhos	2.2	0.24	300	60	16.0	70.89%	12.41%
[(Allyl)PdCl]2	1.9%	JackiePhos	2.2	0.24	300	60	16.0	63.55%	19.35%
Pd(OAc)2	3.8%	Cy-JohnPhos	2.2	0.24	300	60	16.0	79.99%	5.03%
[(Allyl)PdCl]2	1.9%	Cy-JohnPhos	2.2	0.24	300	60	16.0	61.59%	5.82%
Pd(OAc)2	3.8%	Cy-DavePhos	2.2	0.24	300	60	16.0	77.67%	8.28%
[(Allyl)PdCl]2	1.9%	Cy-DavePhos	2.2	0.24	300	60	16.0	73.73%	10.17%
Pd(OAc)2	3.8%	Xantphos	1.1	0.24	300	60	16.0	78.55%	1.94%
[(Allyl)PdCl]2	1.9%	Xantphos	1.1	0.24	300	60	16.0	***83.99%***	2.42%
Pd(Xantphos)Cl2	3.8%			0.24	300	60	16.0	78.32%	1.93%
Pd(Xantphos)Cl2	3.8%			0.24	300	60	16.0	77.43%	1.91%
Pd(OAc)2	3.8%	Cy-Xantphos	1.1	0.24	300	60	16.0	39.13%	10.95%
[(Allyl)PdCl]2	1.9%	Cy-Xantphos	1.1	0.24	300	60	16.0	11.60%	17.53%
Pd(OAc)2	3.8%	tB-Xantphos	1.1	0.24	300	60	16.0	5.25%	18.84%
[(Allyl)PdCl]2	1.9%	tB-Xantphos	1.1	0.24	300	60	16.0	27.39%	13.41%
Pd(OAc)2	3.8%	DPEphos	1.1	0.24	300	60	16.0	***80.82%***	2.22%
[(Allyl)PdCl]2	1.9%	DPEphos	1.1	0.24	300	60	16.0	77.42%	3.70%

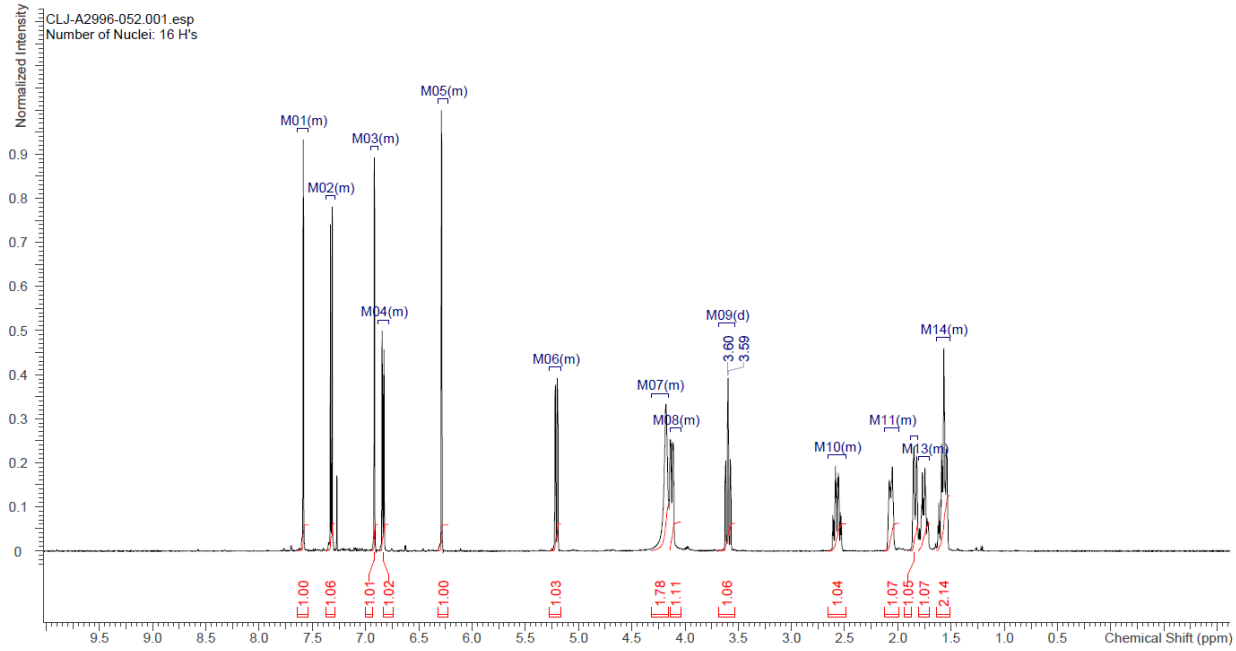
Pd(OAc)2	3.8%	DCEPhos	1.1	0.24	300	60	16.0	***80.50%***
[(Allyl)PdCl]2	1.9%	DCEPhos	1.1	0.24	300	60	16.0	78.95%
Pd(OAc)2	3.8%	DPPE	1.1	0.24	300	60	16.0	44.43%
[(Allyl)PdCl]2	1.9%	DPPE	1.1	0.24	300	60	16.0	63.64%
Pd(OAc)2	3.8%	DCPP	1.1	0.24	300	60	16.0	17.33%
[(Allyl)PdCl]2	1.9%	DCPP	1.1	0.24	300	60	16.0	21.99%
Pd(OAc)2	3.8%	DPPB	1.1	0.24	300	60	16.0	68.18%
[(Allyl)PdCl]2	1.9%	DPPB	1.1	0.24	300	60	16.0	59.36%
Pd(OAc)2	3.8%	DCPB HBF4	1.1	0.24	300	60	16.0	34.89%
[(Allyl)PdCl]2	1.9%	DCPB HBF4	1.1	0.24	300	60	16.0	44.96%
Pd(OAc)2	3.8%	DPPPent	1.1	0.24	300	60	16.0	55.33%
[(Allyl)PdCl]2	1.9%	DPPPent	1.1	0.24	300	60	16.0	49.11%
Pd(OAc)2	3.8%	BISBI	1.1	0.24	300	60	16.0	39.71%
[(Allyl)PdCl]2	1.9%	BISBI	1.1	0.24	300	60	16.0	48.27%
Pd(OAc)2	3.8%	DPPF	1.1	0.24	300	60	16.0	60.77%
[(Allyl)PdCl]2	1.9%	DPPF	1.1	0.24	300	60	16.0	63.16%
Pd(OAc)2	3.8%	DCyPF	1.1	0.24	300	60	16.0	40.01%
[(Allyl)PdCl]2	1.9%	DCyPF	1.1	0.24	300	60	16.0	41.52%
Pd(OAc)2	3.8%	DPP-DtBPF	1.1	0.24	300	60	16.0	***90.34%***
[(Allyl)PdCl]2	1.9%	DPP-DtBPF	1.1	0.24	300	60	16.0	***88.88%***
Pd(OAc)2	3.8%	BIPHEP	1.1	0.24	300	60	16.0	32.78%
[(Allyl)PdCl]2	1.9%	BIPHEP	1.1	0.24	300	60	16.0	57.39%
Pd(OAc)2	3.8%	Cy-BIPHEP	1.1	0.24	300	60	16.0	18.06%
[(Allyl)PdCl]2	1.9%	Cy-BIPHEP	1.1	0.24	300	60	16.0	18.72%



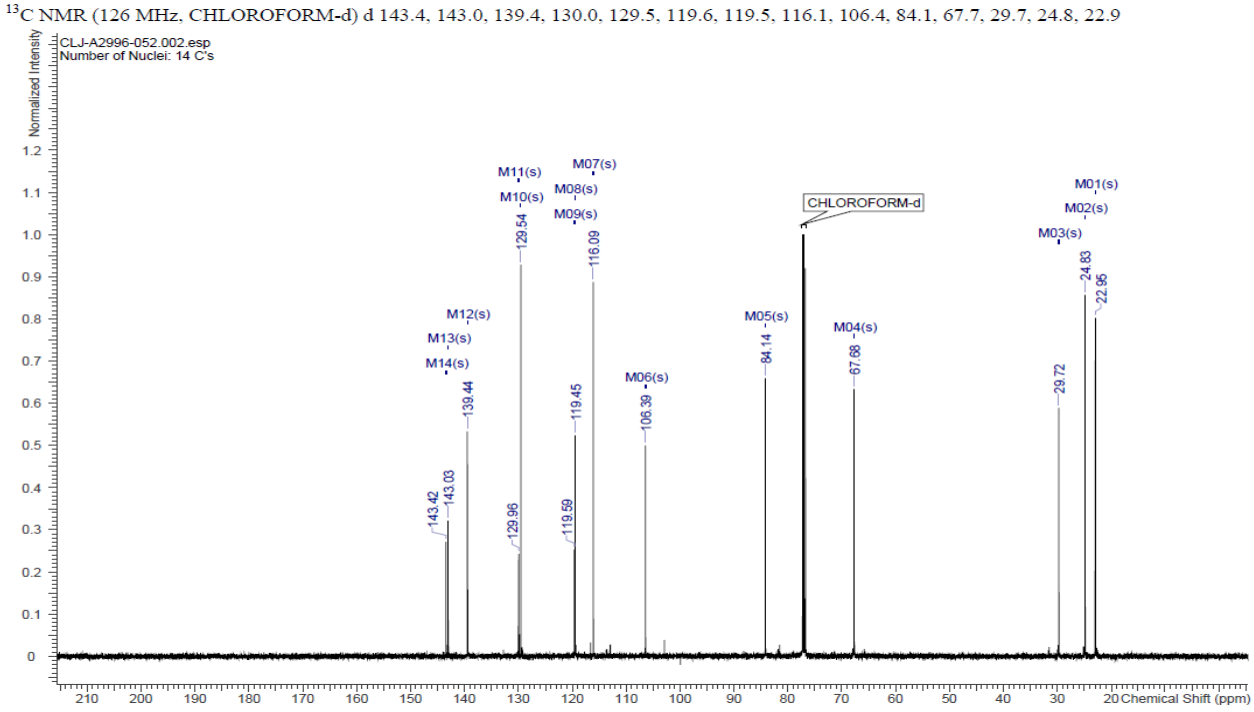
2-chloro-5-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)aniline (**1**)
Chemical Formula: $C_{14}H_{16}ClN_3O$
Exact Mass: 277.0982
Molecular Weight: 277.7520

^{1}H NMR Spectrum (500 MHz, chloroform-*d*) of 2-chloro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)aniline (**1**)

^{1}H NMR (500 MHz, CHLOROFORM-d) d 7.64 - 7.54 (m, 1H), 7.38 - 7.29 (m, 1H), 6.96 - 6.88 (m, 1H), 6.88 - 6.79 (m, 1H), 6.32 - 6.22 (m, 1H), 5.27 - 5.16 (m, 1H), 4.32 - 4.16 (m, 2H), 4.14 - 4.04 (m, 1H), 3.60 (d, *J*=1.5 Hz, 1H), 2.66 - 2.49 (m, 1H), 2.13 - 1.99 (m, 1H), 1.88 - 1.81 (m, 1H), 1.81 - 1.70 (m, 1H), 1.64 - 1.51 (m, 2H)



^{13}C NMR Spectrum (126 MHz, chloroform-*d*) of 2-chloro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)aniline (**1**)



In situ FTIR Spectroscopy

A SiComp (Silicon) probe was inserted into a 250-mL Chemglass reactor and the reaction was run according to the general procedure. Analysis of the ReactIR data was carried out at 935 cm^{-1} and 1110 cm^{-1}.

Reaction Calorimetry

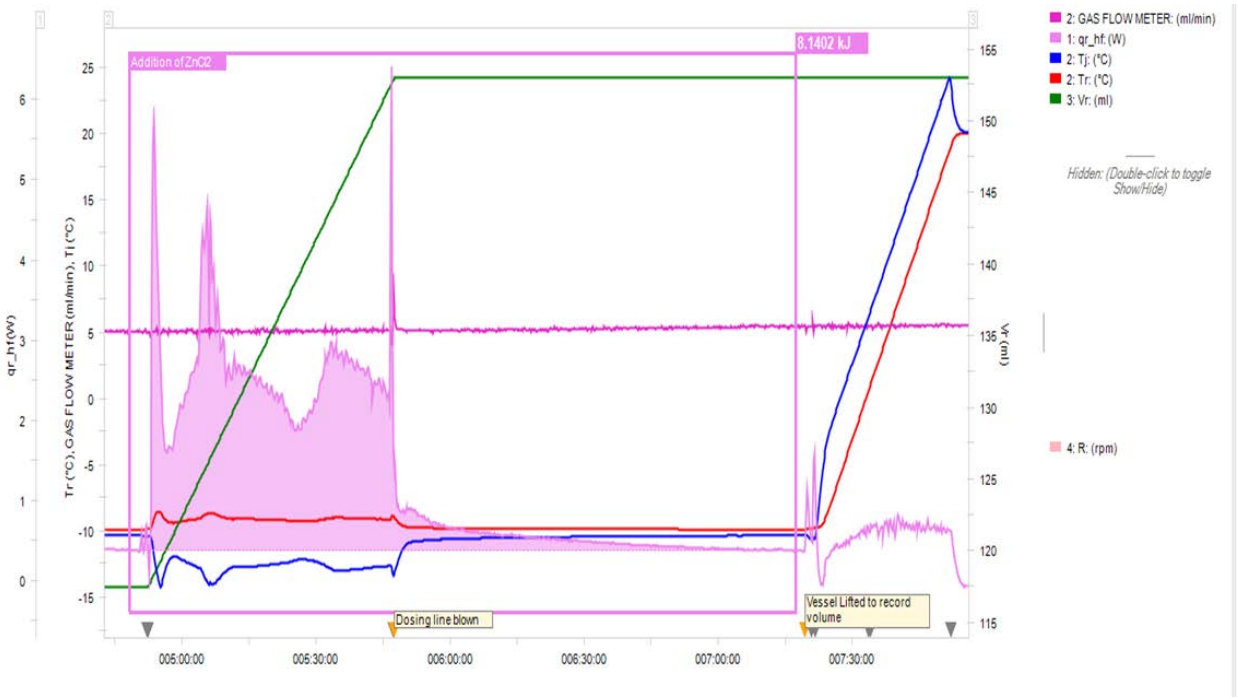
Experimental Procedure

In a Mettler-Toledo EasyMax 402 Calorimeter, hexyllithium (20.0 g, 28.5 mL, 2.3M solution in hexane) was charged to a 0 °C solution of **1** (9.58 g, 40 mmol) in THF (97 mL) at a rate of 1.64 g/min with agitation at 300 RPM. The slurry was warmed to 15 °C and the $ZnCl_2$ solution (37.9 g, 35.5 mL, 1.9 M in 2-methyltetrahydrofuran) was charged at a rate of 0.56 g/mL with agitation at 300 RPM. Calorimetry data for these two steps was collected and is shown below.

Figure S1. Reaction Calorimetry Data for Hexyllithium Addition

Calorimetry			
Energy released		9.621	kJ
Maximum power		8.500	W
Energy released per mole	5-bromo-2-chloroanilin	210.664	kJ
Adiabatic Temperature rise		44.002	K
Maximum power per mole	5-bromo-2-chloroanilin	186.118	W

Figure S2. Reaction Calorimetry Data for $ZnCl_2$ Addition



Calorimetry			
Energy released		8.140	kJ
Maximum power		5.500	W
Energy released per mole	5-bromo-2-chloroaniline	167.638	kJ
Adiabatic Temperature rise		34.901	K
Maximum power per mole	5-bromo-2-chloroaniline	113.266	W