

Aryldiazonium Tetrafluoroborate salts as Green and Efficient Coupling Partners for the Suzuki-Miyaura Reaction: From Optimisation to Mole Scale.

Aymeric P. Colleville,^{†,‡,*} Richard A. J. Horan[†] and Nicholas C. O. Tomkinson[‡]

[†]Global API Chemistry, GlaxoSmithKline Research and Development Ltd., Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.

[‡]WestCHEM, Department of Pure and Applied Chemistry, Thomas Graham Building, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, U.K.

Corresponding author: Aymeric P. Colleville, email: aymeric.p.colleville@gsk.com

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1. GENERAL EXPERIMENTAL

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H -NMR) homogeneous material, unless otherwise stated.

HPLC Method: HPLC analysis was conducted on a Hewlett Packard series 1100 using a Phenomenex Luna C18 column (50 mm x 2.1 mm i.d. 3.0 μm packing diameter) at 40 $^\circ\text{C}$.

Eluent A = Water + 0.05%v/v trifluoroacetic acid

Eluent B = Acetonitrile + 0.05%v/v trifluoroacetic acid

Gradient :

Time (min)	Flow rate (mL/min)	% A	% B
0	1.0	100	0
8	1.0	5	95
8.5	1.0	5	95
8.6	1.0	100	0
10.0	1.0	100	0

The UV detection was performed at 225 nm.

LC/MS Method: HPLC analysis was conducted on a Waters ZQ using a Phenomenex Luna C18 column (50 mm x 2.1 mm i.d. 3.0 μm packing diameter) at 40 $^\circ\text{C}$.

Eluent A = Water + 0.05%v/v trifluoroacetic acid

Eluent B = Acetonitrile + 0.05%v/v trifluoroacetic acid

Gradient:

Time (min)	Flow rate (mL/min)	% A	% B
0	1.0	100	0
8	1.0	5	95
8.5	1.0	5	95
8.6	1.0	100	0
10.0	1.0	100	0

The UV detection was a summed signal of the range 205 nm to 400 nm.

Mass Spectrometry was conducted on a Waters ZQ.

Ionisation mode: Positive Electrospray

Scan Range: 100 to 1000 AMU

Scan Time: 0.5 second

Inter scan Delay: 0.05 seconds

Silica gel chromatography

Silica gel chromatography purification were performed on a Biotage SP4, using prepacked Biotage silica cartridges (KP-Sil) monitored by UV.

Nuclear magnetic resonance spectrometry

400 MHz ^1H NMR spectra were recorded on Bruker AV 400 NMR spectrometers. Signals are reported as: chemical shift δ /ppm (multiplicity, number of protons, coupling constants). Chemical shifts are reported to the nearest 0.01 ppm and coupling constant to the nearest 0.1 Hz (s = singlet, d = doublet, t = triplet, q =

quartet, m = multiplet, b = broad, a = apparent). 100 MHz ^{13}C spectra were recorded on the same spectrometers.

High-Resolution Mass Spectrometry: High Resolution Mass Spectrometry was carried out by the Mass Spectrometry Service in Swansea.

Differential Scanning Calorimetry analysis

Samples were run in high pressure gold 40 μL crucibles from 20 $^{\circ}\text{C}$ to 350 $^{\circ}\text{C}$ at 2 $^{\circ}\text{C}/\text{min}$ on a Mettler Toledo DSC823e device.

2. SAFETY WARNING



Aryldiazonium compounds are inherently unstable molecules and decompose to release a molar equivalent of nitrogen. Solid diazonium salts have been reported to spontaneously decompose very violently, leading to injuries or fatalities. The work described in this document has been undertaken at GlaxoSmithKline under a registered specific risk assessment. None of the aryldiazonium tetrafluoroborate salt presented in this paper detonated during shock (hammer test), friction or high temperature (300 $^{\circ}\text{C}$ hot plate test).

While no incident has been observed when handling the reported aryldiazonium salts using stainless steel spatulas on small scale, the authors have not studied the potential for metal implements to initiate decomposition. The larger scale reactions described in this paper made use of plastic spatulas and filters and these are recommended.

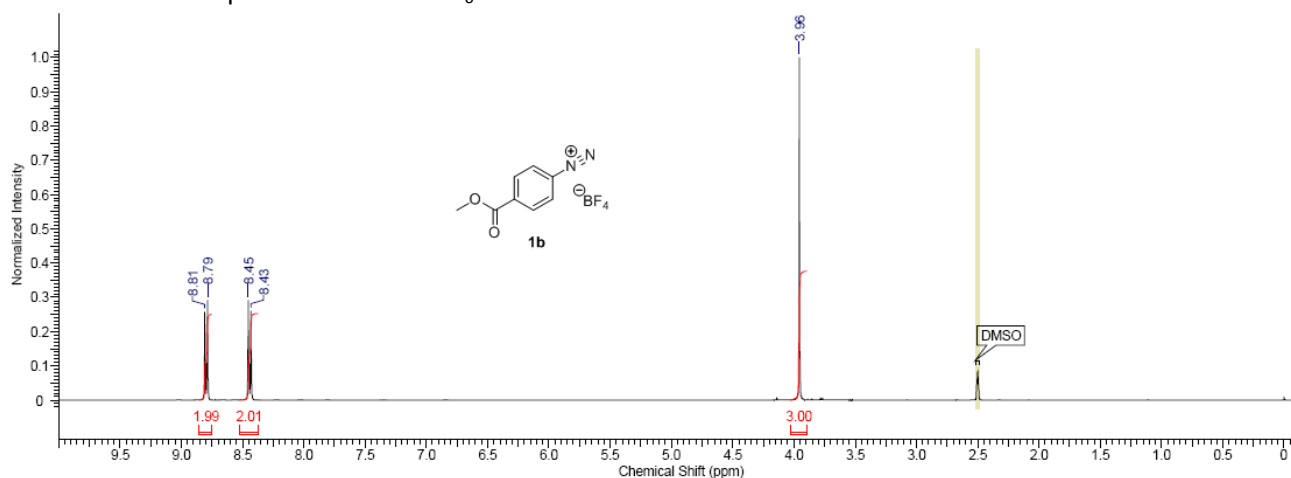
3. GENERAL PROCEDURES FOR DIAZOTISATION

General diazotisation procedure with tert-butyl nitrite: To a stirred solution of the aniline (1.0 eq) in reported solvent at 0 $^{\circ}\text{C}$ was added $\text{BF}_3 \cdot \text{THF}$ complex (1.5 eq) followed by dropwise addition of *tert*-butyl nitrite (1.2 eq) over 15 minutes. The resulting reaction mixture was stirred for 30 minutes at 0 $^{\circ}\text{C}$ and was allowed to warm to room temperature for 30 minutes. The product precipitates from solution. After careful filtration, the product was washed with a small amount of the same solvent and dried at room temperature. When indicated, the product was purified by dissolving the crude in a minimum amount of acetone followed by precipitation by dropwise addition of TBME.

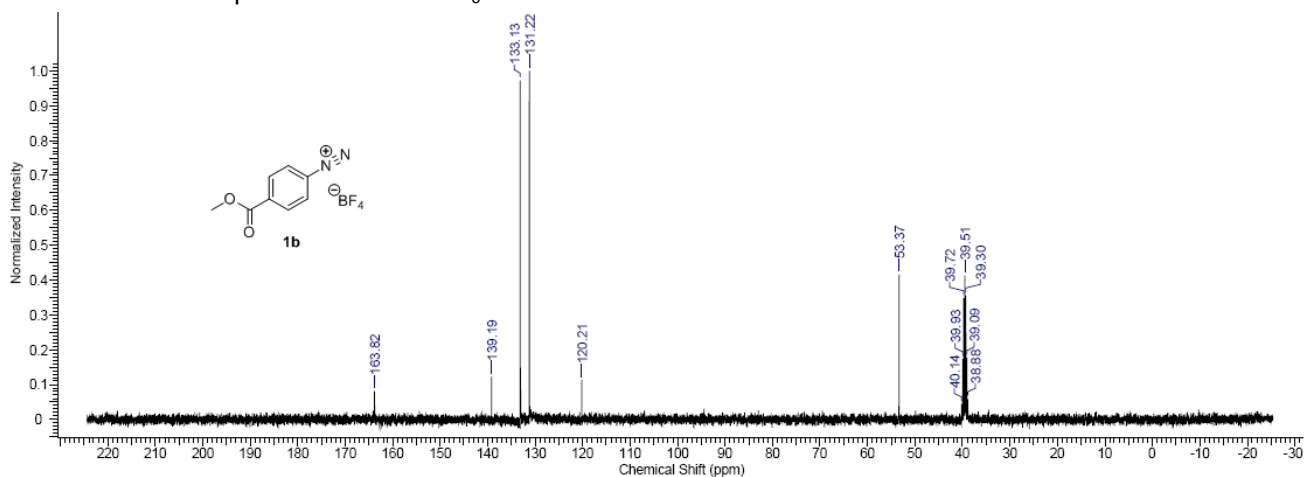
General diazotisation procedure with sodium nitrite: To a slurry of the aniline (1.0 eq) in 3 vol of water at 0 $^{\circ}\text{C}$, was added 2.5 vol of a 48% solution of HBF_4 in water (2.6 eq) and a solution of sodium nitrite (1.1 eq) in 1.5 volumes of water was added dropwise to the previous mixture under stirring. The resulting reaction mixture was stirred for 30 minutes at 0 $^{\circ}\text{C}$ and was allowed to warm to room temperature for 30 minutes. The product precipitates from solution. After careful filtration, the product was washed with a small amount of water and dried at room temperature. The crude product was purified by dissolution in a minimum amount of acetone and precipitated by dropwise addition of TBME in every case.

Methyl 4-benzoatediazonium tetrafluoroborate (1b). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 66 volumes of THF. The product was purified *via* acetone/TBME reprecipitation, 68%-77% yield.

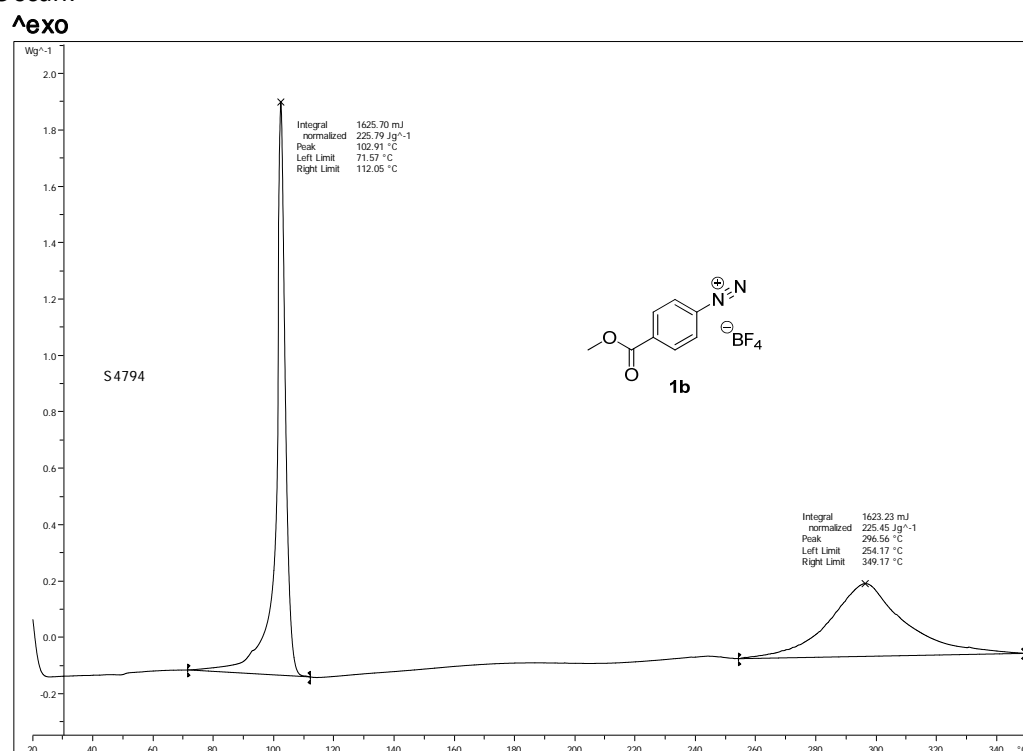
400 MHz ^1H NMR spectrum in DMSO-d_6 :



100 MHz ^{13}C NMR spectrum in DMSO-d_6 :



DSC scan:

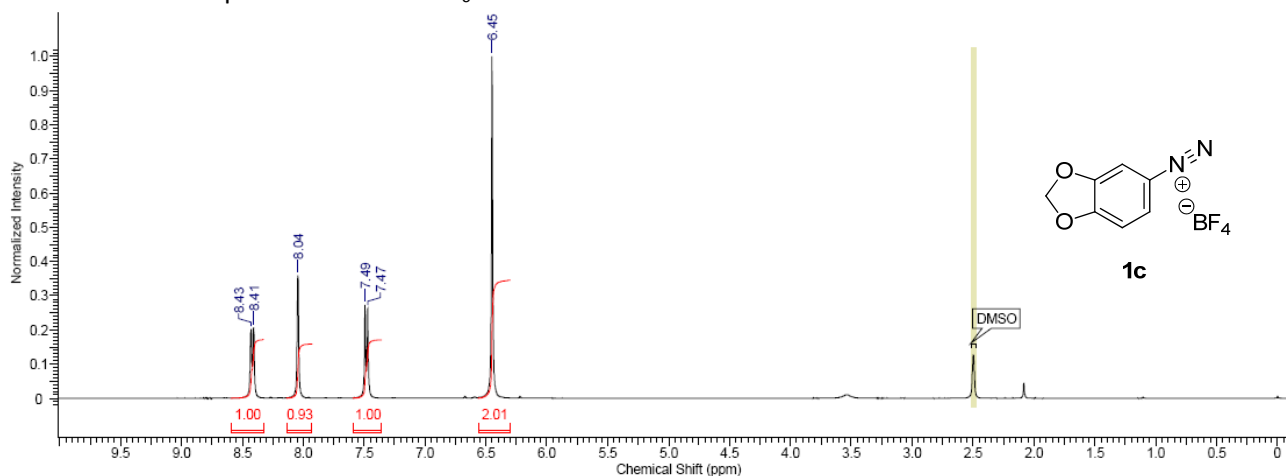


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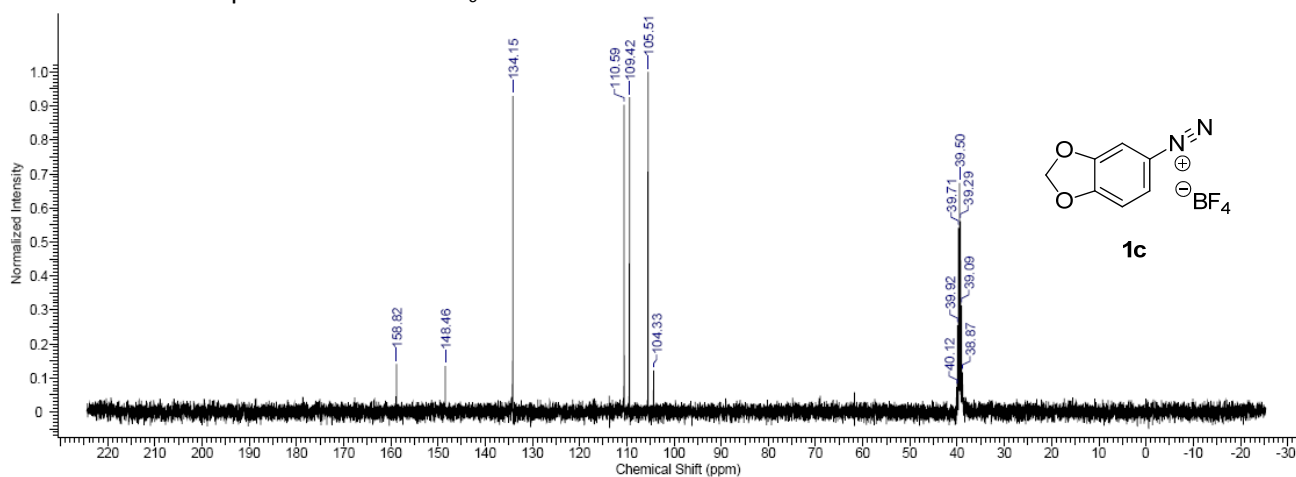
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3,4-Methylenedioxy-benzenediazonium salt (1c). Prepared according to the general diazotisation procedure with sodium nitrite. 1.20 g isolated, 51% yield.

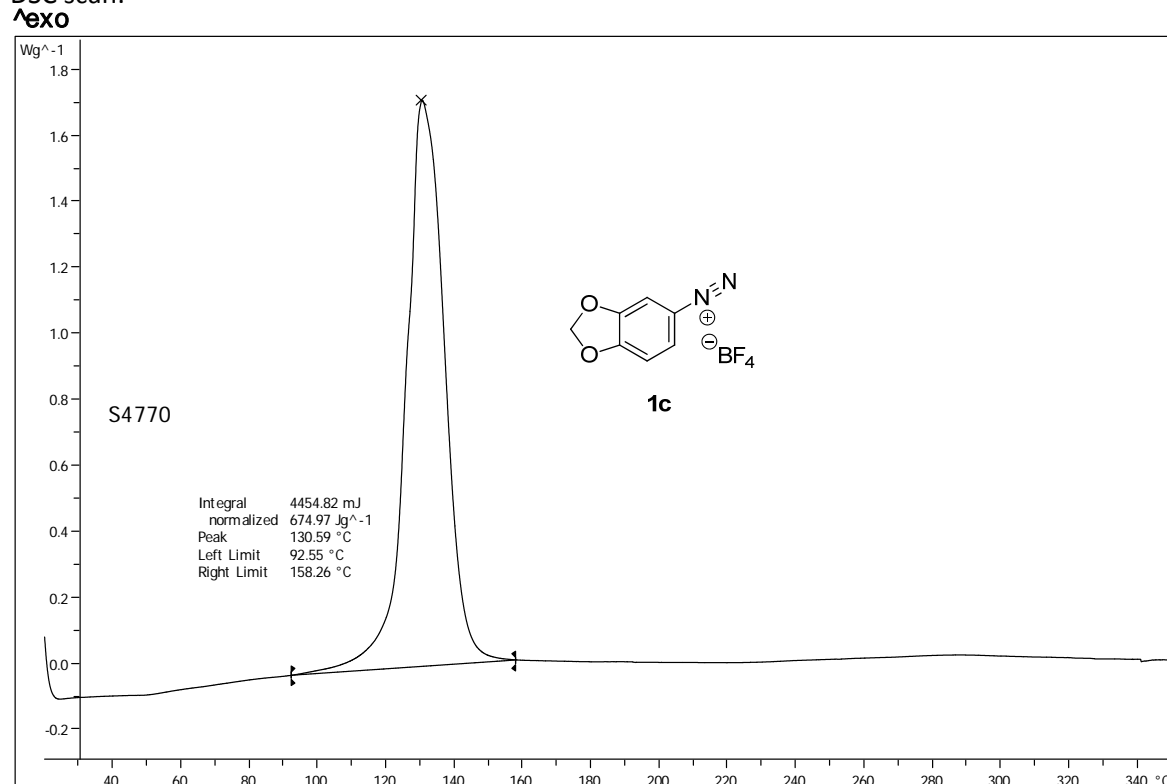
400 MHz ^1H NMR spectrum in $\text{DMSO}-d_6$:



100 MHz ^{13}C NMR spectrum in $\text{DMSO}-d_6$:

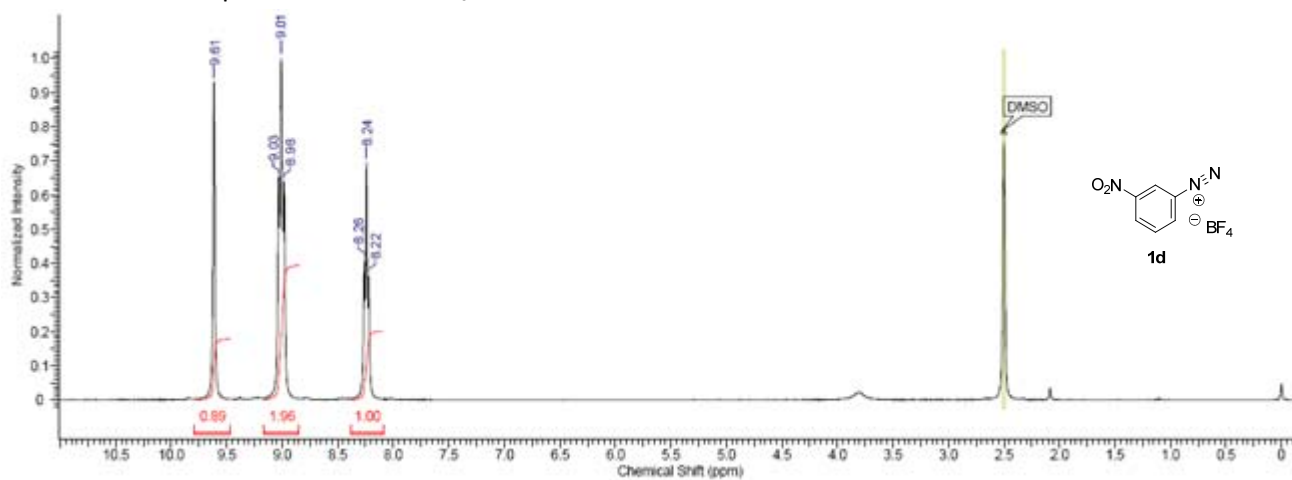


DSC scan:

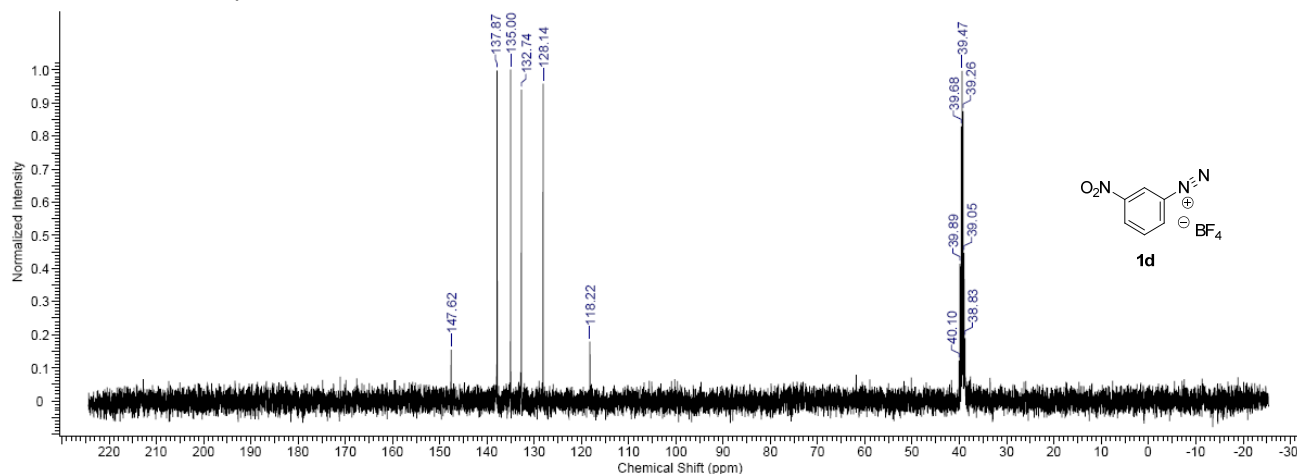


3-Nitro-benzenediazonium tetrafluoroborate (1d). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of THF. The product was purified *via* acetone/TBME reprecipitation. 73% yield.

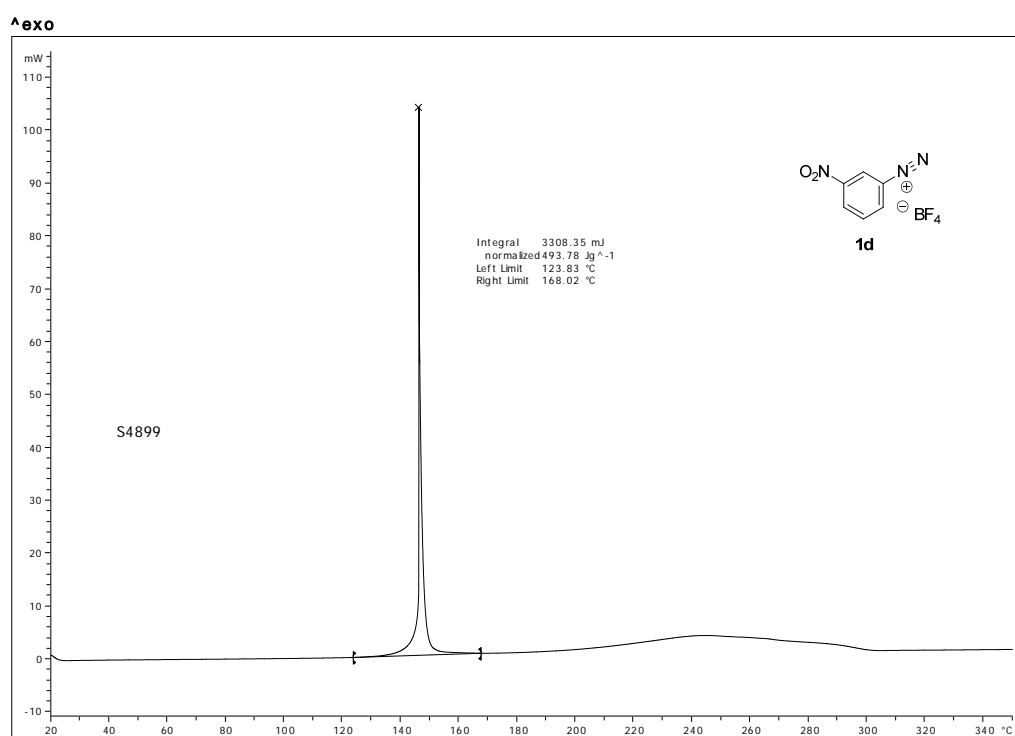
400 MHz ^1H NMR spectrum in DMSO-d_6 :



100 MHz ^{13}C NMR spectrum in DMSO-d_6 :

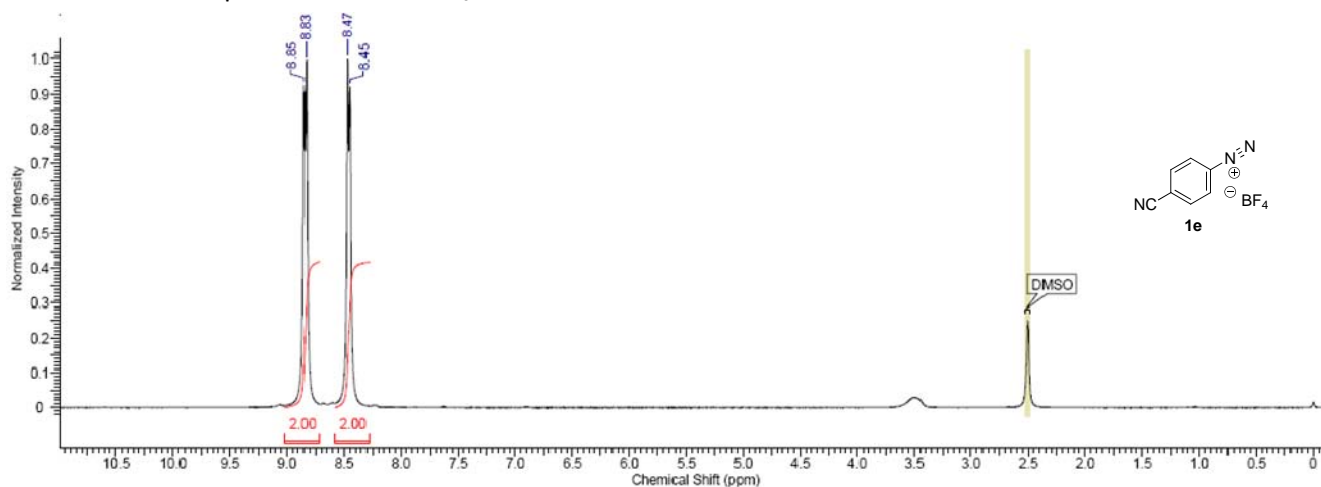


DSC scan:

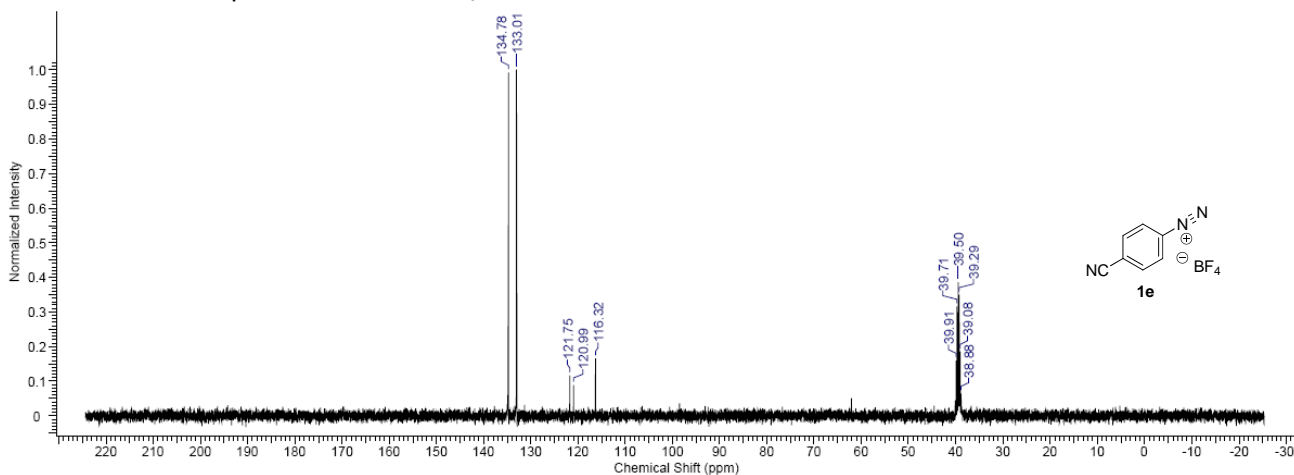


4-Cyano-benzenediazonium tetrafluoroborate (1e). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of isopropanol. The product was not purified further. White solid, 1.68 g, 91% yield.

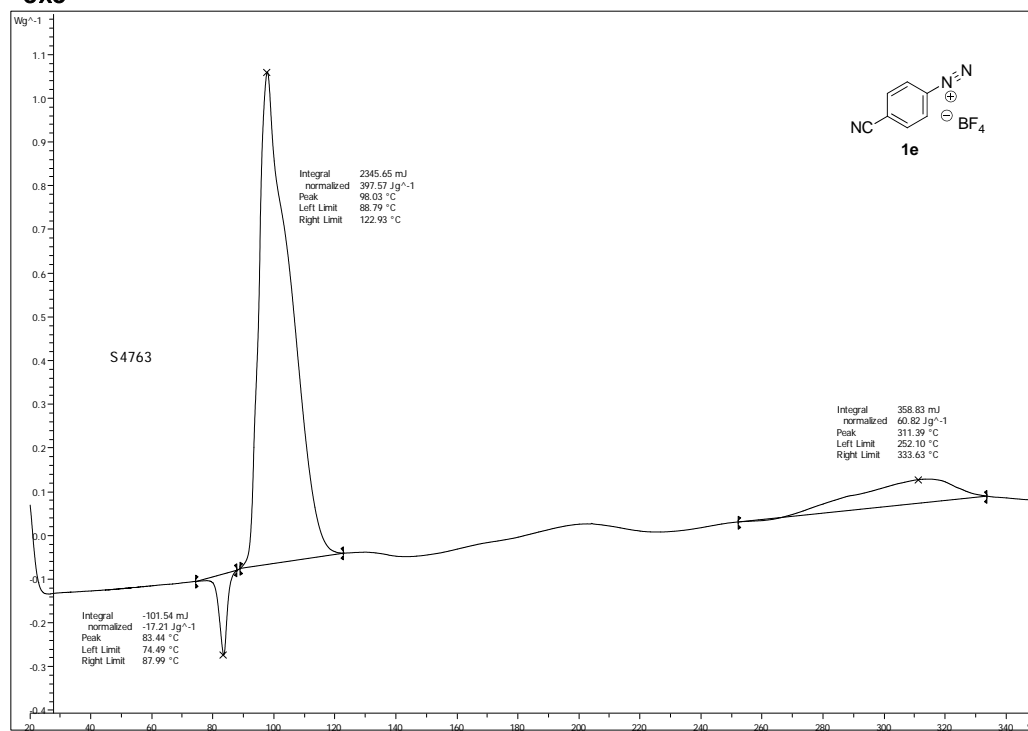
400 MHz ^1H NMR spectrum in DMSO-d_6 :



100 MHz ^{13}C NMR spectrum in DMSO-d_6 :

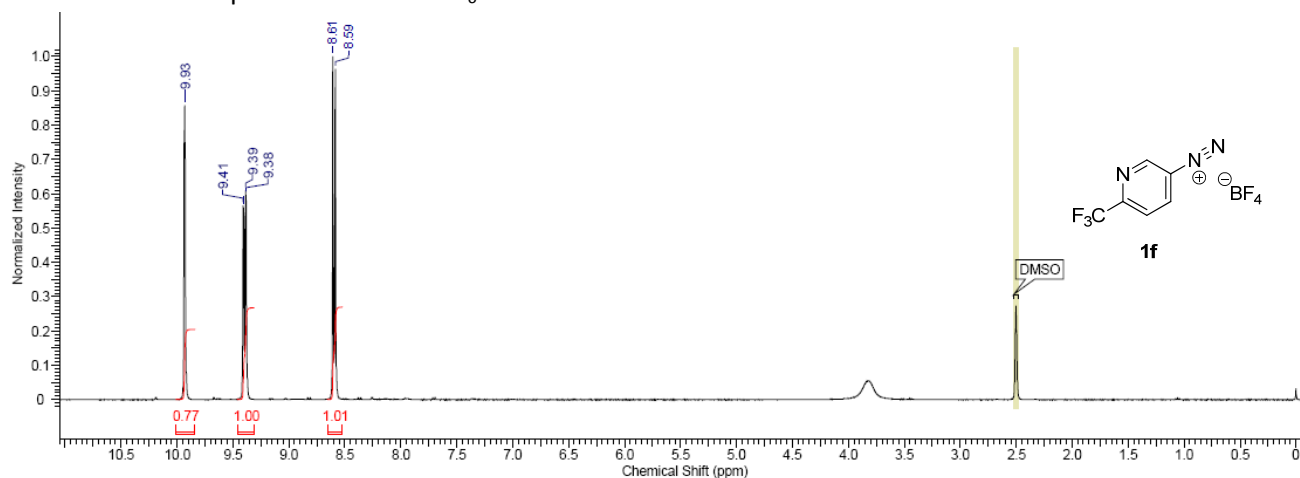


DSC scan:
exo

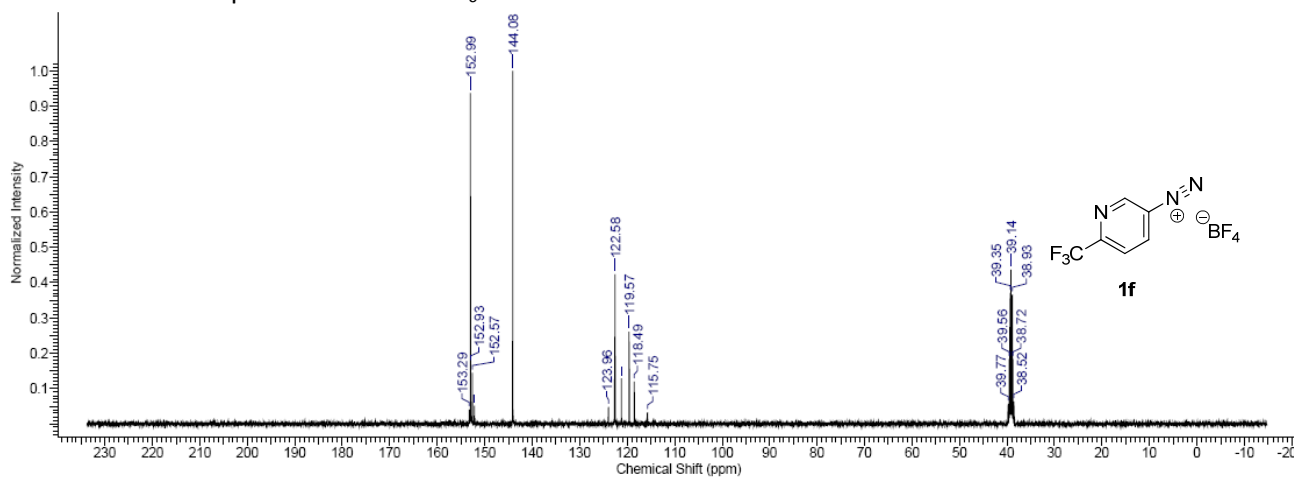


2-Trifluoromethyl-pyridine-5-diazonium tetrafluoroborate (1f). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of ethanol. The product was not purified further. White solid, 2.25 g, 70% yield.

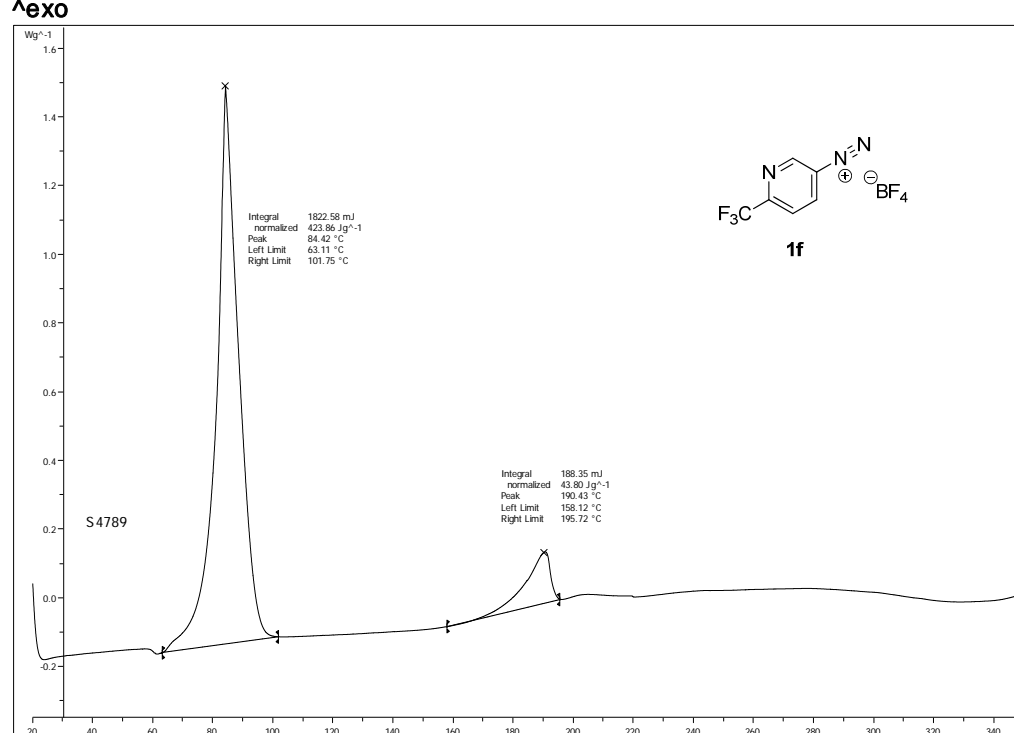
400 MHz ^1H NMR spectrum in DMSO-d_6 :



100 MHz ^{13}C NMR spectrum in DMSO-d_6 :

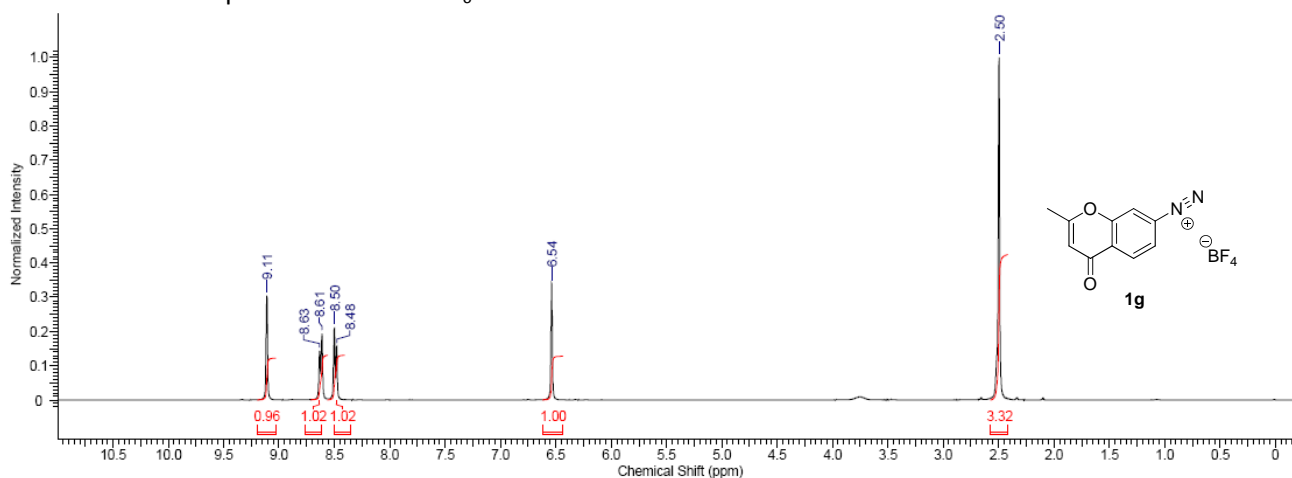


DSC scan:

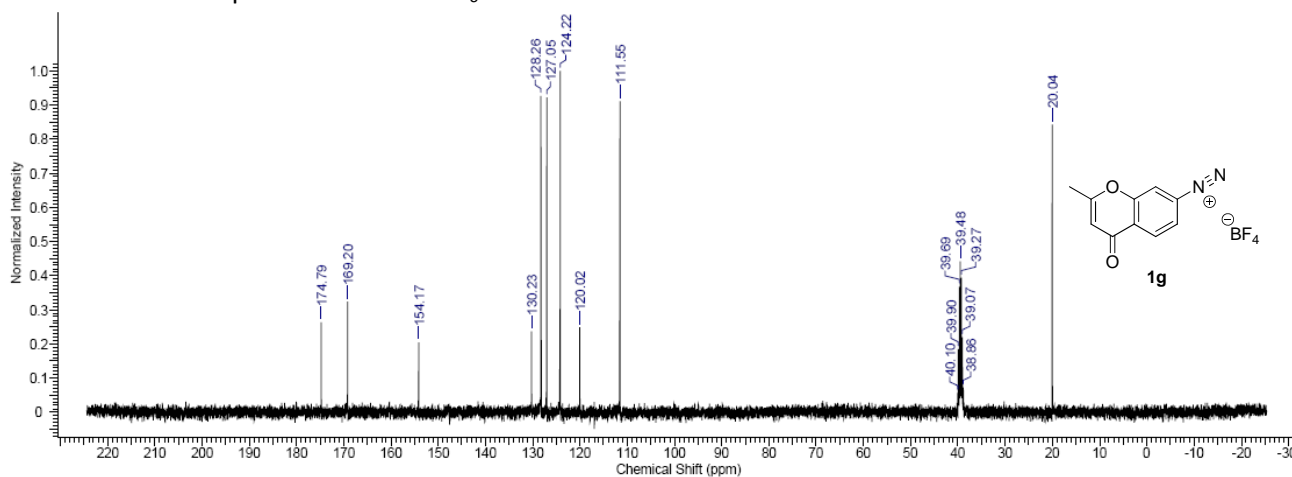


2-Methyl-chromone-7-diazonium tetrafluoroborate (1g). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 30 volumes of ethanol. The product was not purified further. 69%-88% yield.

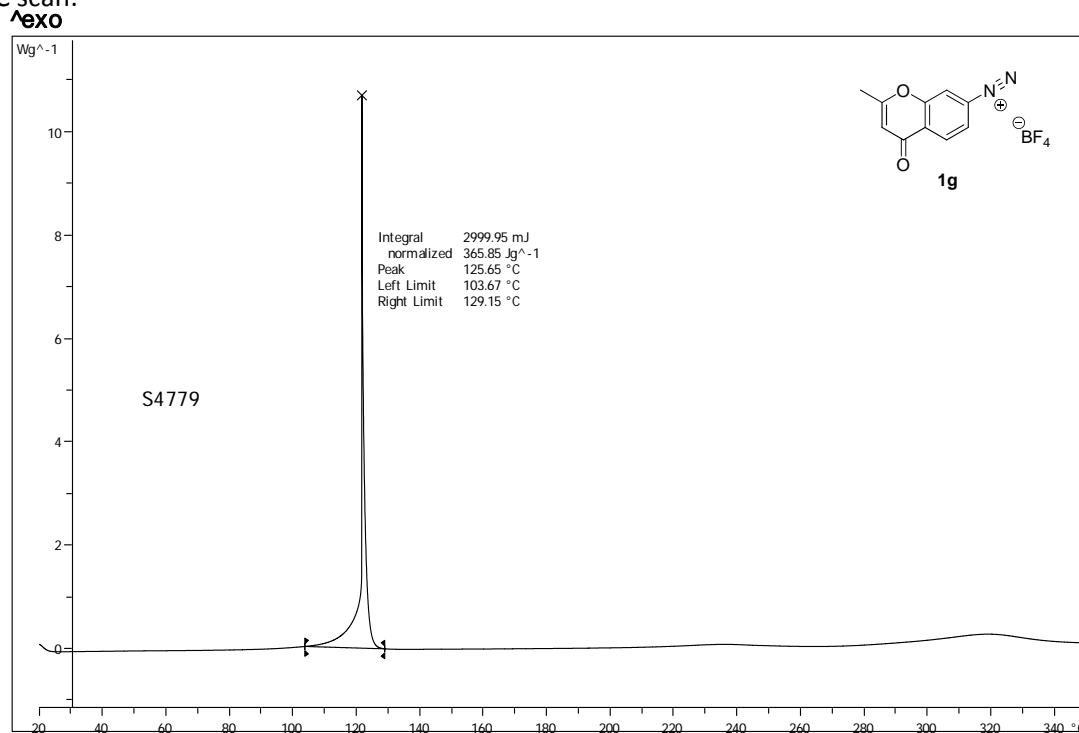
400 MHz ^1H NMR spectrum in DMSO- d_6 :



100 MHz ^{13}C NMR spectrum in DMSO- d_6 :



DSC scan:

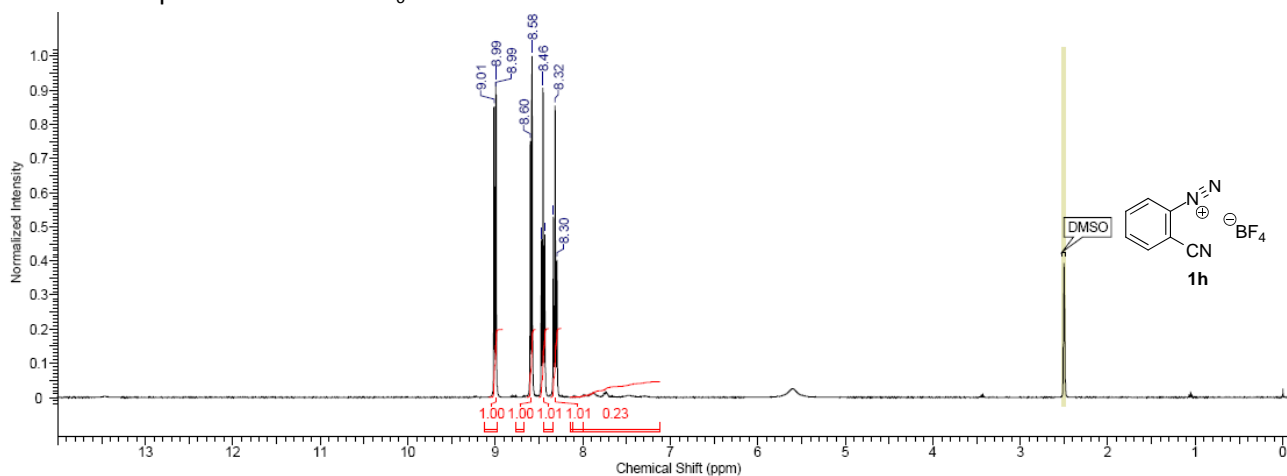


Lab: METTLER

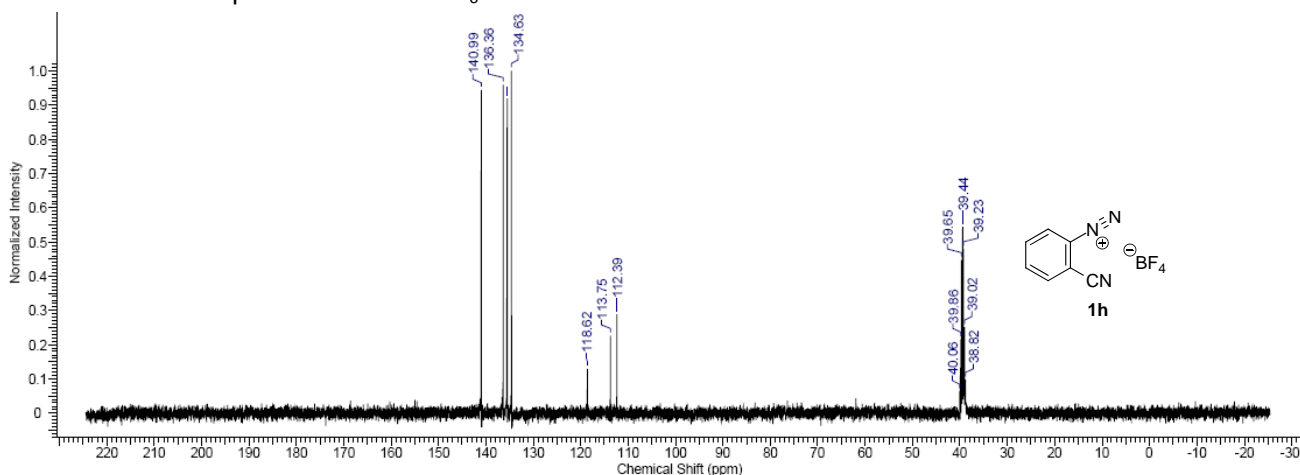
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2-Cyano-benzenediazonium tetrafluoroborate (1h). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of ethanol. The product was not purified further. 86%-89% yield.

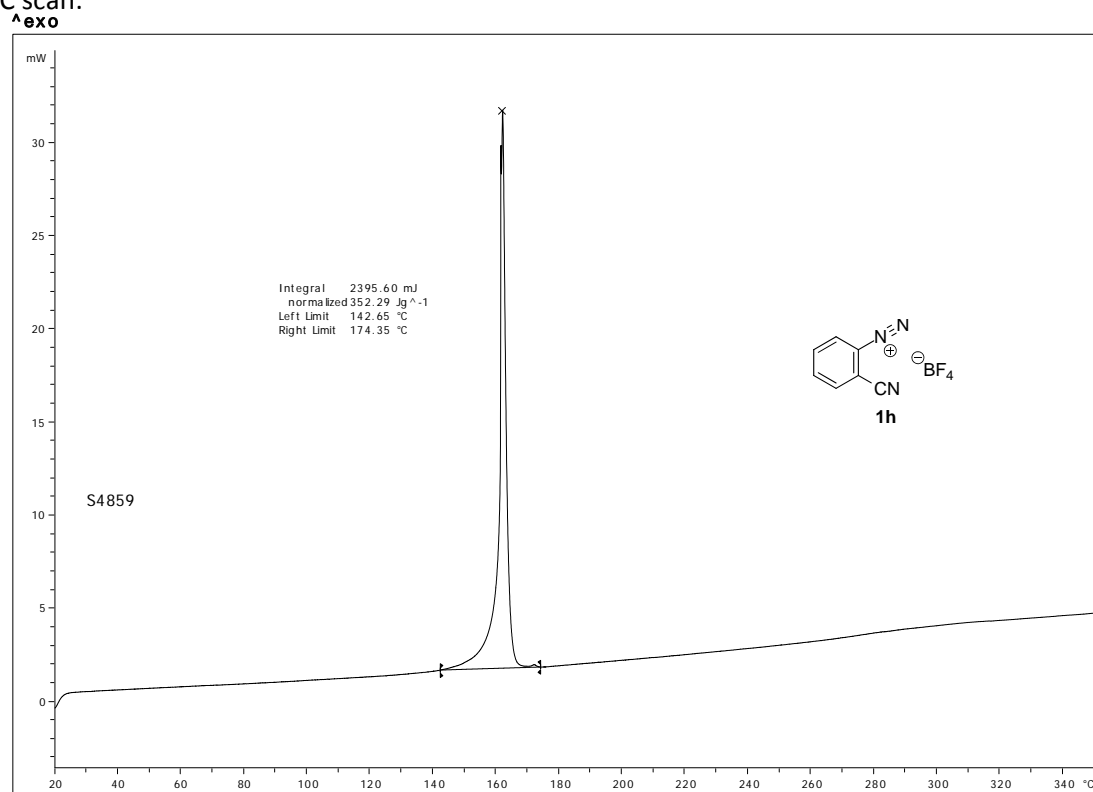
400 MHz ^1H spectrum in DMSO- d_6 :



100 MHz ^{13}C NMR spectrum in DMSO- d_6 :



DSC scan:

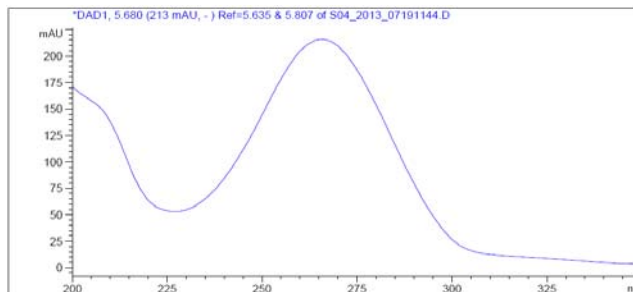


4. CALIBRATION CURVE USED FOR COMPOUND 3b

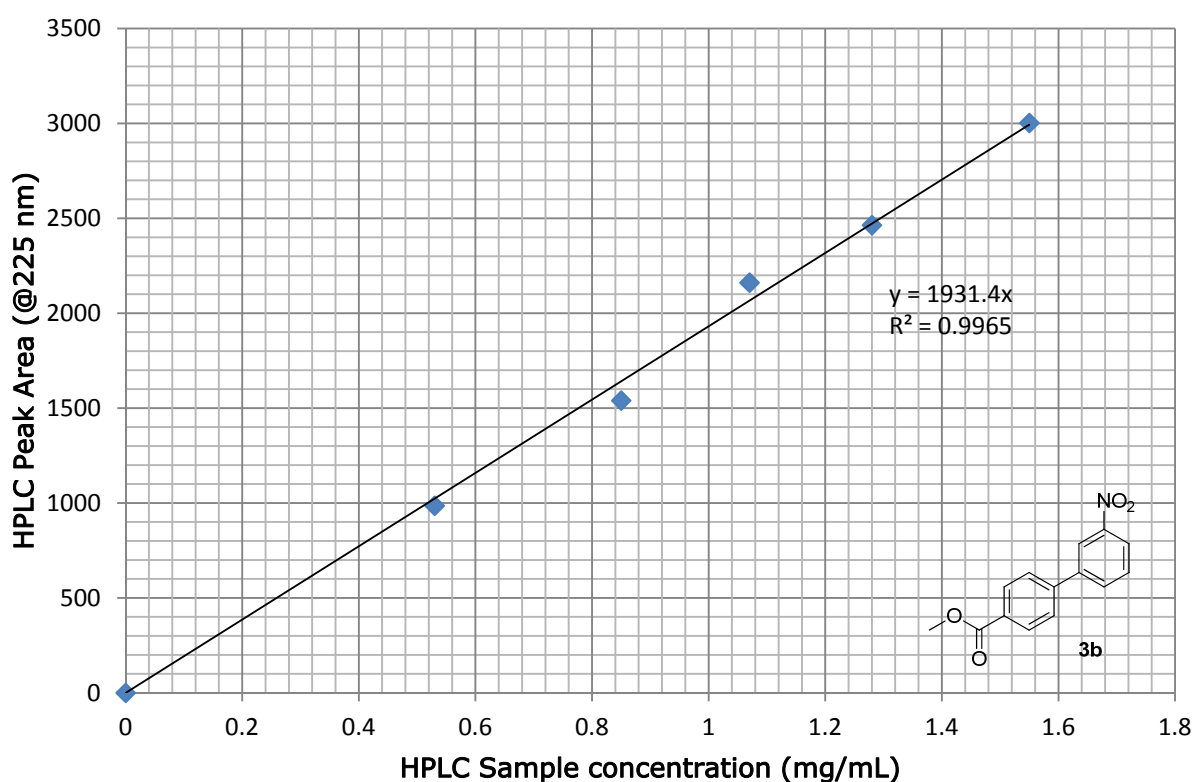
Solutions (in acetonitrile + 0.1% TFA v/v) were preparing by dissolving the corresponding amount of material in 25 mL volumetric flasks and analysed by HPLC.

Sample concentration (mg/mL)	HPLC Peak area (225 nm)
0	0
0.53	985.759
0.85	1540.316
1.07	2161.559
1.28	2464.461
1.55	3003.013

Results table used for the calibration curve



UV spectrum of 3b

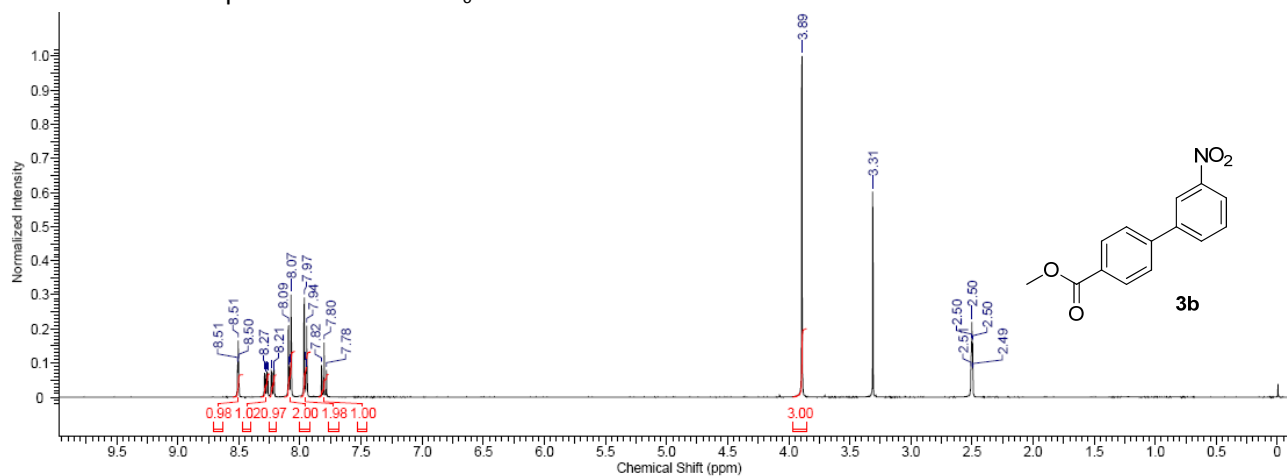


5. GENERAL PROCEDURES FOR SUZUKI-MIYaura CROSS-COUPPLINGS

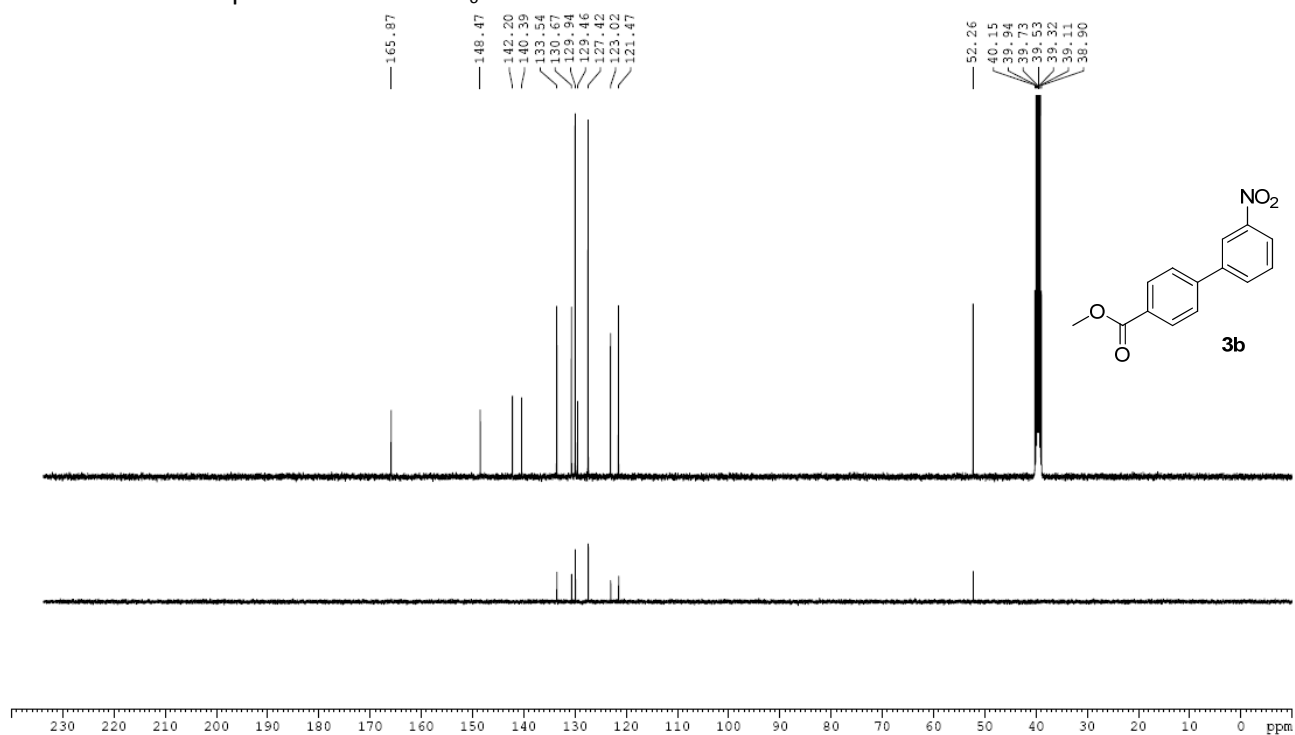
Catalyst and solvent screening reactions: To a glass tube equipped with a stir bar were introduced 3-nitrophenyl boronic acid **2b** (56 mg, 0.335 mmol), methyl 4-benzoatediazonium tetrafluoroborate **1b** (126 mg, 0.503 mmol) and palladium catalyst (1.0 mol%). The air inside was replaced by nitrogen *via* vacuum/nitrogen cycles. Solvent (5 mL) is then injected into the glass tube and the reaction mixture is stirred under a nitrogen atmosphere at 25 °C for 24 h. Ethyl acetate was then added to the mixture to solubilise the product and allow the removal of Pd/C by filtration over Celite® in a volumetric flask to have an accurate HPLC yield using the previously established calibration curve. The residues were washed with ethyl acetate and the filtrate was evaporated to dryness before being purified by silica gel chromatography eluting with a heptane / ethyl acetate mixture to give **3b** as a white solid.

4'-methylbenzoate-3-nitro-biphenyl (3b).

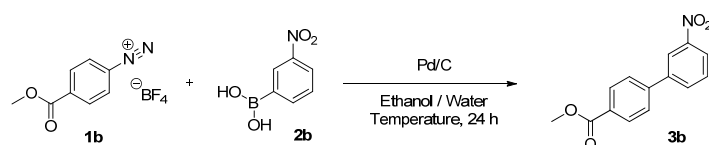
400 MHz ^1H NMR spectrum in DMSO-d_6 :



100 MHz ^{13}C NMR spectrum in DMSO-d_6 :



Design of Experiments reactions: To a glass tube equipped with a stir bar were introduced 3-nitro-phenyl boronic acid **2b** (1.0 eq), methyl 4-benzoatediazonium tetrafluoroborate **1b** (indicated number of equivalents) and Johnson Matthey 5% Pd/C type 394 (moisture: 56.70%) (indicated loading). The air inside was replaced by nitrogen *via* vacuum/nitrogen cycles. Ethanol (indicated number of volumes vs boronic acid) is then injected into the glass tube and the reaction mixture is stirred under a nitrogen atmosphere at the indicated temperature for 24 hr. Ethyl acetate was then added to the mixture to solubilise the product and allow the removal of Pd/C by filtration over Celite® in a volumetric flask to have an accurate HPLC yield using the previously established calibration curve.

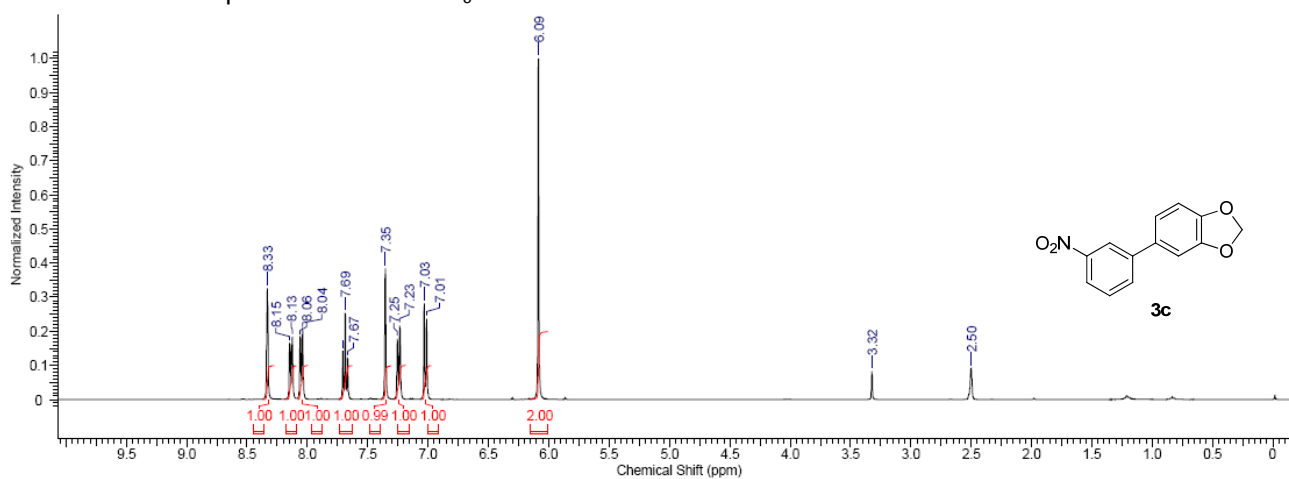


Run	Aryldiazonium Eq. (A)	Temperature (°C) (B)	Pd Loading (mol%) (C)	Solvent volumes (D)	Ethanol (% vs water) (E)	HPLC Yield ^a (%)
1	1.25	20	1.05	55	75	25
2	1.25	20	1.05	55	75	29
3	1	0	2	100	100	1
4	1.5	0	0.1	100	100	0
5	1.5	0	2	10	100	2
6	1	40	2	10	100	69
7	1.5	40	0.1	10	100	3
8	1.5	40	0.1	100	50	1
9	1	0	0.1	100	50	0
10	1.25	20	1.05	55	75	31
11	1	40	0.1	10	50	1
12	1	40	0.1	100	100	5
13	1.5	40	2	100	100	92
14	1.25	20	1.05	55	75	28
15	1.5	40	2	10	50	61
16	1	40	2	100	50	54
17	1.5	0	0.1	10	50	0
18	1.5	0	2	100	50	1
19	1	0	2	10	50	1
20	1	0	0.1	10	100	1

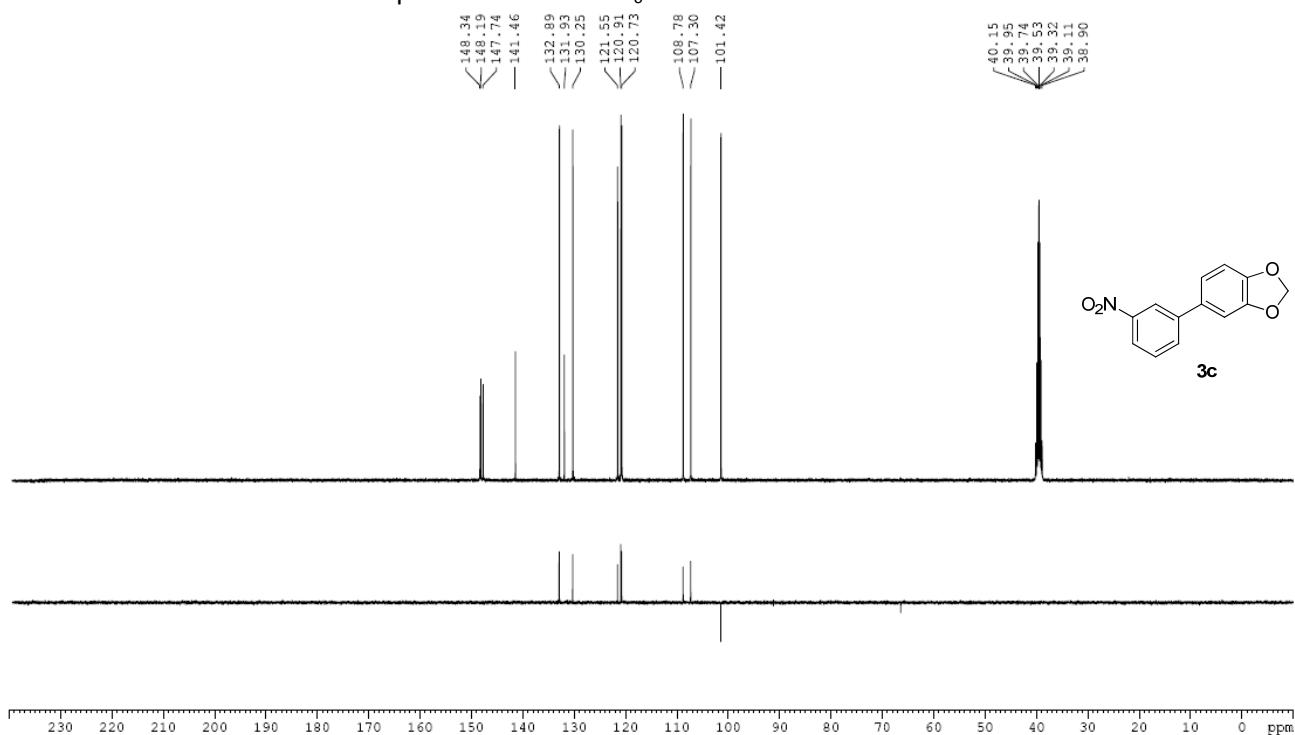
General cross-coupling procedure for substrate scope: To a glass tube equipped with a stir bar were introduced aryl boronic acid (500 mg, 1.0 eq), aryldiazonium tetrafluoroborate (1.1 eq) and catalyst (Johnson Matthey 5% Pd/C type 394, moisture: 56.70%, 1.0 mol %). The air inside was replaced by nitrogen *via* vacuum/nitrogen cycles. Ethanol (5 mL, 10 vol) was then injected into the glass tube and the reaction mixture was stirred under a nitrogen atmosphere at 30 °C for 24 h. Ethyl acetate or acetone was then added to the mixture and the catalyst removed by filtration over Celite®. The filtrate was evaporated to dryness and the crude product was purified by silica gel chromatography eluting with heptane/ethyl acetate or heptane/acetone mixtures to give the bi-aryl product.

3'-Nitro-3,4-methylenedioxy-biphenyl (3c). Beige solid, mp 119-120 °C. 6%-90% yield.

400 MHz ^1H NMR spectrum in DMSO-d_6 :

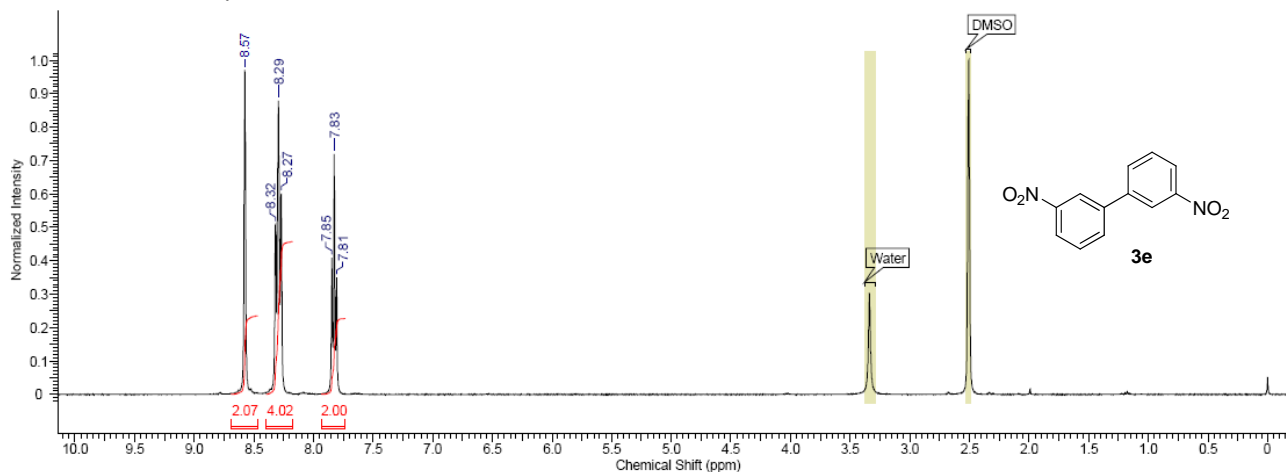


100 MHz ^{13}C NMR and DEPT135 spectrum in DMSO-d_6 :

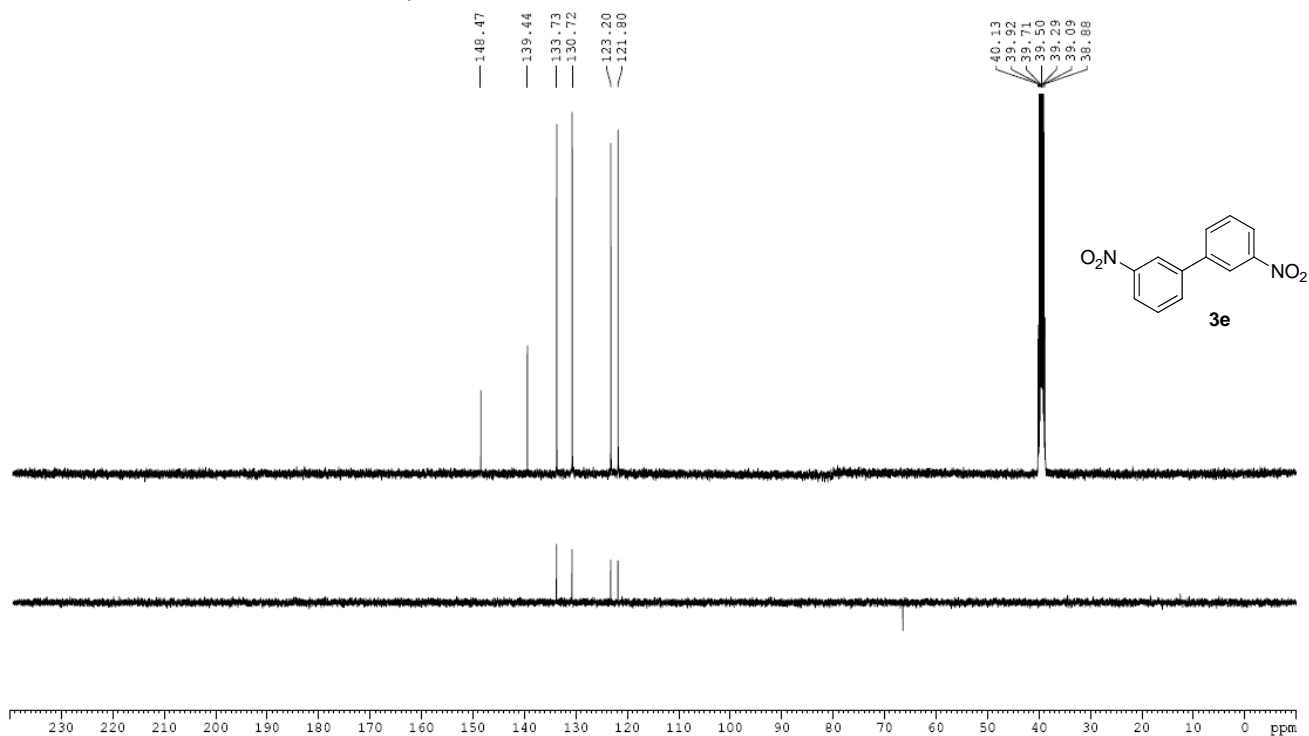


3',3'-Dinitro-biphenyl (3e). White solid, mp 207-208 °C. 688 mg, 94% yield.

400 MHz ^1H NMR spectrum in DMSO-d_6 :

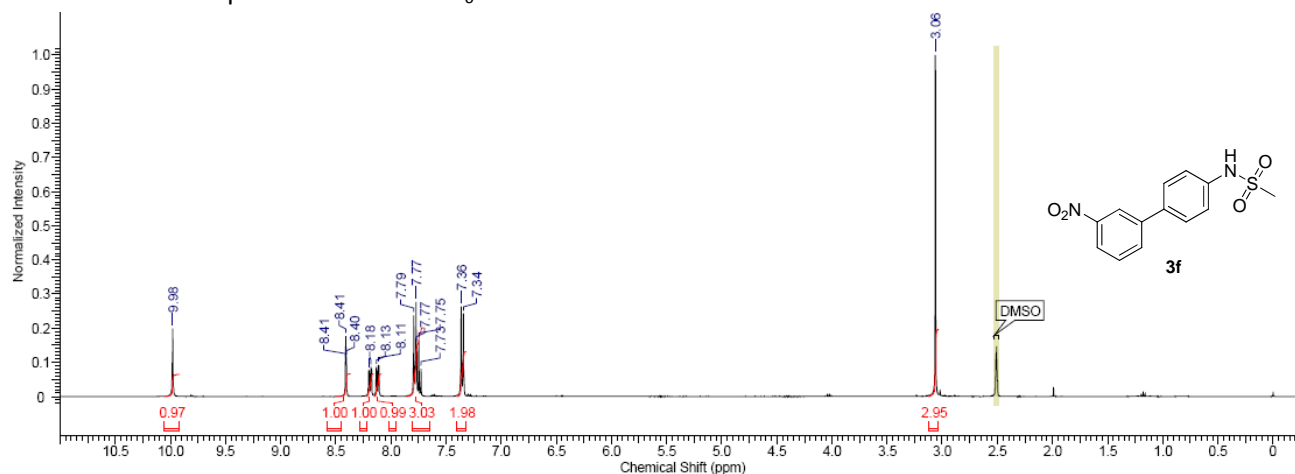


100 MHz ^{13}C NMR and DEPT 135 spectrum in DMSO-d_6 :

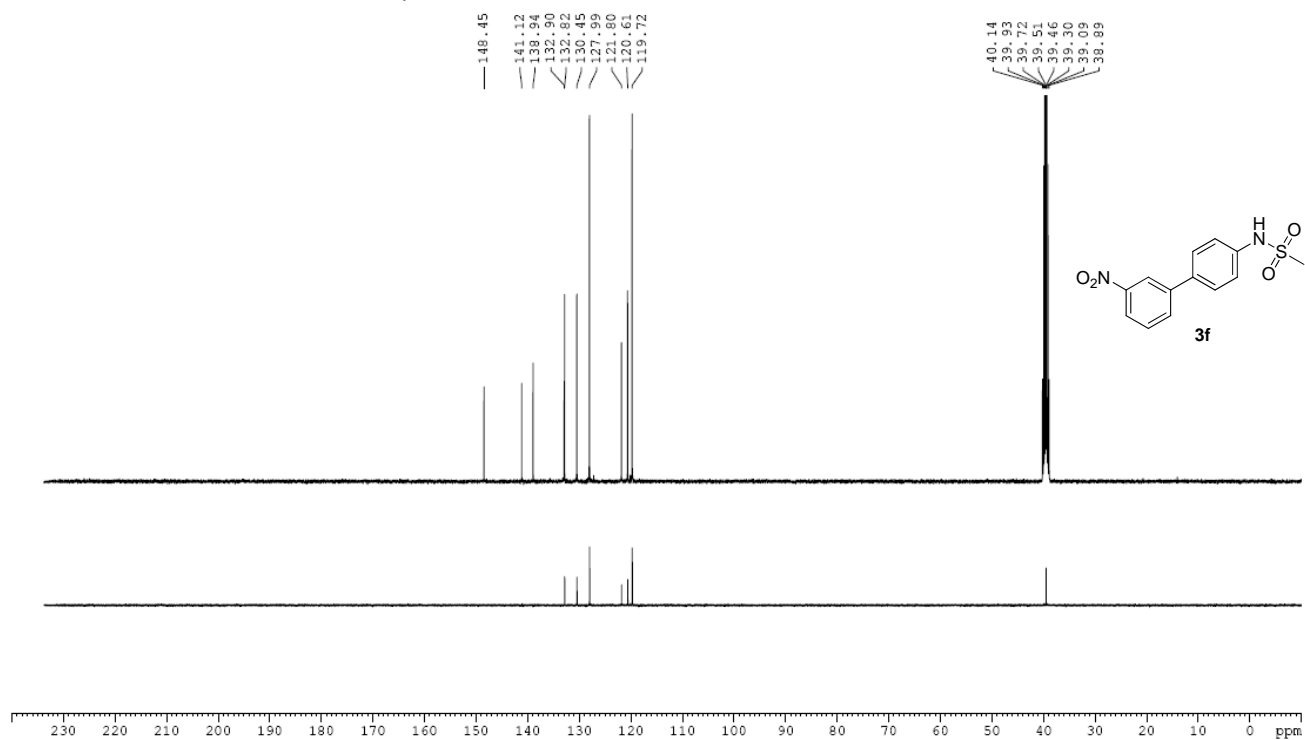


3'-Nitro-4-*N*-methylsulfonamide-biphenyl (3f). Beige solid, mp 145-150 °C. 612 mg, 90% yield.

400 MHz ^1H NMR spectrum in $\text{DMSO}-d_6$:

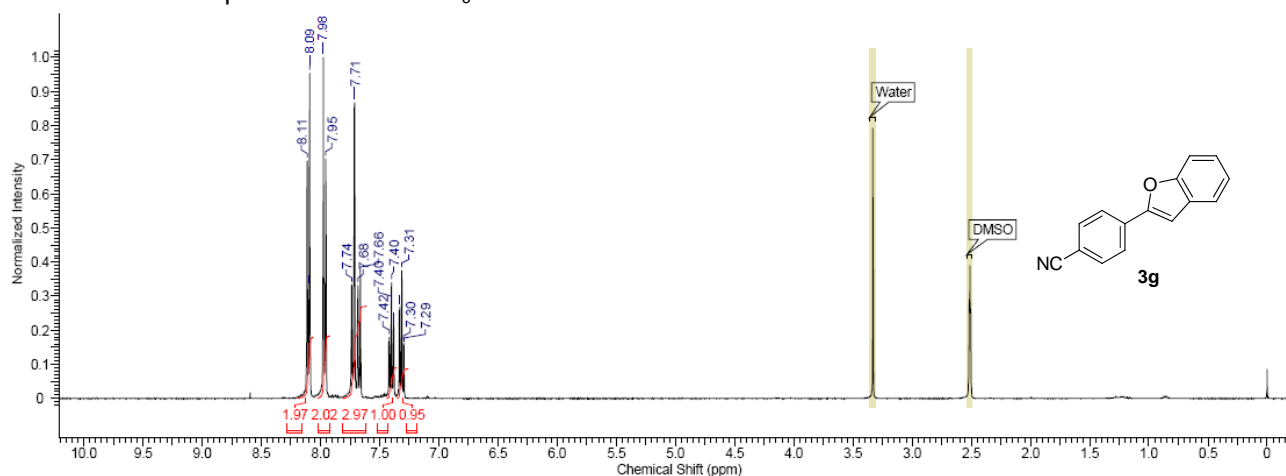


100 MHz ^{13}C NMR and DEPT135 spectrum in $\text{DMSO}-d_6$:

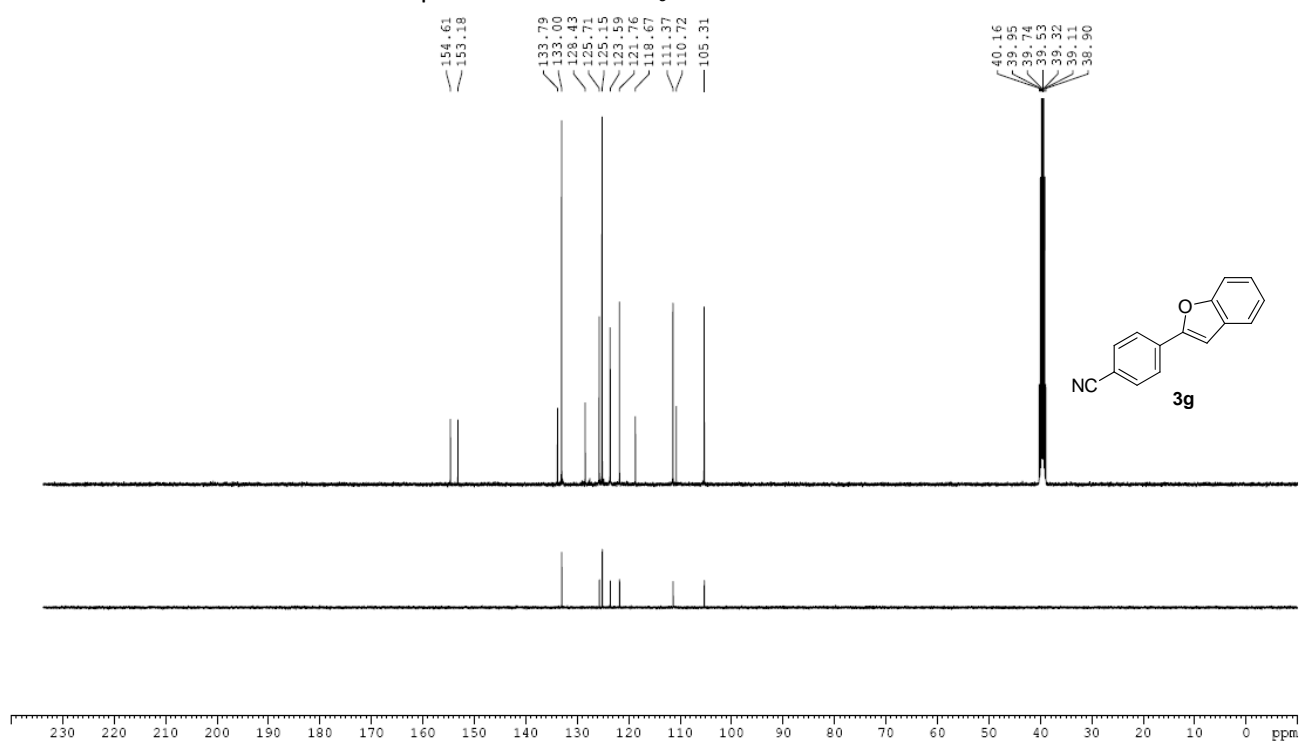


4-(Benzofuran-2-yl)-benzonitrile (3g). White solid, mp 141-144 °C. 237 mg, 35% yield.

400 MHz ^1H NMR spectrum in DMSO- d_6 :

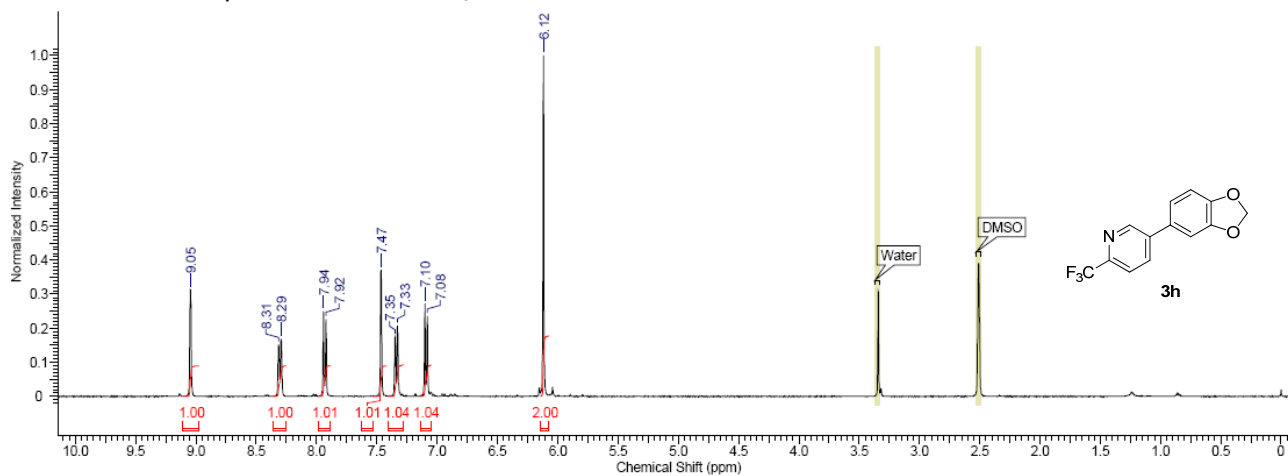


100 MHz ^{13}C NMR and DEPTC 135 spectrum in DMSO- d_6 :

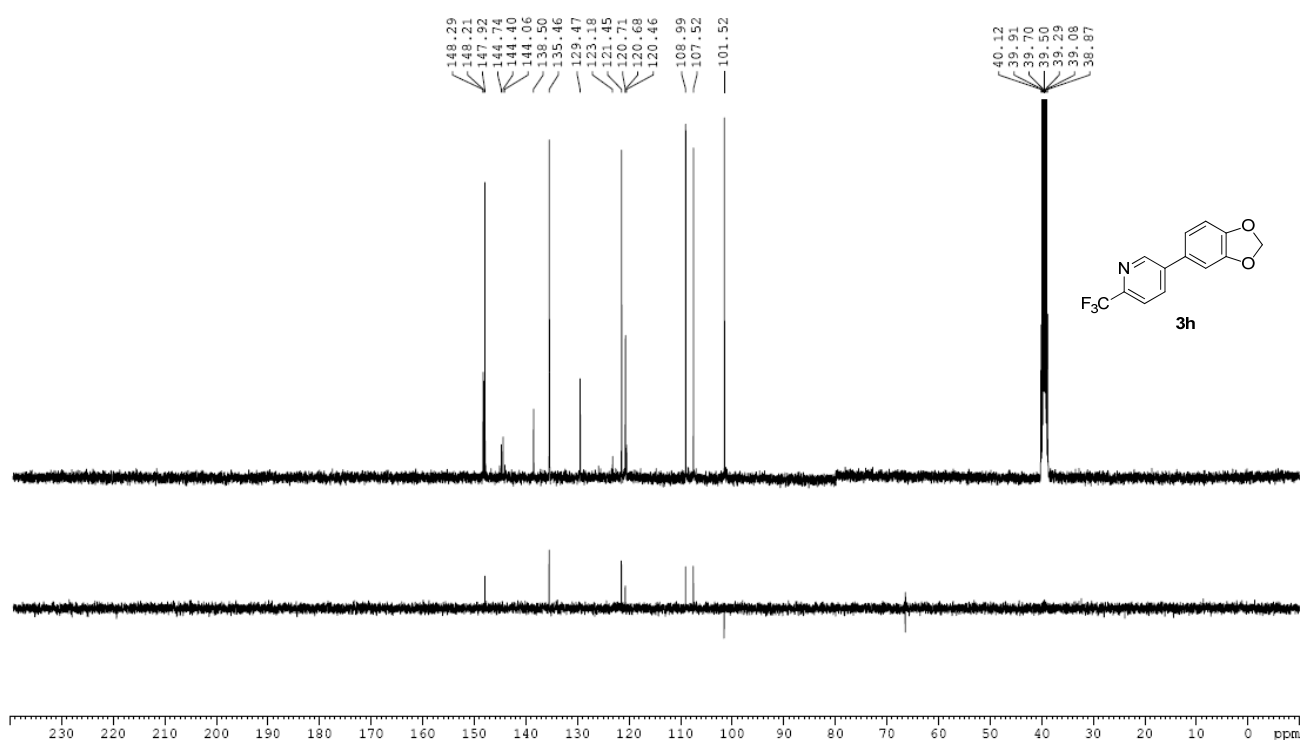


5-(3',4'-Methylenedioxyphenyl)-2-trifluoromethyl-pyridine (3h). Off-white solid, mp 117-125 °C. 7%-35% yield.

400 MHz ^1H NMR spectrum in DMSO-d_6 :

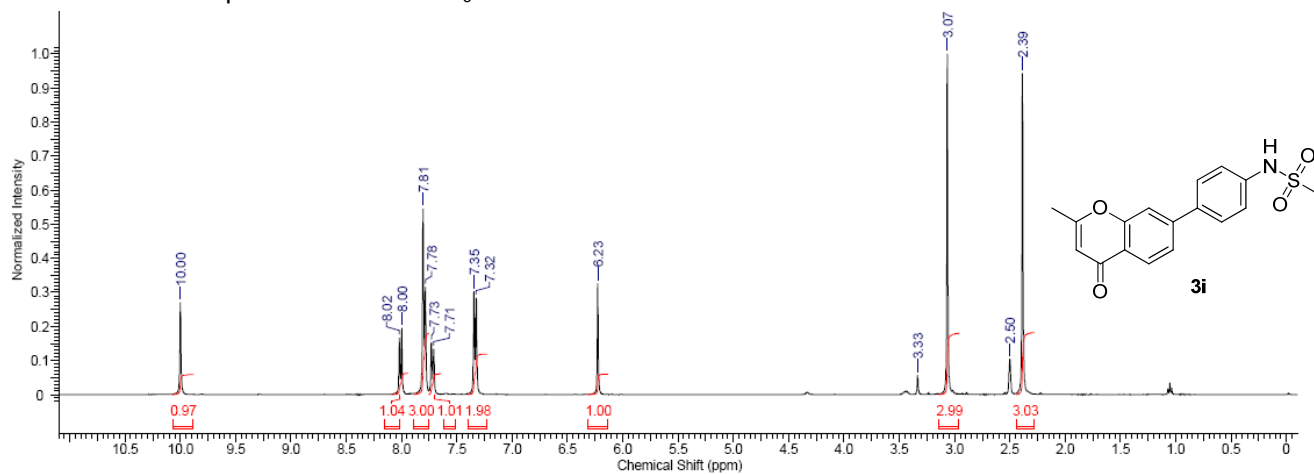


100 MHz ^{13}C NMR and DEPT135 spectrum in DMSO-d_6 :

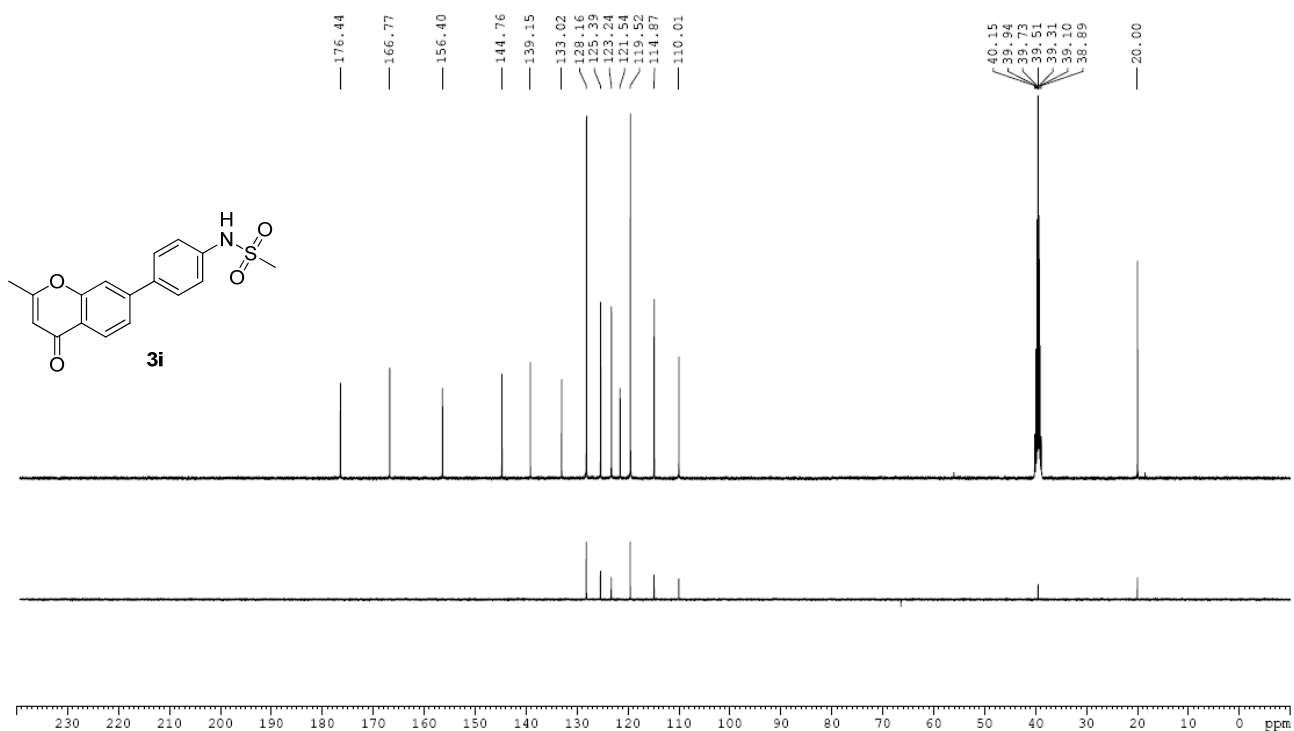


7-(4'-*N*-Methylsulfonamid-phenyl)-2-methyl-chromone (3i). Off-white solid, mp 226-228 °C. 705 mg, 92% yield.

400 MHz ^1H NMR spectrum in DMSO- d_6 :

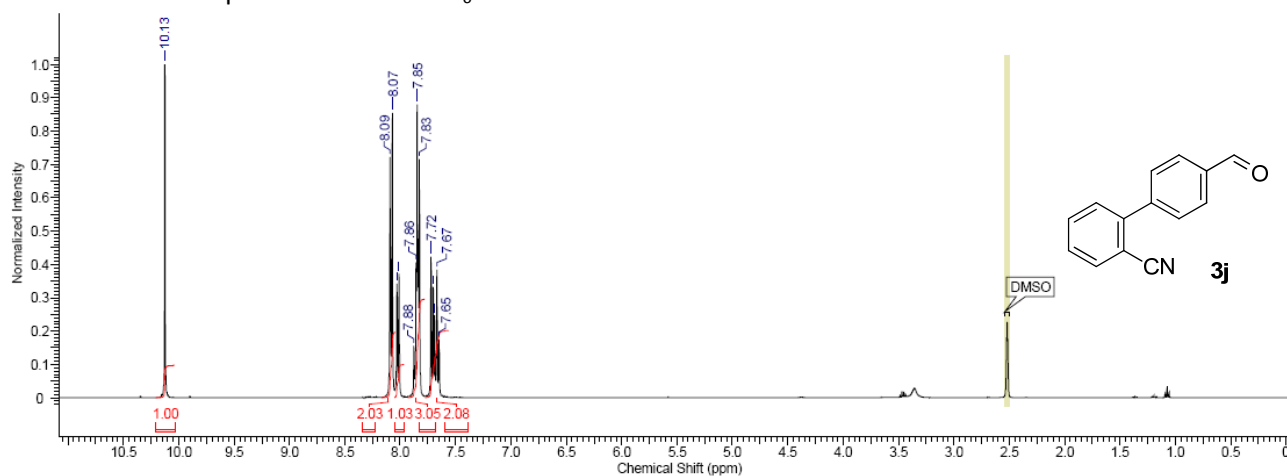


100 MHz ^{13}C NMR and DEPT135 spectrum in DMSO- d_6 :

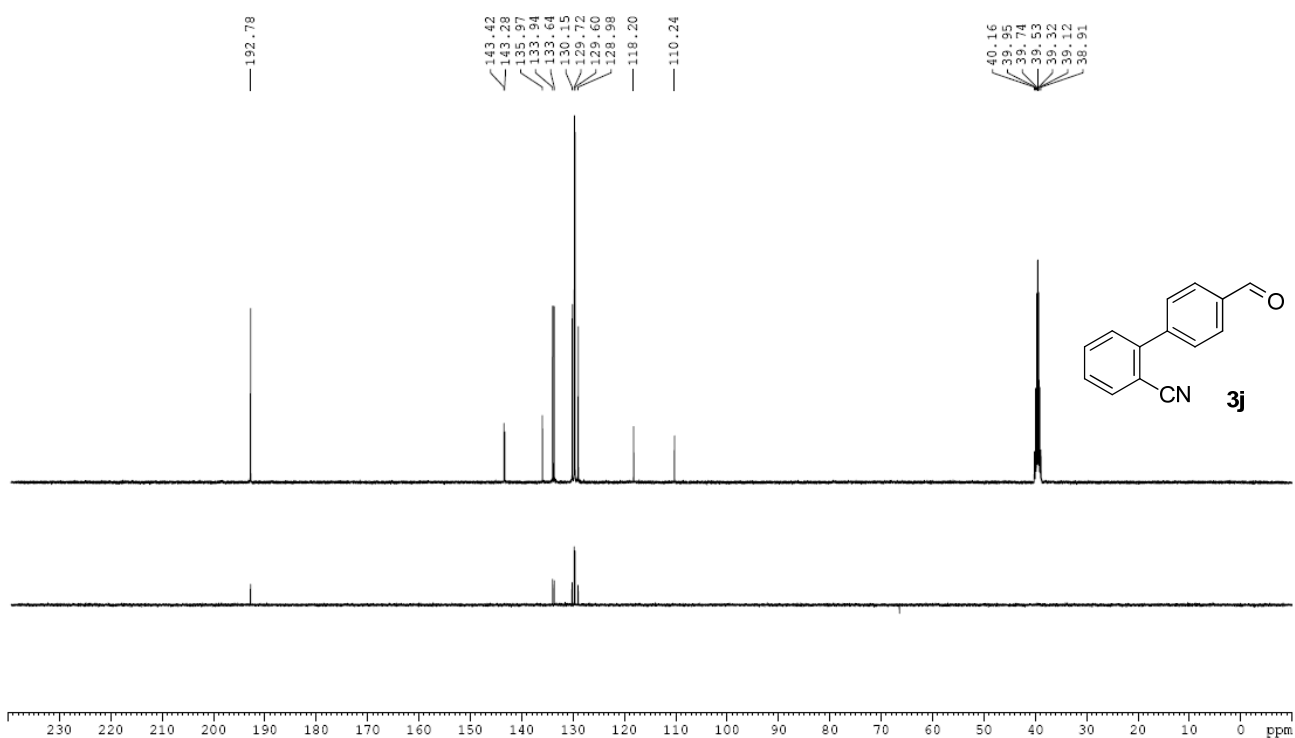


2'-Cyano-4-formyl-biphenyl (3j). White to beige solid, mp 164-165 °C. 18%-72% yield.

400 MHz ^1H NMR spectrum in DMSO-d_6 :

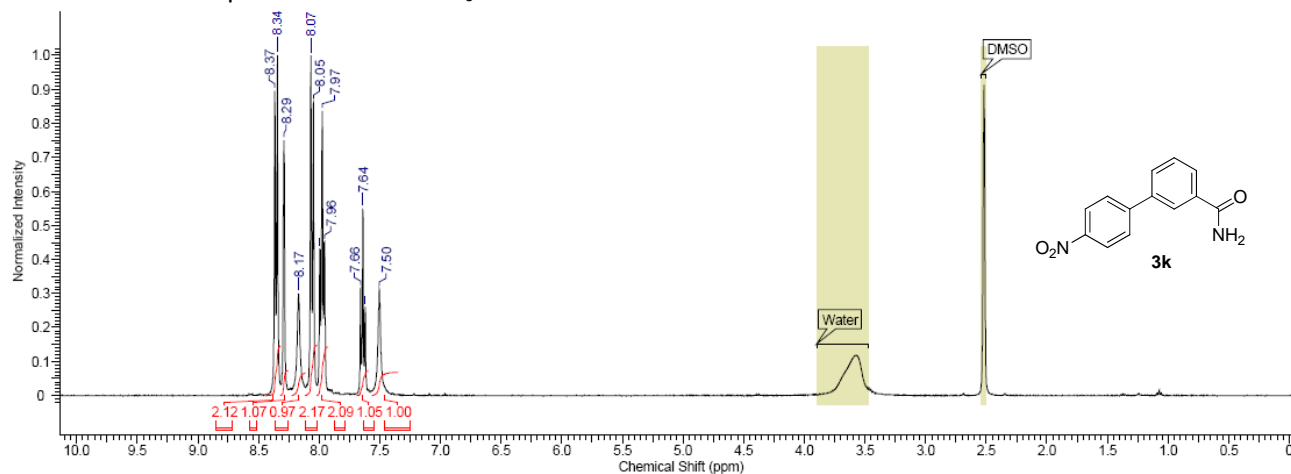


100 MHz ^{13}C NMR spectrum in DMSO-d_6 :

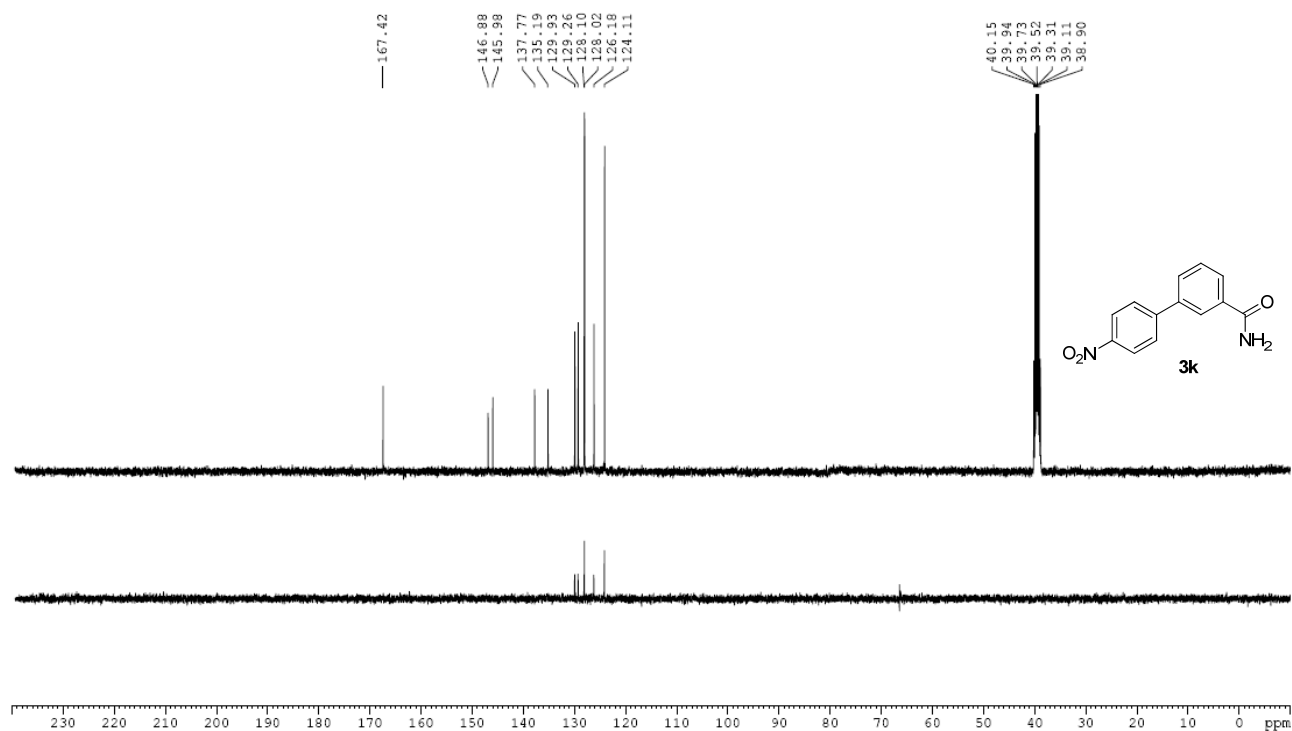


3'-Carboxamido-4-nitro-biphenyl (3k). White solid, mp 182-186 °C. 529 mg, 72% yield.

400 MHz ^1H NMR spectrum in DMSO-d_6 :

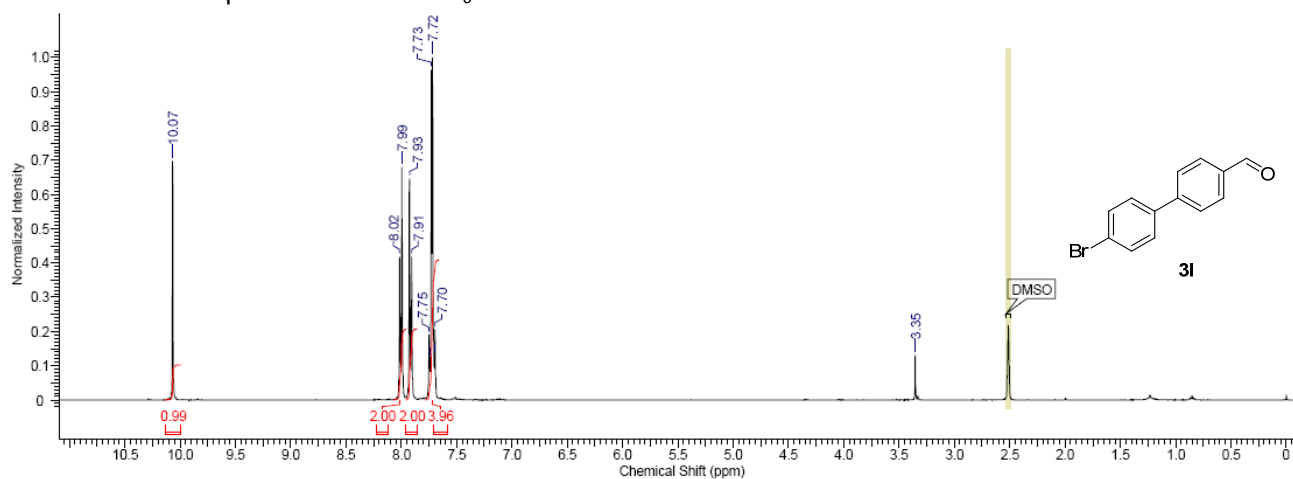


100 MHz ^{13}C NMR spectrum in DMSO-d_6 :

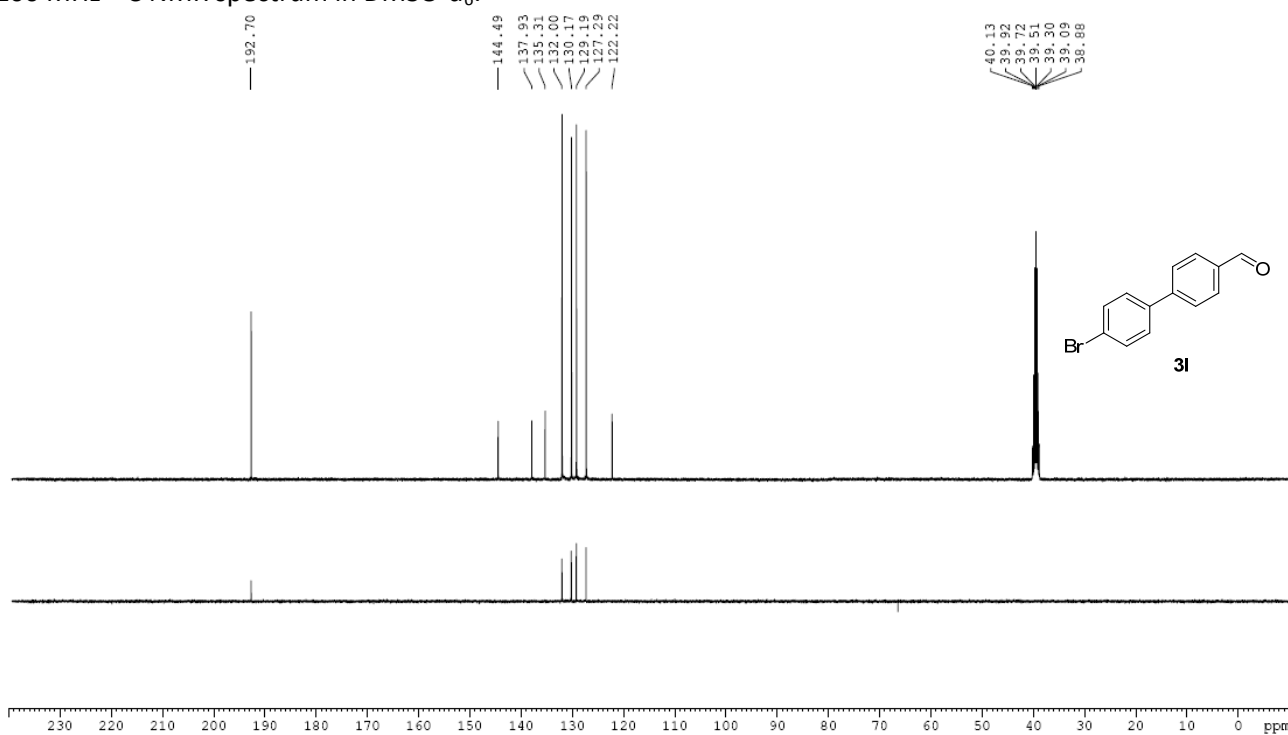


4'-Formyl-4-bromo-biphenyl (3I). White solid, mp 144-149 °C. 366 mg, 42% yield.

400 MHz ^1H NMR spectrum in DMSO- d_6 :



100 MHz ^{13}C NMR spectrum in DMSO- d_6 :



6. GENERAL PROCEDURES FOR SCALE-UP

Multi-mole scale diazotisation step: A 20 L CLR reactor fitted with an overhead stirrer was flushed with nitrogen and charged with 500 g of 2-aminobenzonitrile **4** (4.23 mol, 1.0 eq) followed by 10 L of ethanol. The solution was cooled to 0 °C and 700 mL of BF₃•THF complex (6.35 mol, 1.5 eq) were charged portionwise to the reactor without significant exotherm. 673 mL of *tert*-butyl nitrite (technical grade 90%, 5.08 mol, 1.2 eq) were pumped into the reactor with a peristaltic pump over 20 min and the temperature rose from -1.2 °C to +6.7 °C. The reaction was stirred with a mechanical stirrer for 30 minutes at 0 °C and 30 minutes at 20 °C. The product precipitated from ethanol and the slurry was filtered. The resulting solid was collected and dried in a vacuum oven overnight at 20 °C to give 813 g of 2-cyano-benzenediazonium tetrafluoroborate **1h** (3.75 mol, 89% yield).

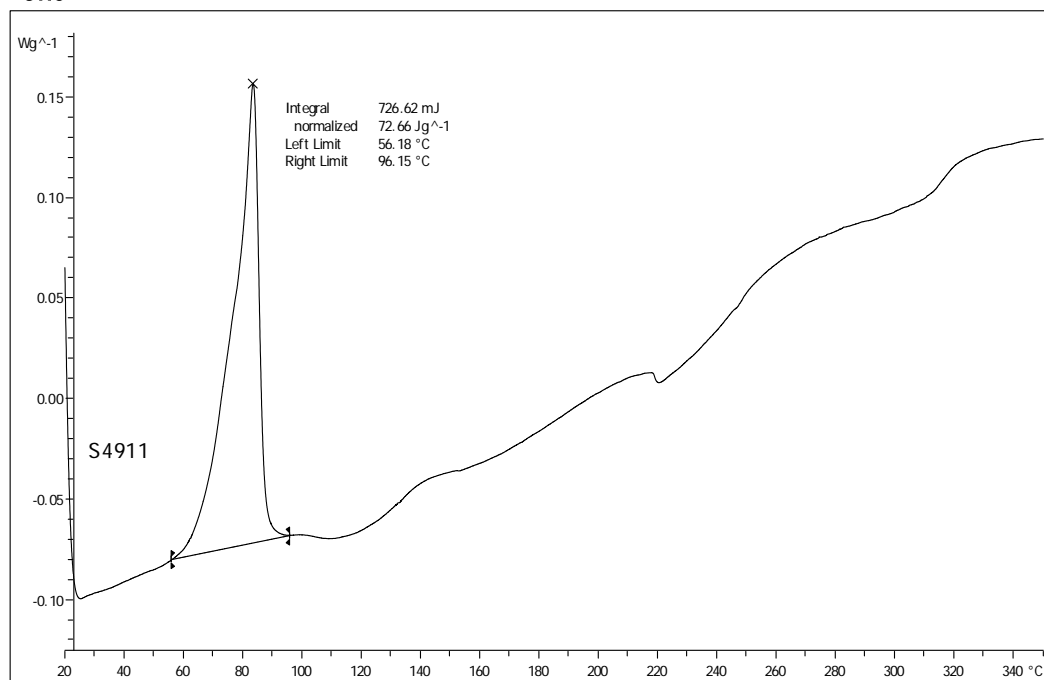
Multi-mole cross-coupling step: A 20 L CLR reactor fitted with an overhead stirrer was flushed with nitrogen and charged with 813 g of 2-cyano-benzenediazonium tetrafluoroborate **1h** (3.75 mol, 1.1 eq), 510 g of 4-formyl-phenylboronic acid **2g** (3.40 mol, 1.0 eq) and 7.64 g of palladium(II) acetate (34.0 mmol, 0.01 eq). 5.1 L of ethanol were then added to the reactor at 25 °C and the temperature rose to 43 °C meanwhile the jacket was reset to -5 °C to control the exotherm. Once the temperature stabilised at 30 °C, the slurry was stirred at 30 °C for 24 hours under a nitrogen atmosphere. 5.1 L of an aqueous solution of *N*-acetyl cysteine (55.5 g, 0.34 mol, 10 mol%) were then added to the reaction mixture and the slurry was stirred for 2 hours at 30 °C before being filtered. The resulting solid was collected and dried in a vacuum oven for 48 hours at 30 °C to give 509 g of 2'-cyano-4-formyl-biphenyl **3j** (2.46 mol, 72% yield). ICP analysis of the product showed it contained 1900 ppm of palladium.

7. PROCESS SAFETY STUDIES

DSC Studies for scale-up

Mixture end of diazotisation

Δ_{exo}

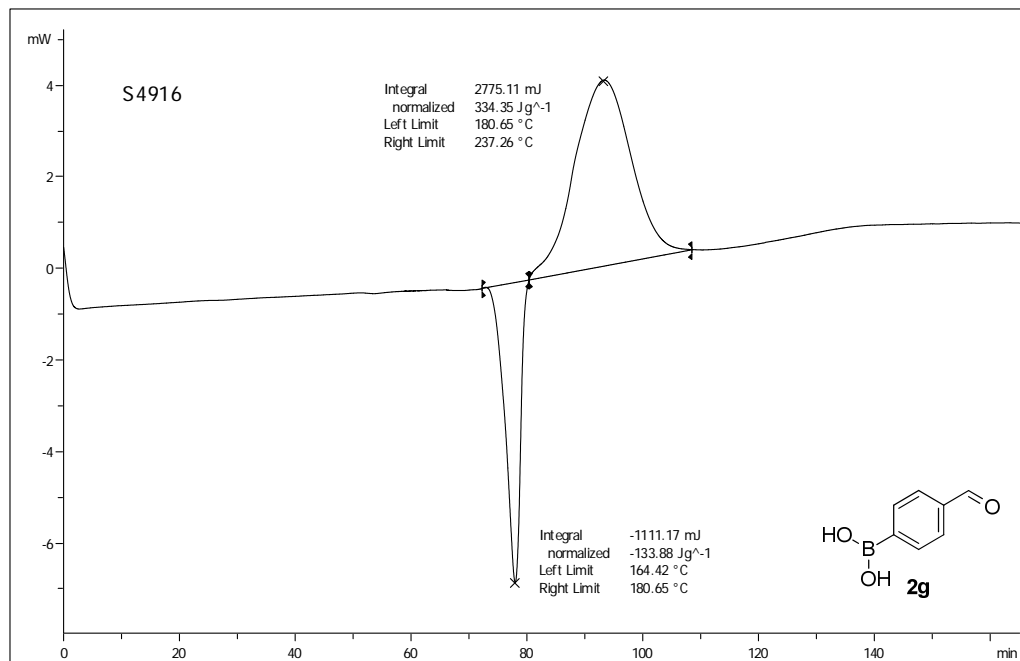


Lab: METTLER

STAR[®] SW 12.00

4-Formyl-phenylboronic acid (2g)

Δ_{exo}

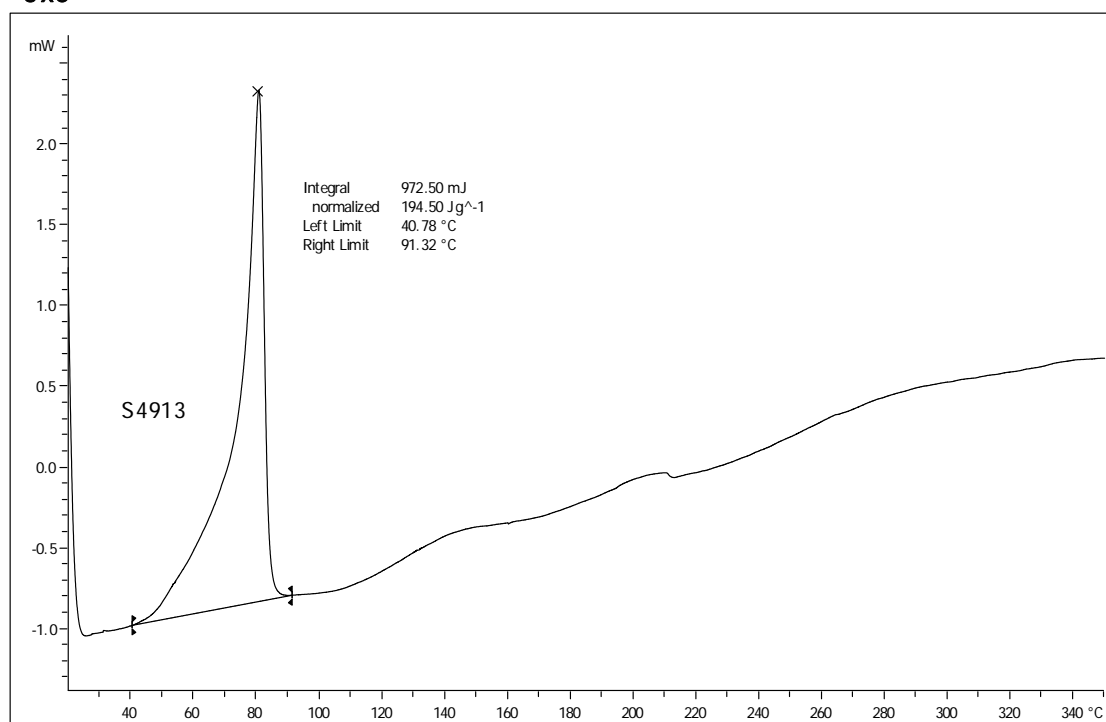


Lab: METTLER

STAR[®] SW 12.00

Mixture 1h + 2g in 10 vol of ethanol before catalyst addition

^exo

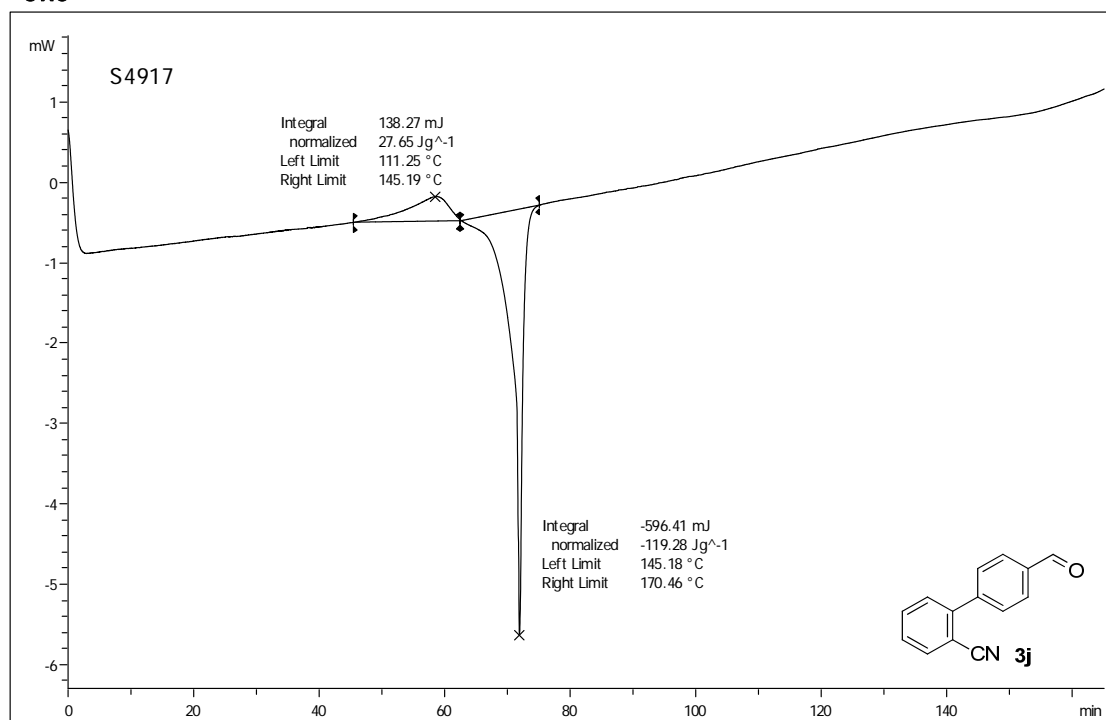


Lab: METTLER

STAR[®] SW 12.00

2'-cyano-4-formyl-biphenyl (3j)

^exo



Lab: METTLER

STAR[®] SW 12.00

2-Cyanobenzenediazonium tetrafluoroborate thermal decomposition: A slurry of 2-cyanobenzenediazonium tetrafluoroborate **1h** (51 mg, 0.235 mmol) in 320 μ L of ethanol was prepared in a HPLC vial. The slurry was gradually heated to 80 °C by increasing the temperature of 10 °C every 10 minutes. The slurry was stirred 20 minutes at 80 °C and was analysed by LC/MS. Analysis showed the formation of a main impurity suspected to be benzonitrile. A sample of commercial benzonitrile was added to the last sample of the reaction mixture and LC/MS confirmed that the product formed was benzonitrile.

2-Cyanobenzenediazonium tetrafluoroborate and 4-formyl-phenylboronic acid thermal decomposition: A slurry of 2-cyanobenzenediazonium tetrafluoroborate **1h** (51 mg, 0.235 mmol) and 4-formyl-phenylboronic acid **2g** (32 mg, 0.213 mmol) in 320 μ L of ethanol was prepared in a HPLC vial. The slurry was gradually heated to 80 °C by increasing the temperature of 10 °C every 10 minutes. The slurry was stirred 20 minutes at 80 °C and was analysed by LC/MS. Analysis showed the formation of two main impurity suspected to be benzonitrile **5** and benzaldehyde **6**. A sample of commercial benzaldehyde **6** was added to the last sample of the reaction mixture and LC/MS confirmed that the product formed was benzaldehyde **6**.