

Bedford-type palladacycle catalyzed Miyaura-borylation of aryl halides with tetrahydroxydiboron in water

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SUPPLEMENTARY MATERIAL

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Table

S1:

Eco

Scale

Calculations

Eco Scale Calculation [1]:

	2-iodophenol (2-OH)				4-iodoanisole (4-OMe)				Eco	Scale	Calculations
	This protocol, yield >99%	Lit [2]: 17%; 3eq. KOAc, 3eq. BBA, EtOH 0.1M, 80°C. 0.5mol% cat. 1mol%L	Lit [3]: Ni-catalyzed, 4-Bromo-phenol, 90%	points	This protocol, yield >99%	Lit [2]: 99%; 3eq. KOAc, 3eq. BBA, EtOH 0.1M, 80°C. 0.5mol% cat. 1mol% L	Lit [3]: Ni-catalyzed, 4-bromo-anisol, 78%	points			
1. yield	(100 - %yield)/2	0.5	41.5	5	0.5	0.5	11				
2. Price of reaction component (to obtain 10 mmol of end product)	€ 125.03	€ 3,472.61	€ 60.92	€ 134.72	€ 600.27	€ 50.96					
Inexpensive (< \$10) = 0	0										
Expensive (> \$10 and < \$50) = 3	3										
Very expensive (> \$50) = 5	5	5	5	5	5	5	5				
3. Safety											
N (dangerous for environment)	5	0	0	0	0	0	0				
T (toxic)	5	0	0	0	0	0	0				
F (highly flammable)	5	0	0	0	0	0	0				
E (explosive)	10	0	0	0	0	0	0				
F+ (extremely flammable)	10	0	10	10	0	10	10				
T+ (extremely toxic)	10	0	0	0	0	0	0				
4. Technical setup											
Common setup	0	0	0	0	0	0	0				
Instruments for controlled addition	1										
Unconventional activation technique	2										
Pressure equipment, > 1 atmd	3										
Any additional special glassware	1										
(Inert) gas atmosphere	1	1	1	1	1	1	1				
Glove box	3										
5. Temperature/time											
Room temperature, < 1 h	0										
Room temperature, < 24 h	1	1		1	1						
Heating, < 1 h	2										
Heating, > 1 h	3	0			0		3				
Cooling to 0°C	4										
Cooling, < 0°C	5										
6. Workup and purification											
None	0										
Cooling to room temperature	0	0	0	0	0	0	0				
Adding solvent	0	0			0						
Simple filtration	0			0	0		0				
Removal of solvent with bp < 150°C	0	0	0	0	0	0	0				
Crystallization and filtration	1	1	1	1	1	1	1				
Removal of solvent with bp > 150°C	2										
Solid phase extraction	2										
Distillation	3										
Sublimation	3		3				3				
Liquid-liquid extraction	3	3	3		3		3				
Classical chromatography	10	10			10						
		21.5	67.5	22	21.5	26.5	30				
Eco-scale value		78.5	32.5	78	78.5	73.5	70				

	M [g/mol]	n [mol]	according Sigma m [g] e 1q [EUR]
BBA	89.65	0.03	2.69 € 24.20
NaOAc	82.03	0.03	2.46 € 0.10
KOAc	98.14	0.03	2.94 € 0.13
4-Iodophenol	220.01	0.01	2.20 € 5.47
2-Iodophenol	220.01	0.01	2.20 € 3.38
4-Bromophenol	173.01	0.01	1.73 € 6.20
4-bromoanisole	187.03	0.01	1.87 € 0.408
water 100mL			0.10 € 21.00
EtOH 100mL			0.10 € 181.00
catalyst MOL	786.8	0.005	3.93 € 127.00
catalyst JE	854.42	0.0001	0.09 € 587.60
2-Phenylphenol	170.21	0.027	4.60 € 0.07
ChiPr2P	152.6	0.02585	3.91 € 13.76
NEt3	101.19	0.0405	4.10 € 3.40
toluene			
PdCl2	177.33	0.027	4.79 € 108.50
toluene			
pentane			
4-OMe	234.03	0.01	2.34 € 7.30
BBA	89.65	0.015	1.34 € 20.80
NiCl2(dppp)	542.04	0.0001	0.05 € 20.80
PPh3	262.29	0.0002	0.05 € 0.19
DIPEA	129.24	0.03	3.88 € 0.77
EtOH 100mL			0.10 € 181.00

includes conversion to pincol esters.

References

- 1 K. Van Aken, L. Strekowski, L. Patiny, *Beilstein Journal of Organic Chemistry* 2006, 2:3, 1-7.
- 2 G. A. Molander, S. L. J. Trice, S. M. Kennedy, S. D. Dreher, M. T. Tudge, *J. Am. Chem. Soc.* 2012, 134, 11667-11673.
- 3 G. A. Molander et al., *J. Org. Chem.* 2013, 78, 6427-6439:

NiCl2(dppp), PPh3, DIPEA in EtOH at 80 °C, 2h, as BF3K salt, 90% Br-Anisol, 78% Br-p-OH, rt

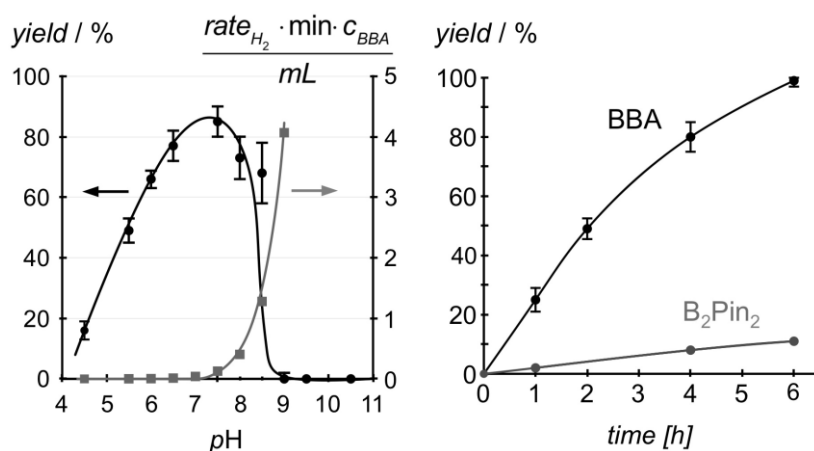


Figure S1. Influence of initial reaction pH (left) and boron source (BBA vs. B₂Pin₂; right) onto the observed borylation yields. The grey curve in the left scheme illustrates the dependence of the hydrogen evolution rate (unit mL*min⁻¹mmol(BBA)⁻¹) from BBA.

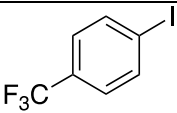
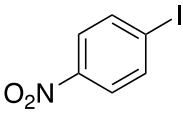
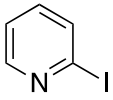
To eliminate any influence of the base other than the *pH* it generated, we evaluated the relationship of yield and reaction *pH* (figure S1) using a buffered system (0.3 M phosphate). To clearly identify reactivity differences, we chose for this study a reaction time that does lead to high but not quantitative conversions (4 h). Highest yields were achieved for 6.5 < *pH* < 7.5. At a reaction *pH* > 9.0 no conversion was observed, while evolution of hydrogen (identified by head space GC/MS) became evident. In a separate experiment, we investigated the change in stability of BBA with varying *pH* in aqueous phase. We found that after an induction period of 5 min, during which the BBA dissolves completely, the rate of BBA decomposition (measured as hydrogen evolution rate) follows the rate law $d[V(H_2)]/dt = k(H_2) \cdot [BBA] \cdot [OH^-]$, with the rate constant for the hydrogen evolution $k(H_2) = 0.13 \text{ mM}(H_2) \cdot s^{-1} \text{ mM}^{-2}$. This rate law indicates a hydroxide or base catalyzed BBA decomposition reaction. Correspondingly, at *pH* < 5, no hydrogen evolution was detectable, while for *pH* > 8.0 the hydrogen evolution reaction consumes BBA at a rate which exceeds that of the palladium catalyzed borylation reaction (initial rate of product formation at *pH* 6.7 under typical test conditions ([4-iodo-phenol] = 100 mM, 3 eq. of BBA): $rate_{ini, product} = 0.03 \text{ mM s}^{-1}$). The half-life time of BBA at *pH* = 7.5 is about 4.5 h, which is reduced to about 9 min at *pH* = 9.0. This *pH* dependent stability profile of BBA explains the observed dependence of product yields on the nature and concentration of the base applied. The constant decomposition of BBA also is presumably responsible for the excess the boron source, which is required to achieve high yields. At a *pH* of 6.7 at least 2 eq. of BBA

are required to achieve full conversion, while a stoichiometric amount of BBA only leads to a yield of 42 % within 6 h. High concentrations of over 5 eq. of BBA lead to acidification of the reaction mixture, which also reduces the reaction rates.

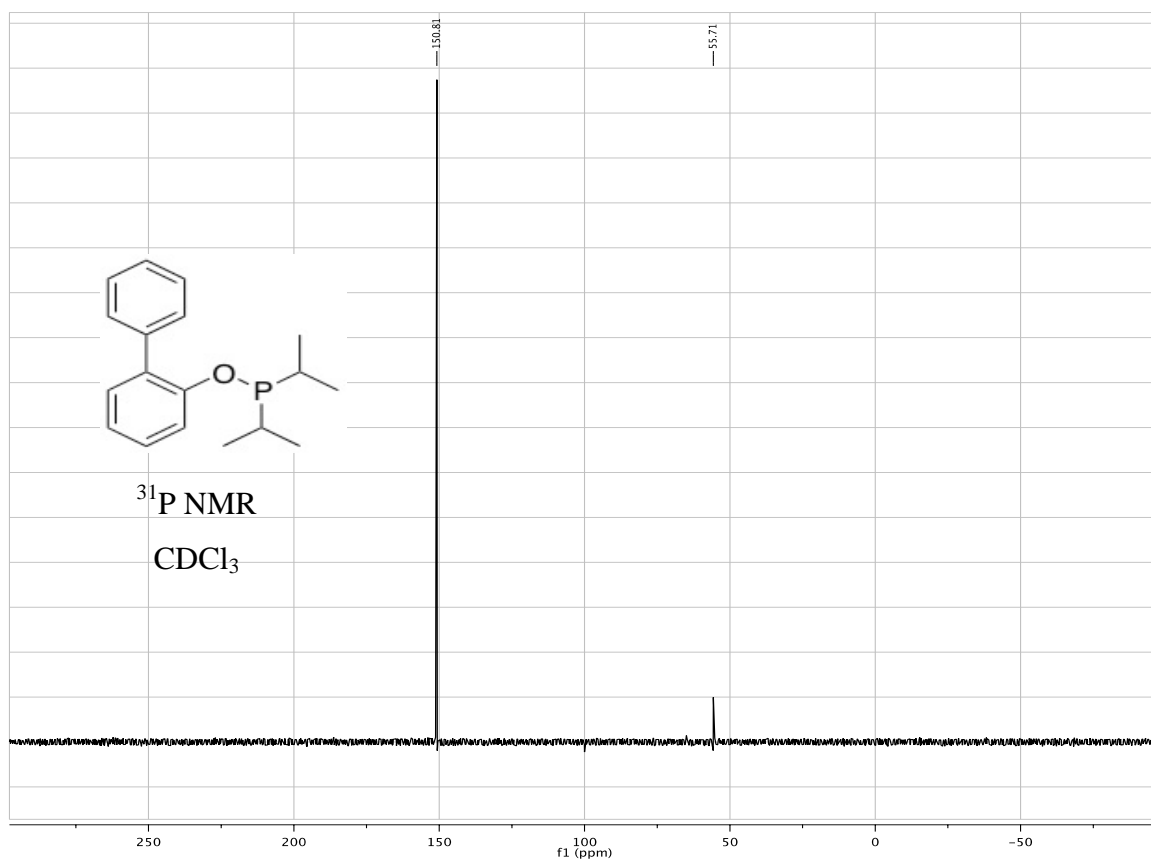
Acidification by 0.3 – 1.1 *pH* occurs during the *Miyaura* borylation, with the extent depending on the buffering potential of the base applied. Since the reaction *pH* strongly influences the outcome, maintaining the proton concentration constant is important to achieve reproducible yields. Correspondingly, results achieved with 1 eq. of borax ($\Delta pH = -0.5$) are not as reproducible as those from runs with 3 eq. of acetate ($\Delta pH = -0.2$). However, buffer concentrations higher than 0.5 M can not be applied due to the reduced solubility of BBA at higher salt strengths, which again translated in reduced yields. The higher ionic strength and a resulting kosmotropic effect of such salts apparently induce “salting out” conditions for the boron source.

No hydrogen evolution was observed when the alternative boron source bis(pinacolato)diboron was applied at a moderately basic *pH* of 9.0. However, only very sluggish conversion is detected for this diboron compound leading to 11% yield after 6 h (figure 1, right panel). Both, increased stability towards hydrogen evolution as well as reduced reactivity in the *Miyaura* borylation is probably a result of the low solubility we find for this substrate in the aqueous phase.

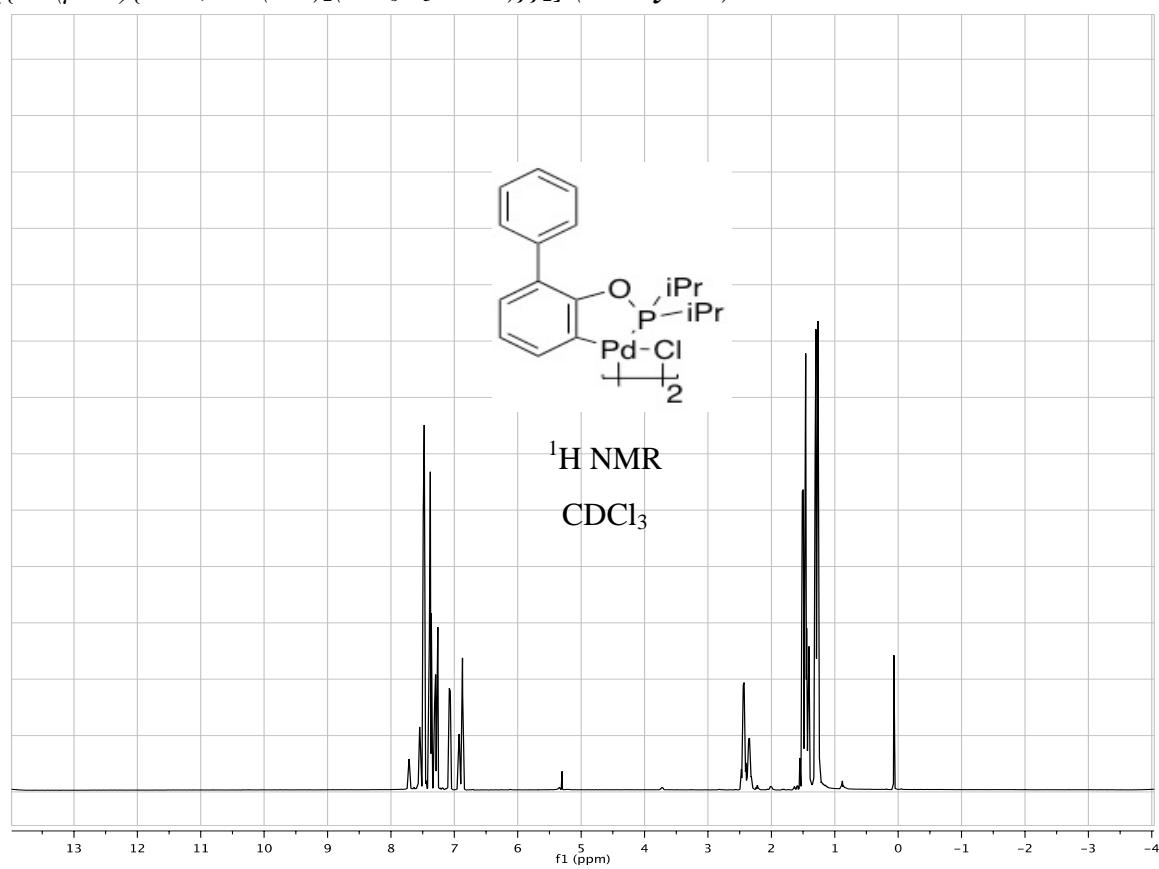
Table S2: Additional Substrate screening

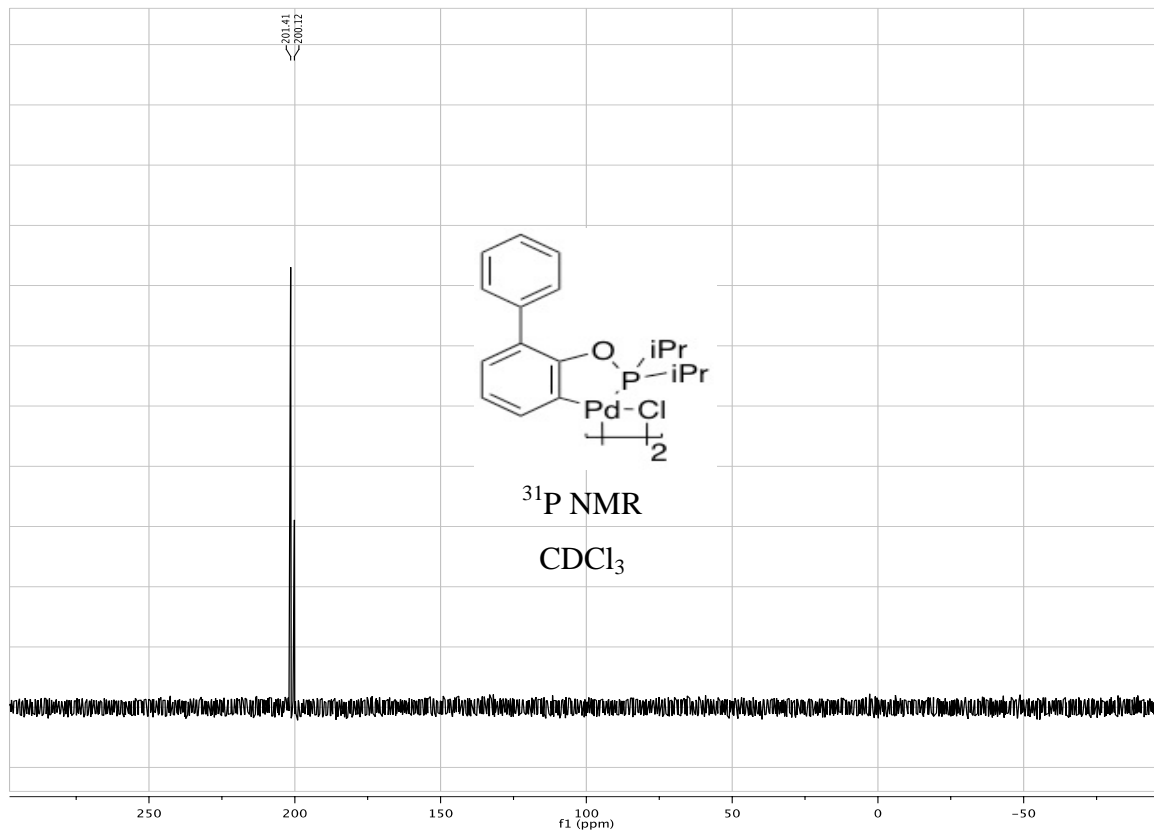
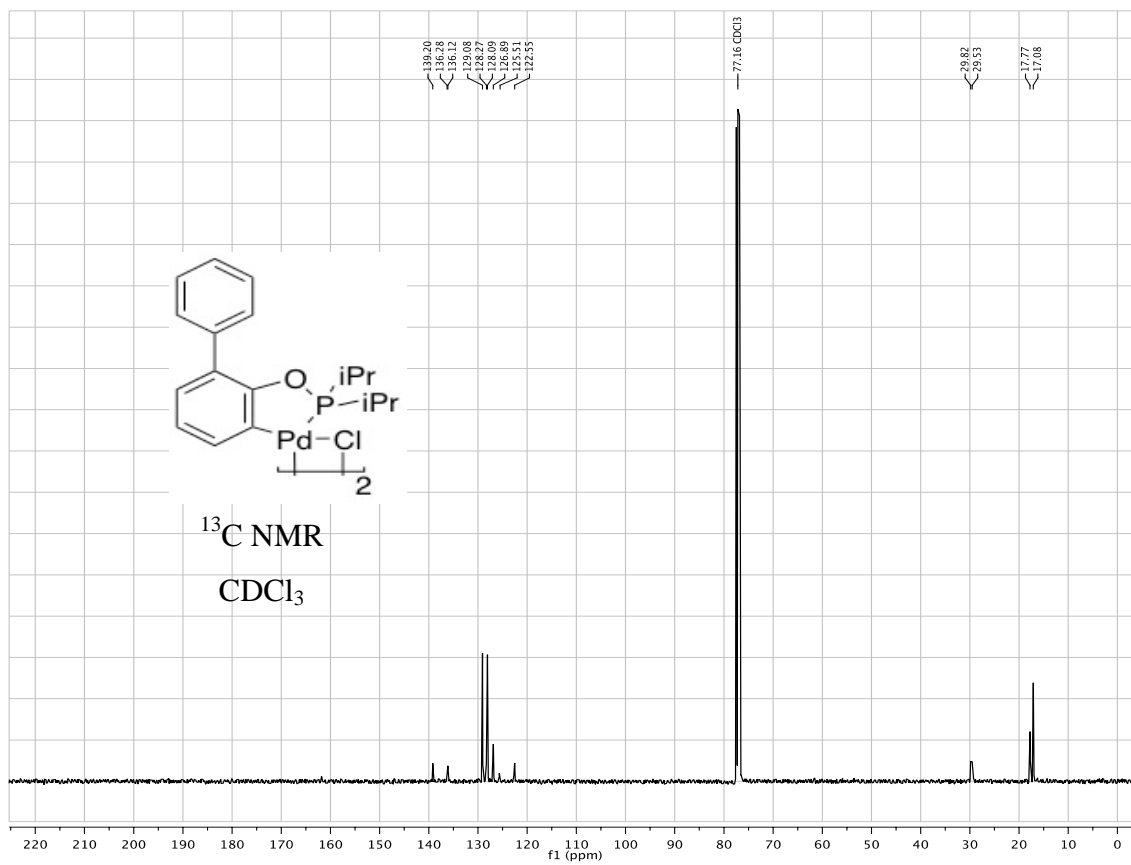
entry	substrate (1)	yield (%) ^b
1		traces
2		0
3		0

^aReaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), NaOAc (1.5 mmol), catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h under argon atmosphere. ^bAll yields mentioned in brackets are NMR yields of product **3**.

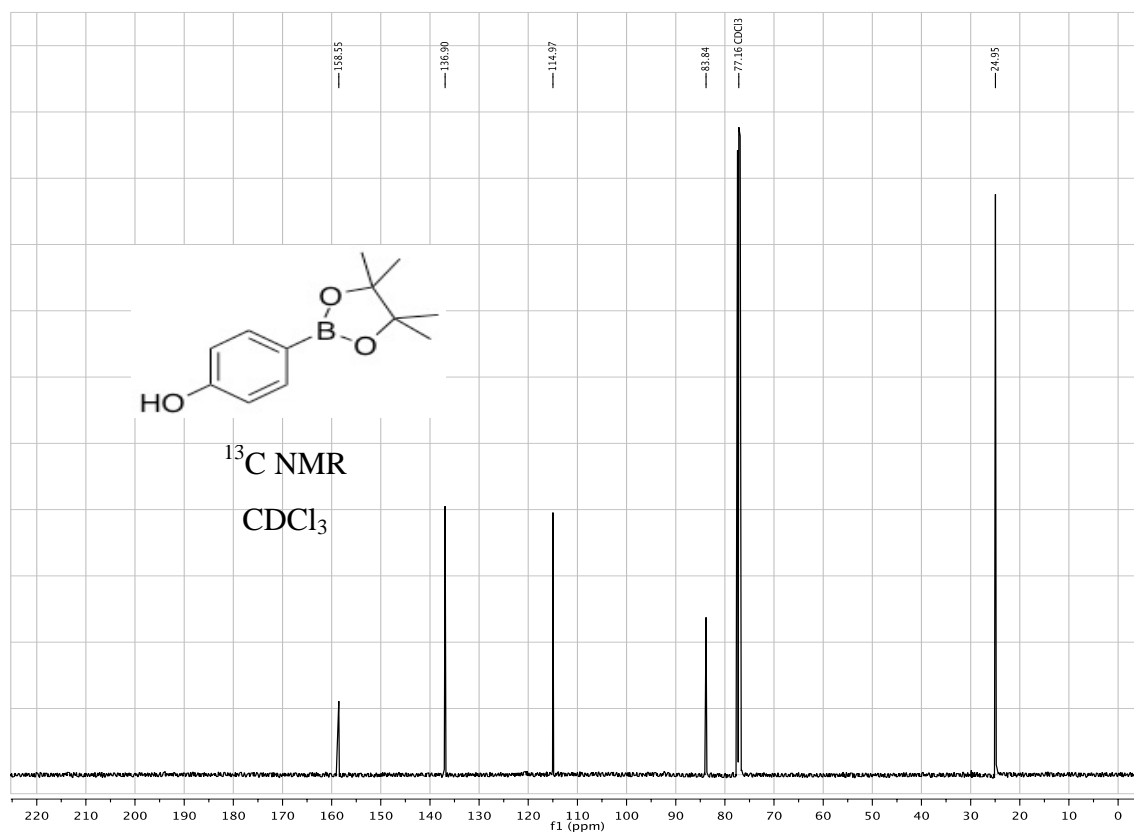
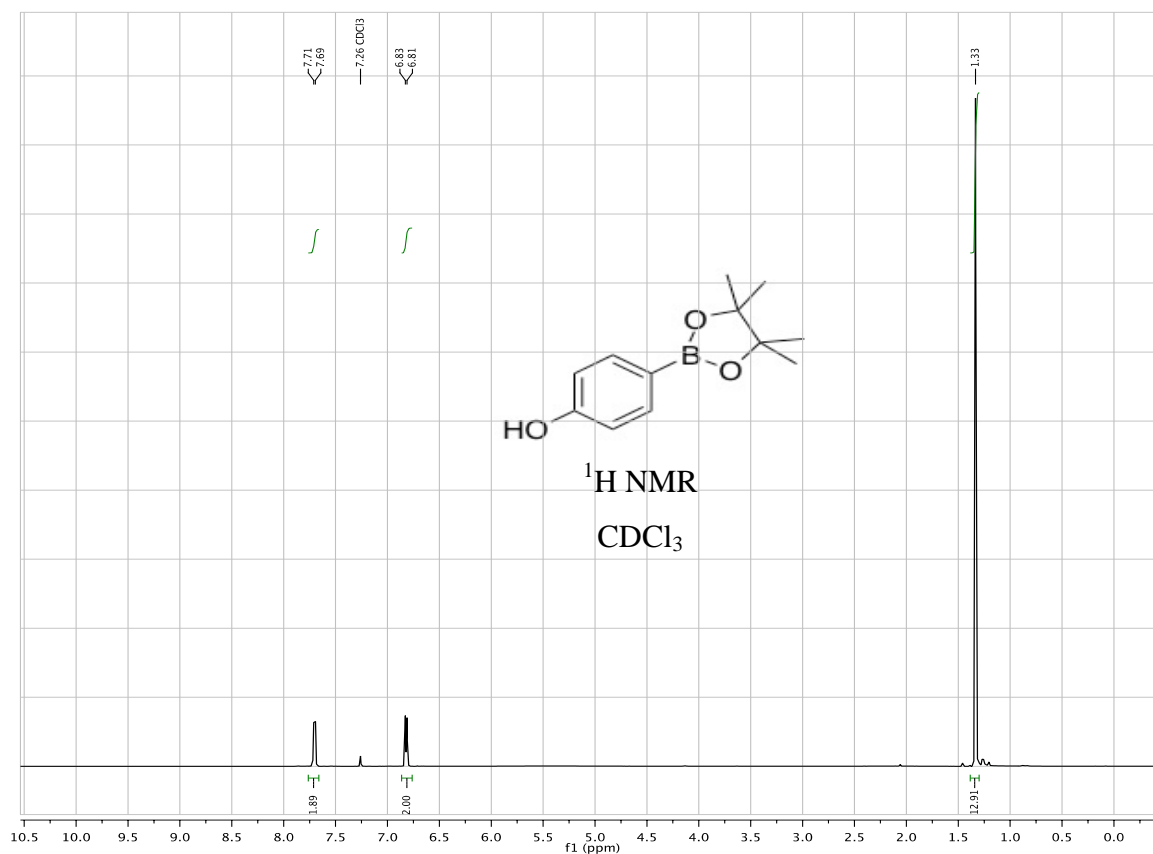


$[\{\text{Pd}(\mu\text{-Cl})\{\kappa^2\text{-P,C-P}(\text{iPr})_2(\text{OC}_6\text{H}_3\text{-2-Ph})\}\}_2]$ (Catalyst A)

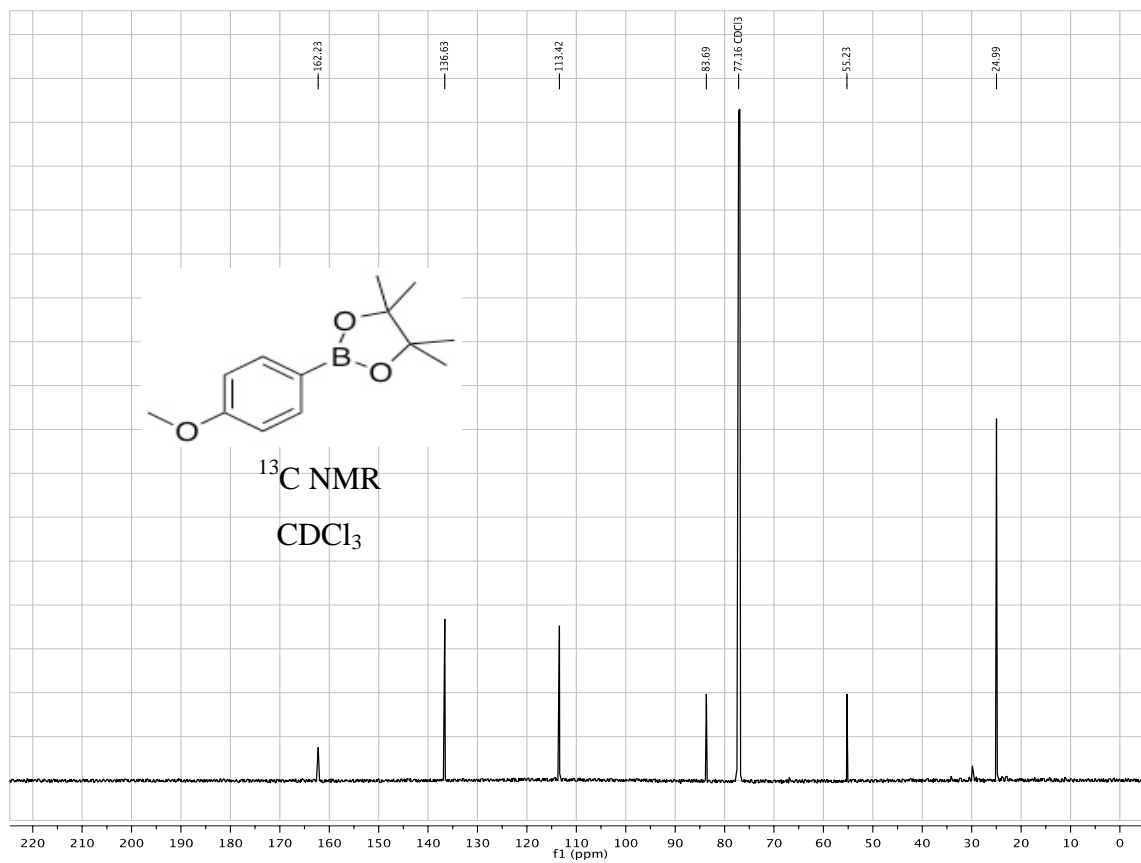
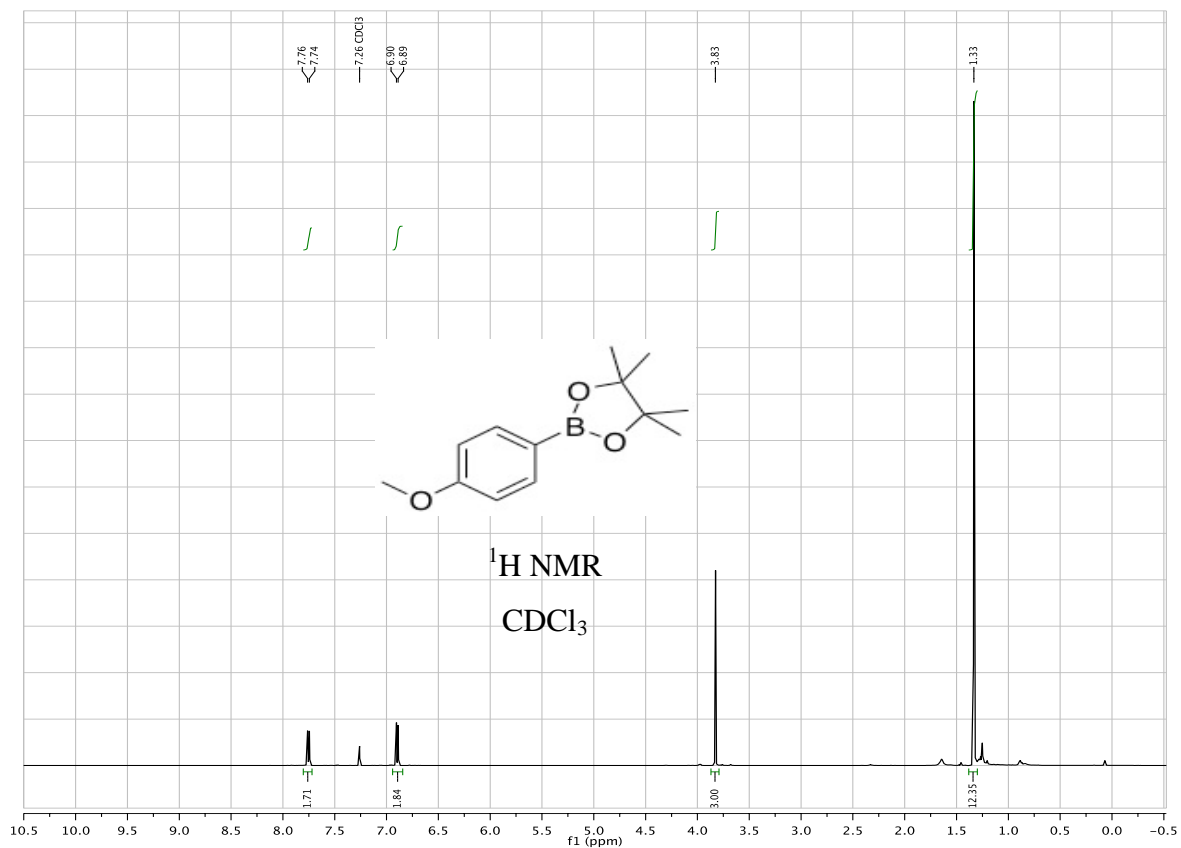




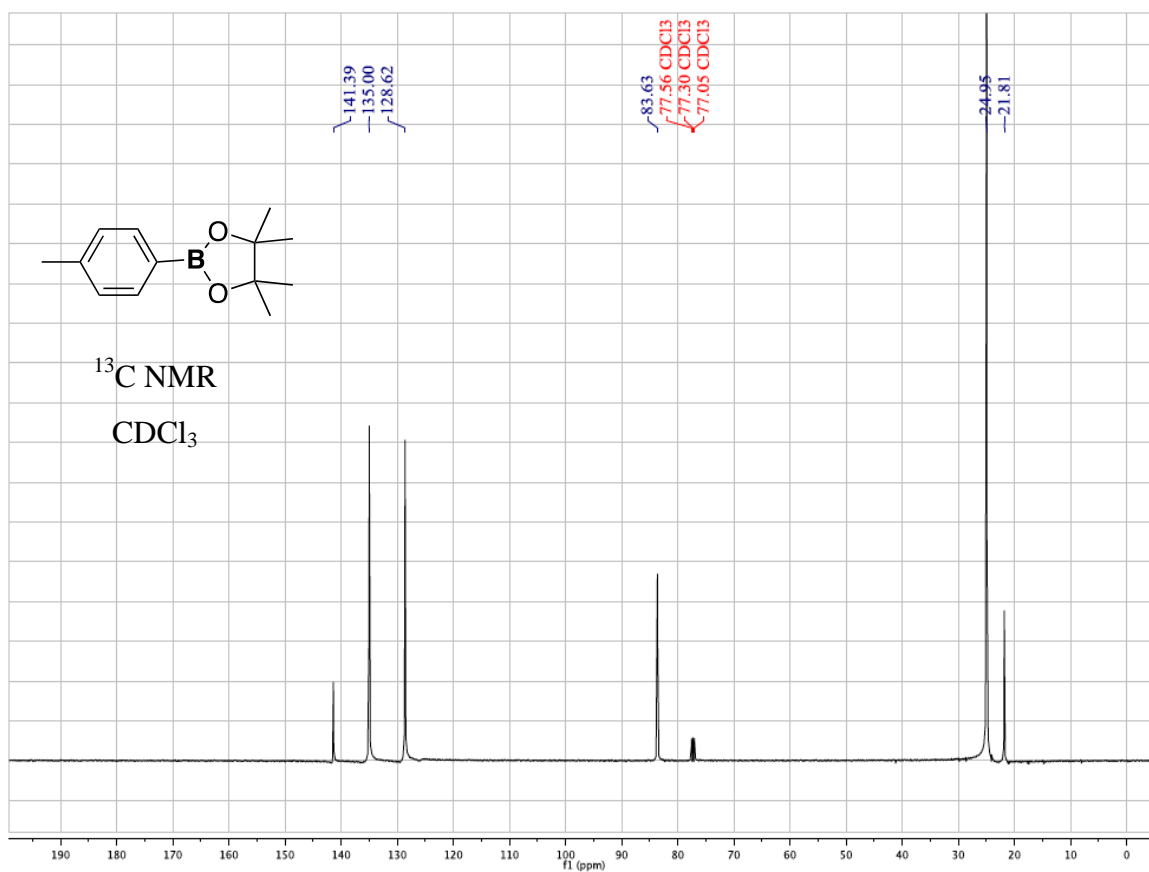
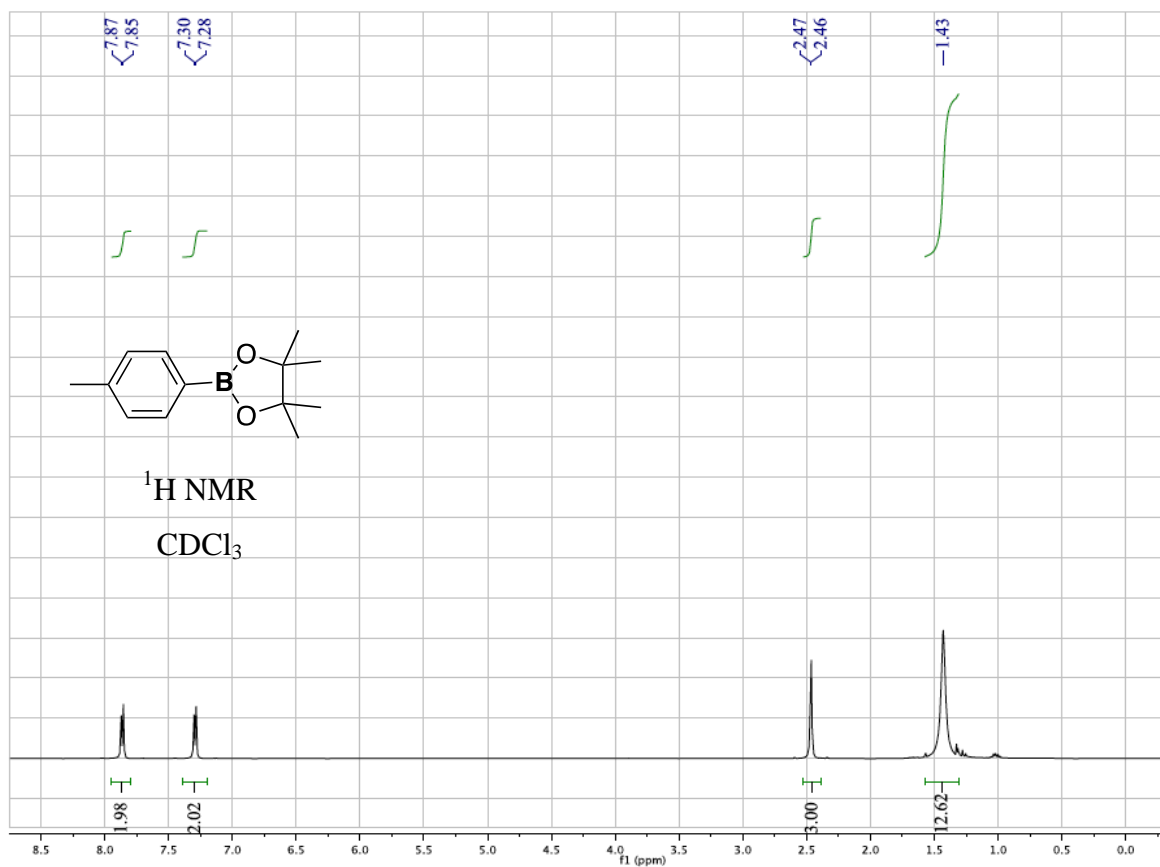
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3a**):



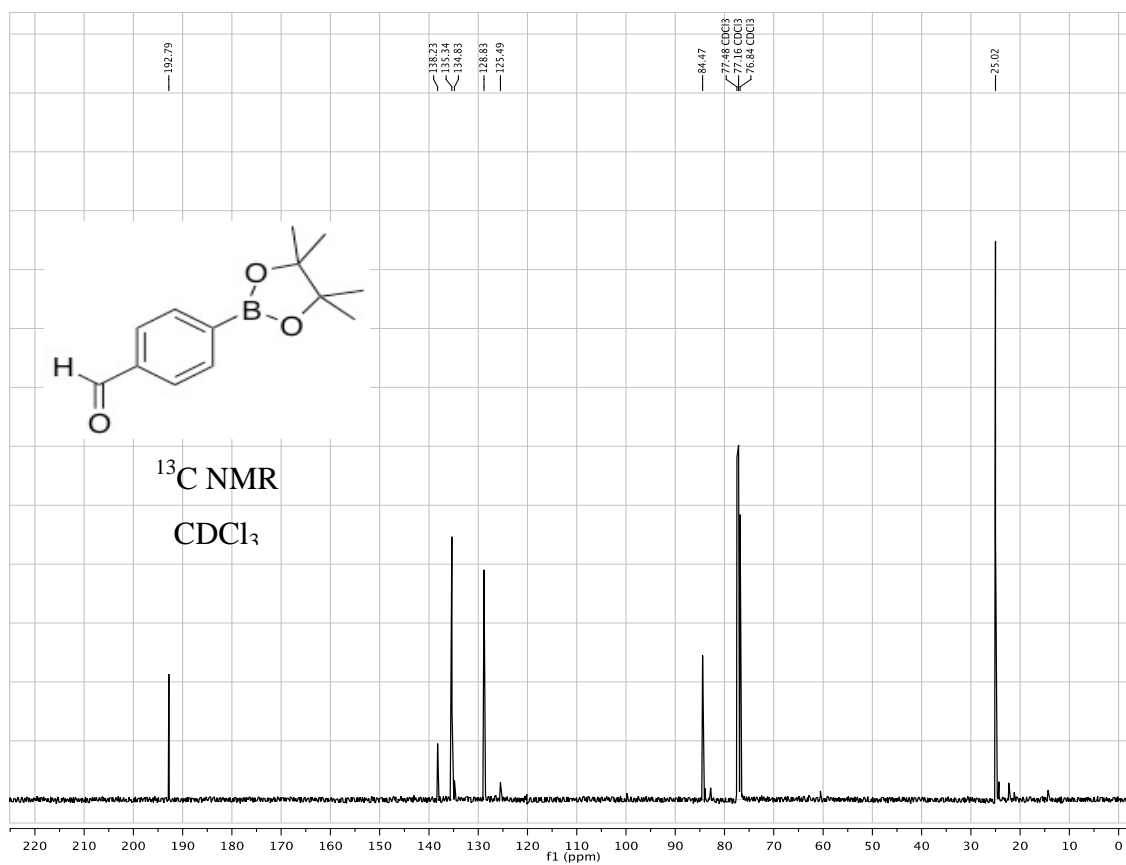
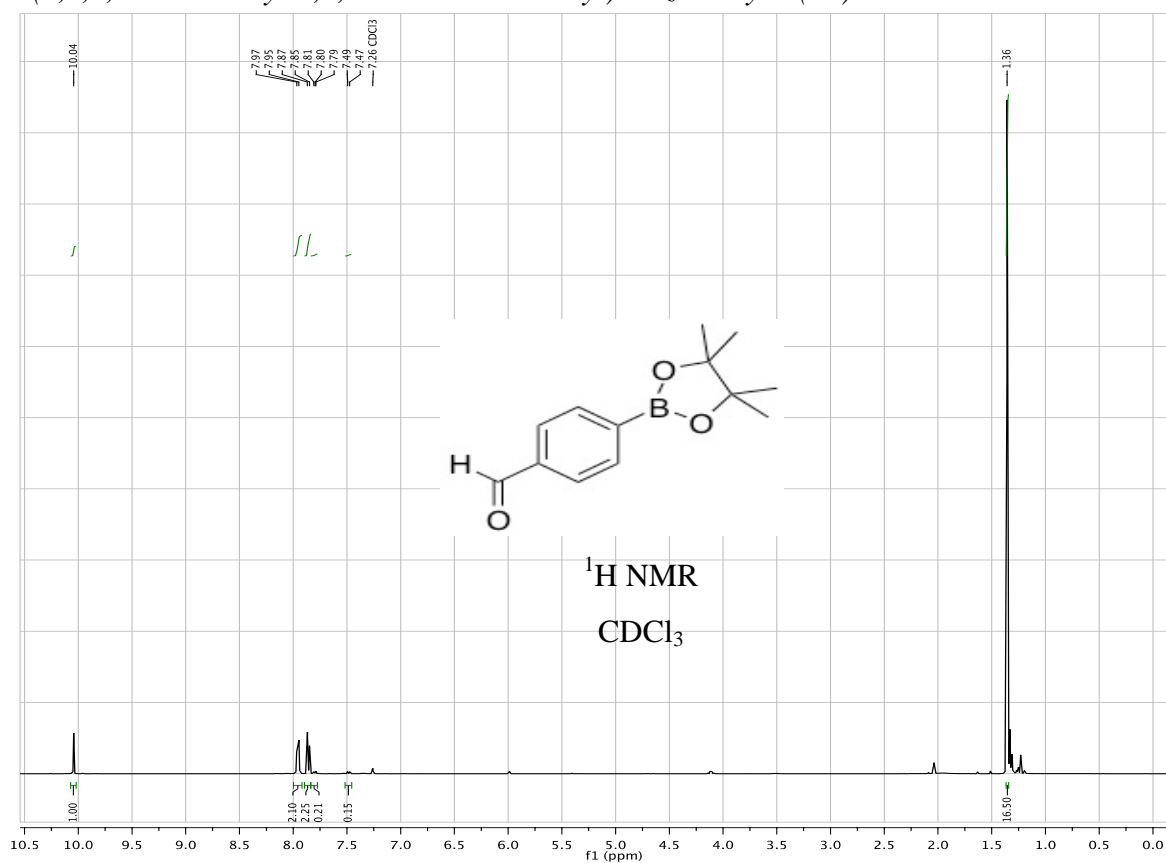
2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3b**):



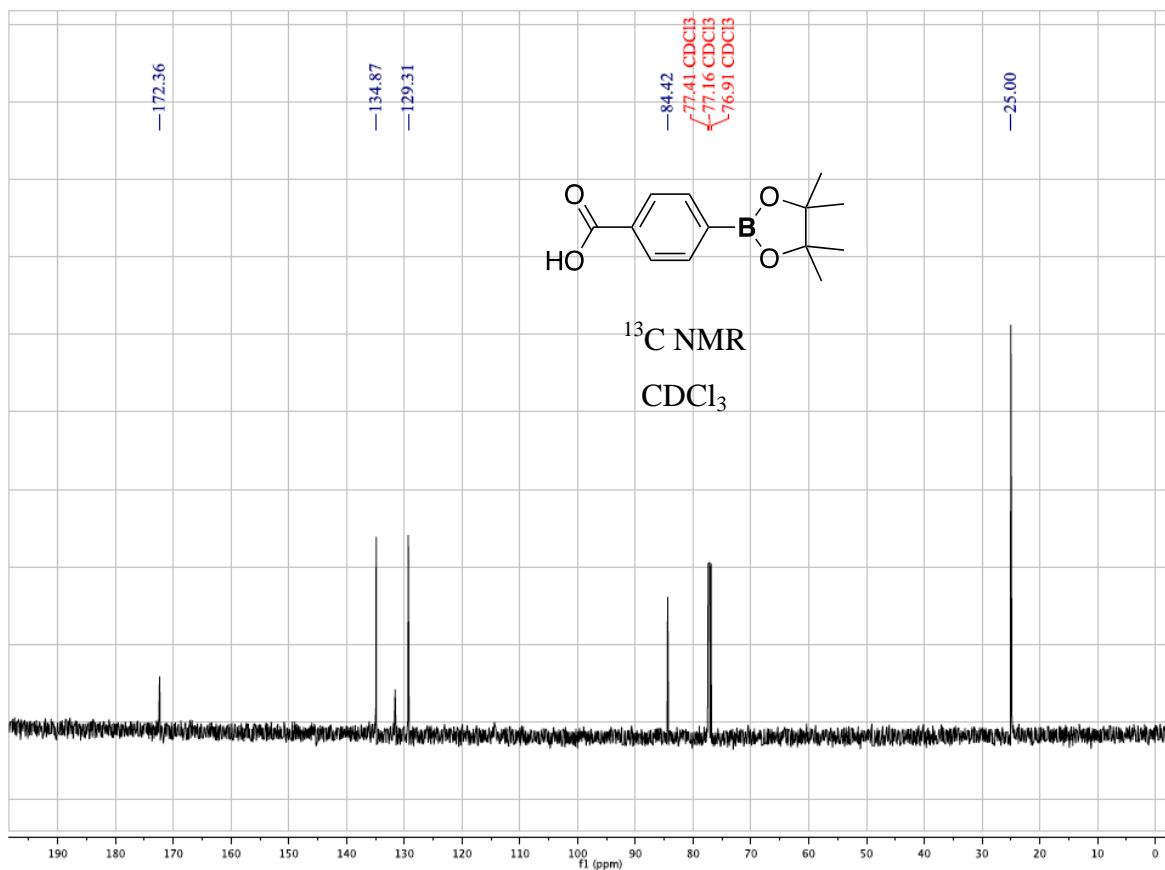
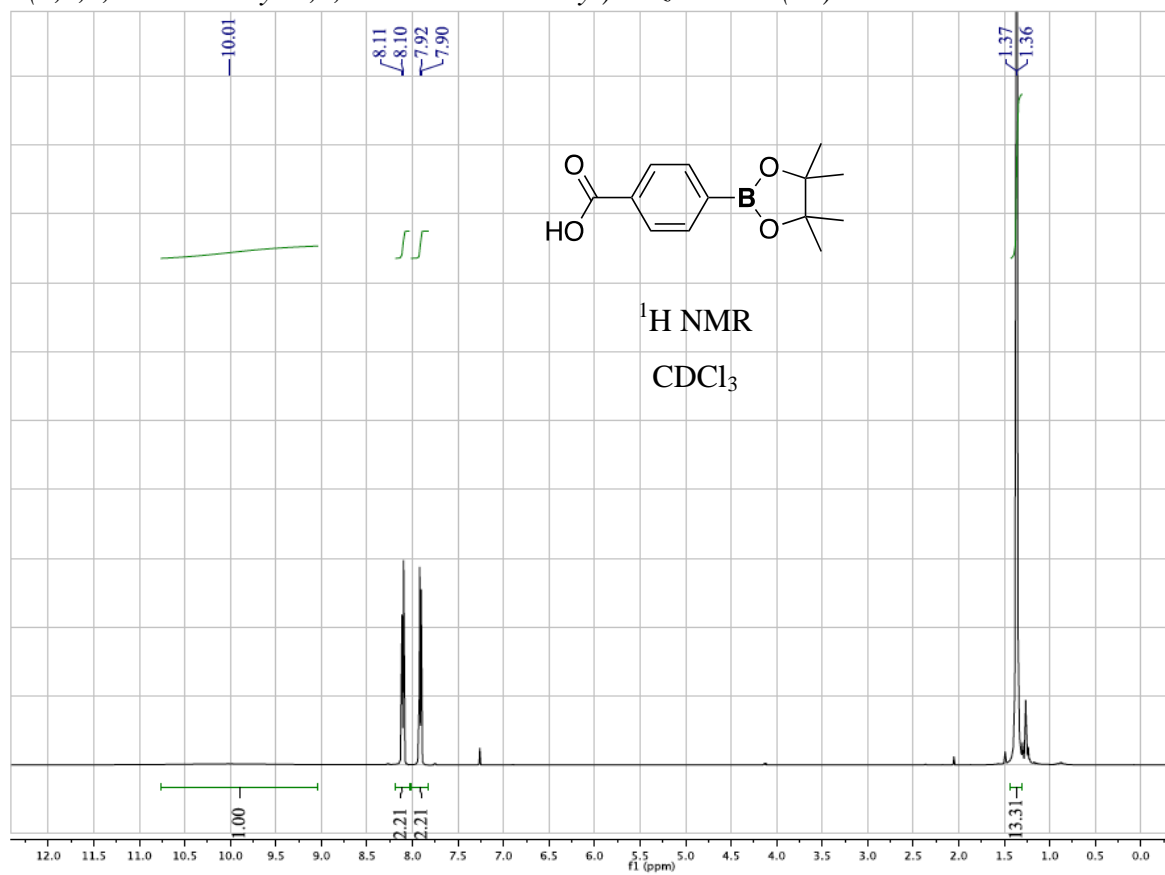
4,4,5,5-tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (**3c**):



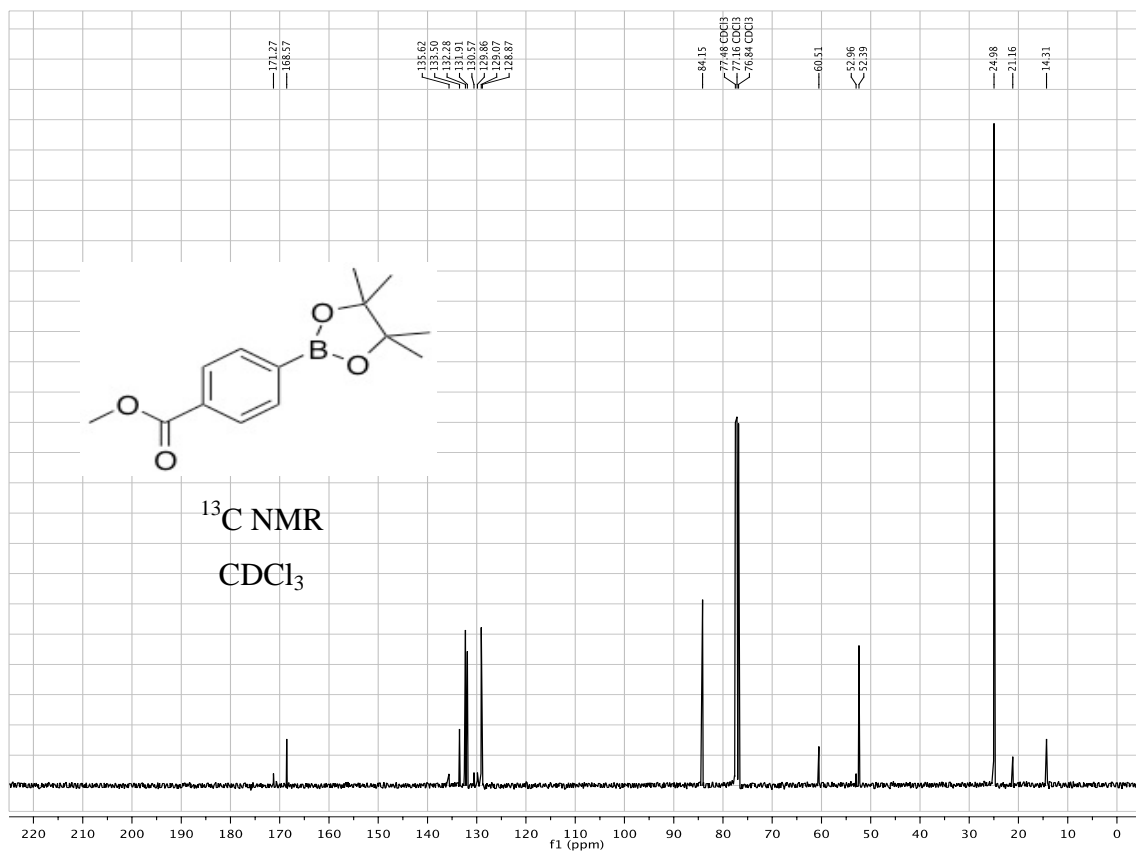
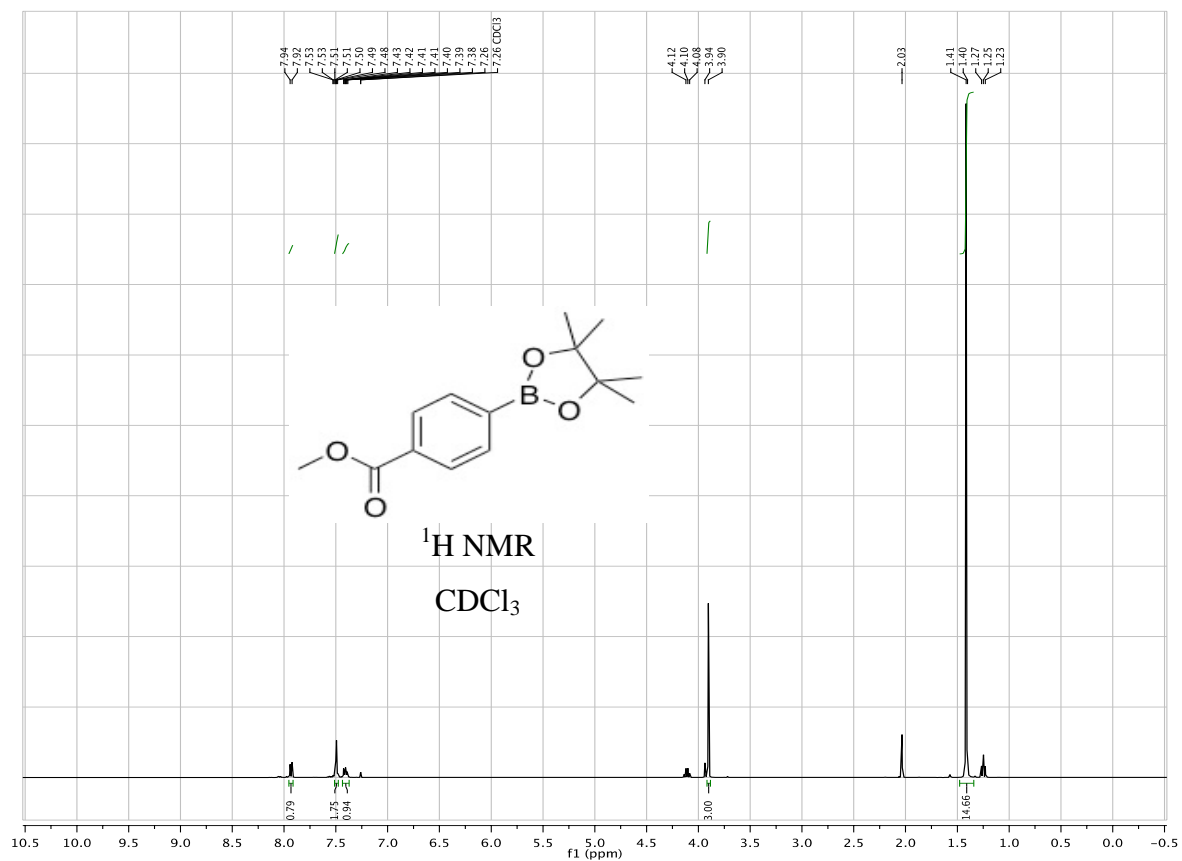
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**3d**):



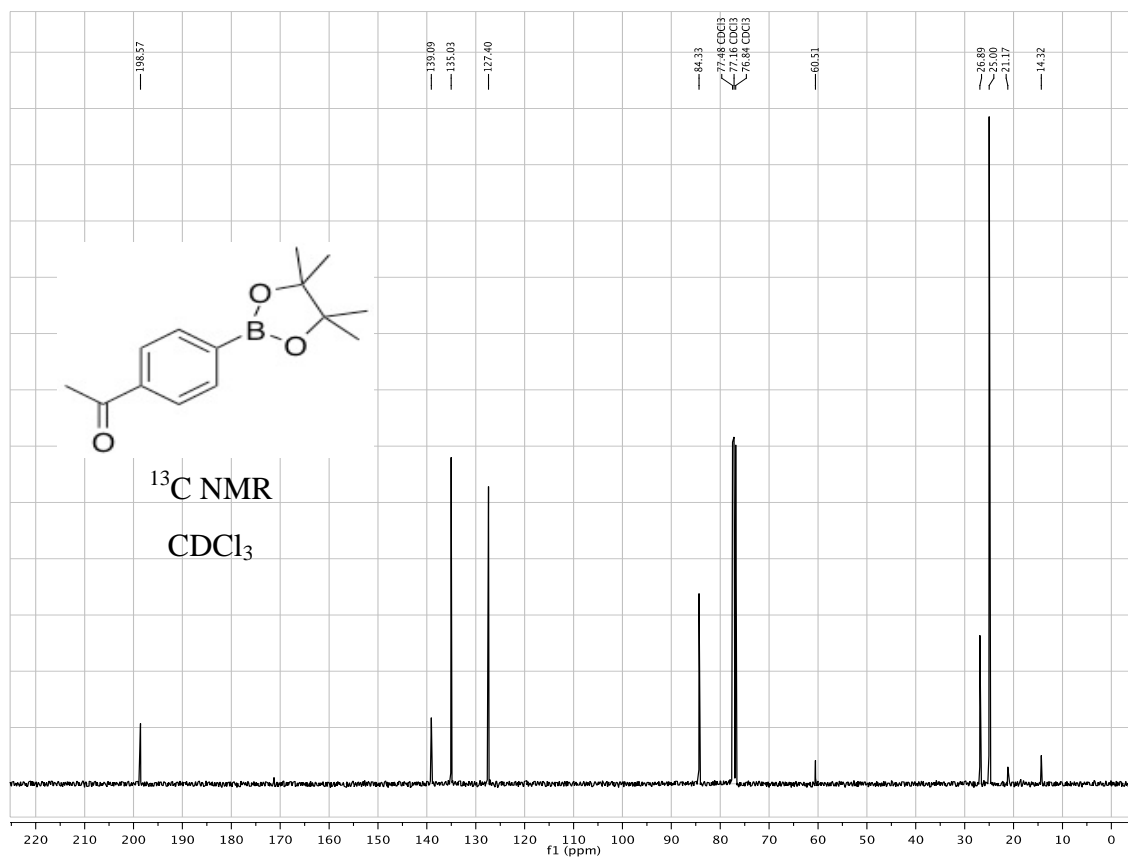
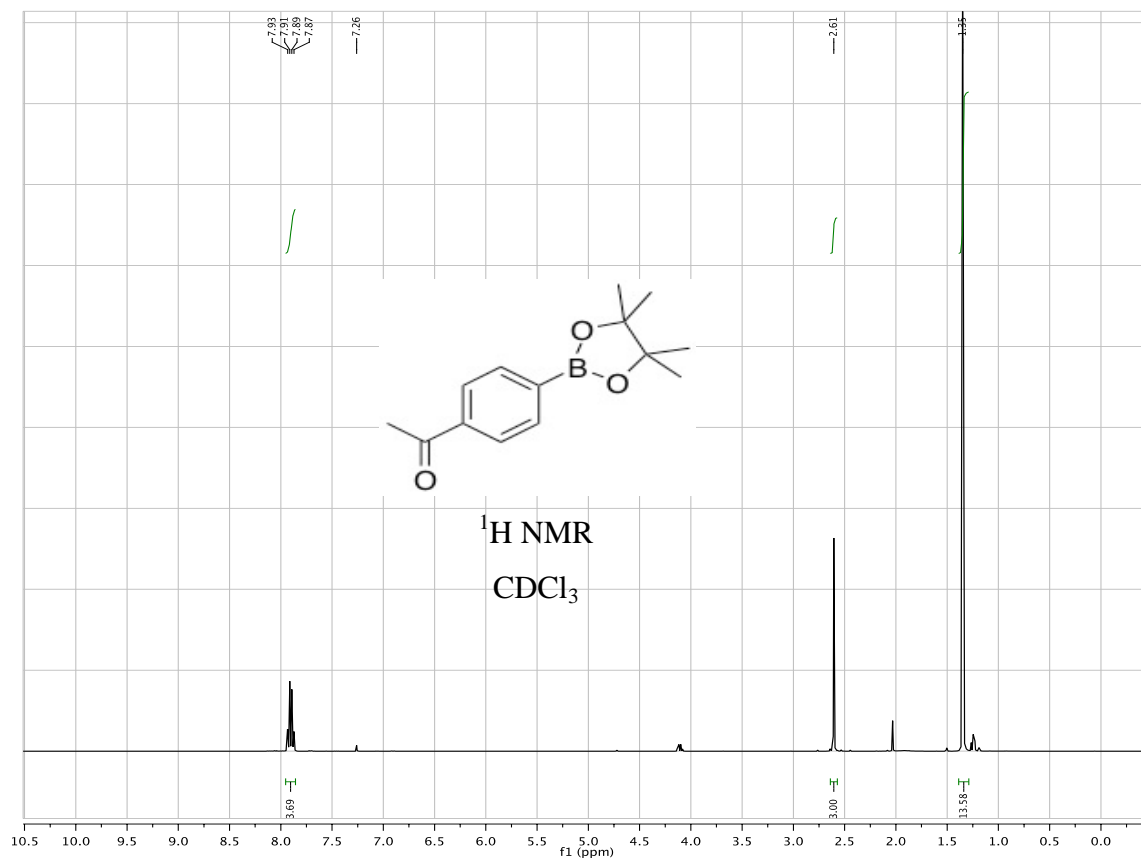
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**3e**):



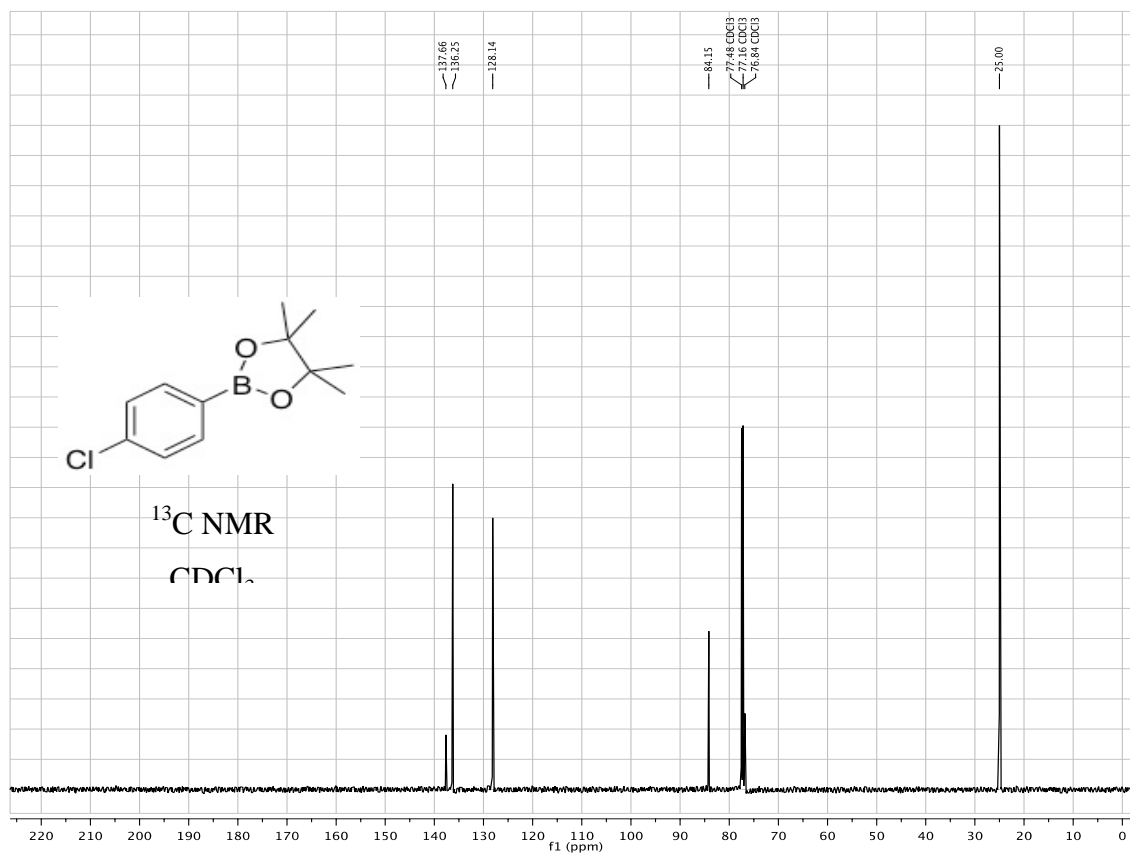
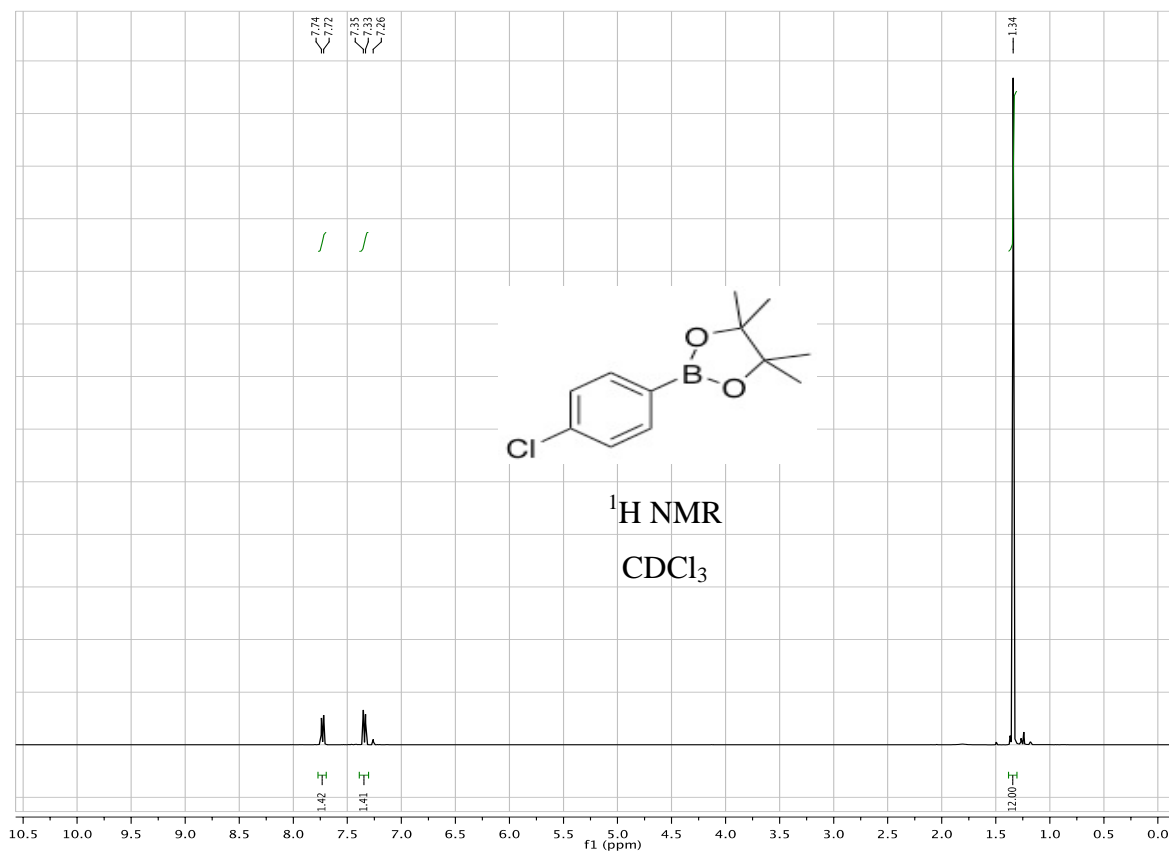
Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**3f**):



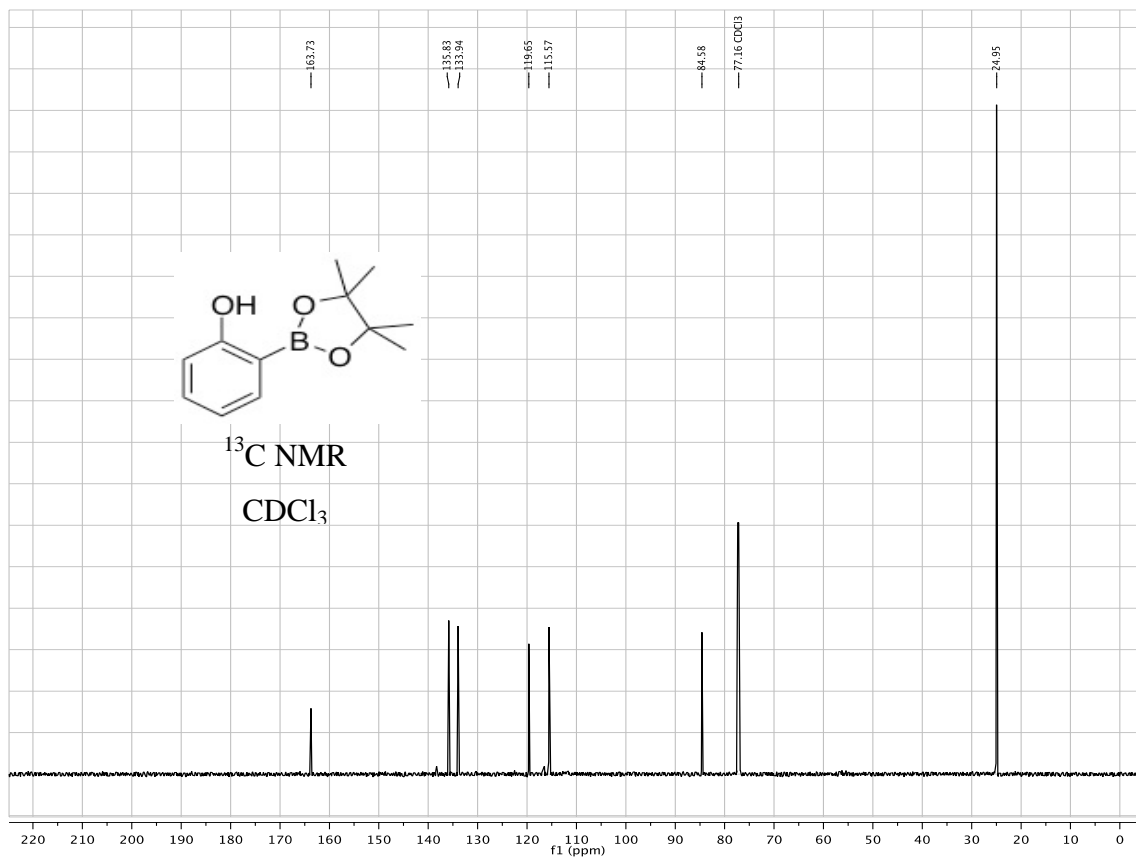
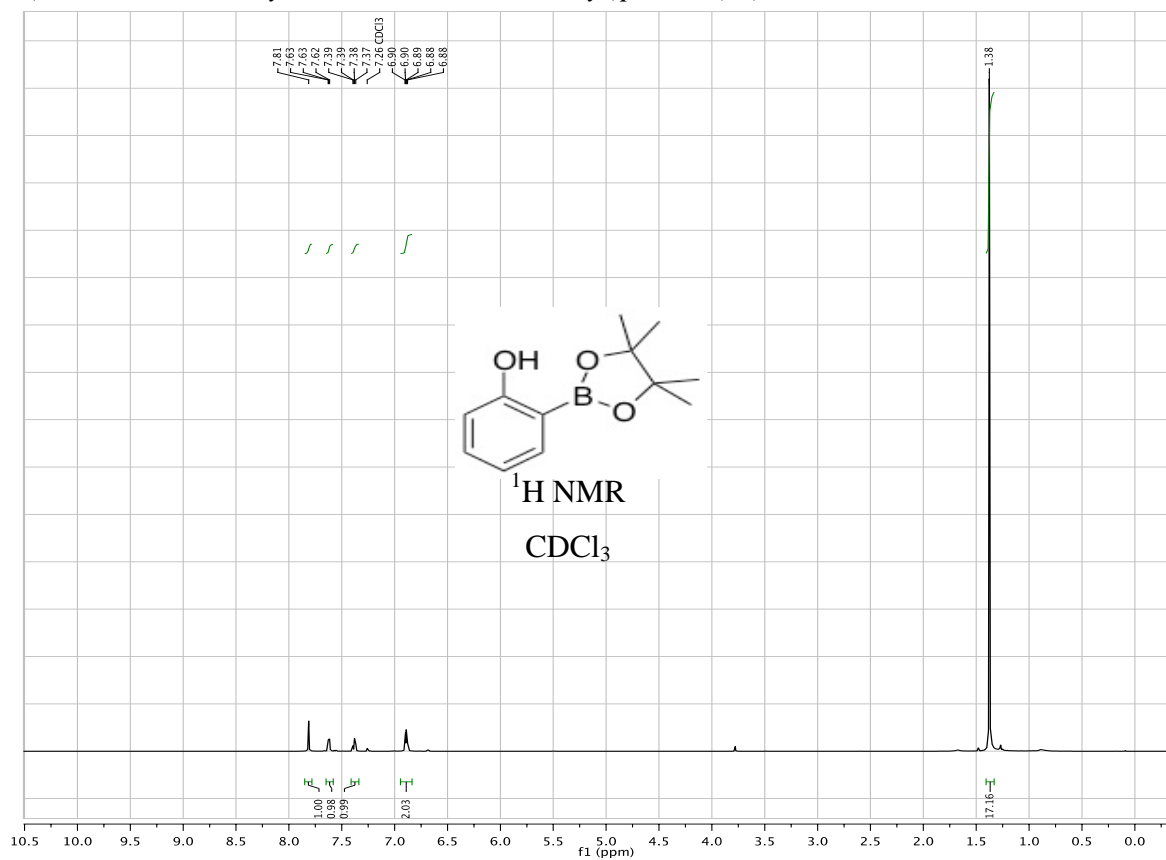
1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (3g):



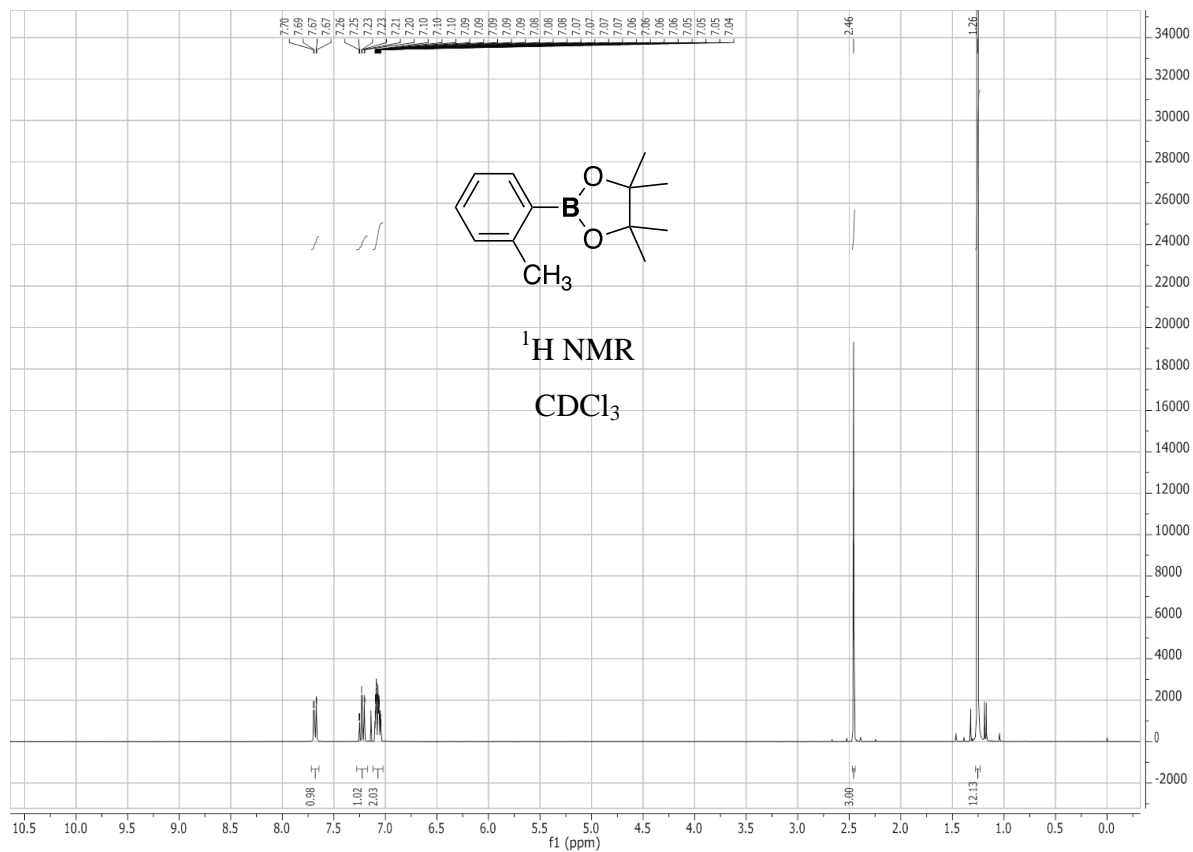
2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3h**):



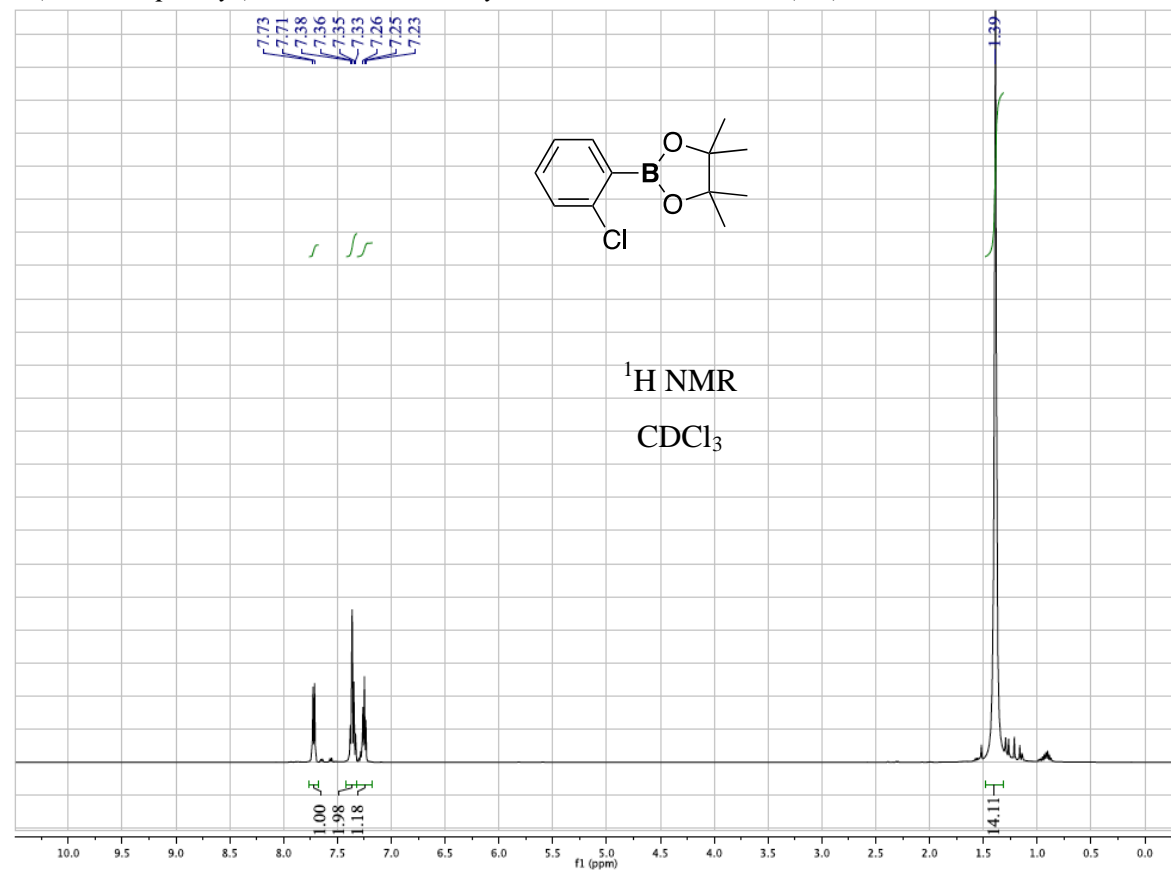
2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3i**):

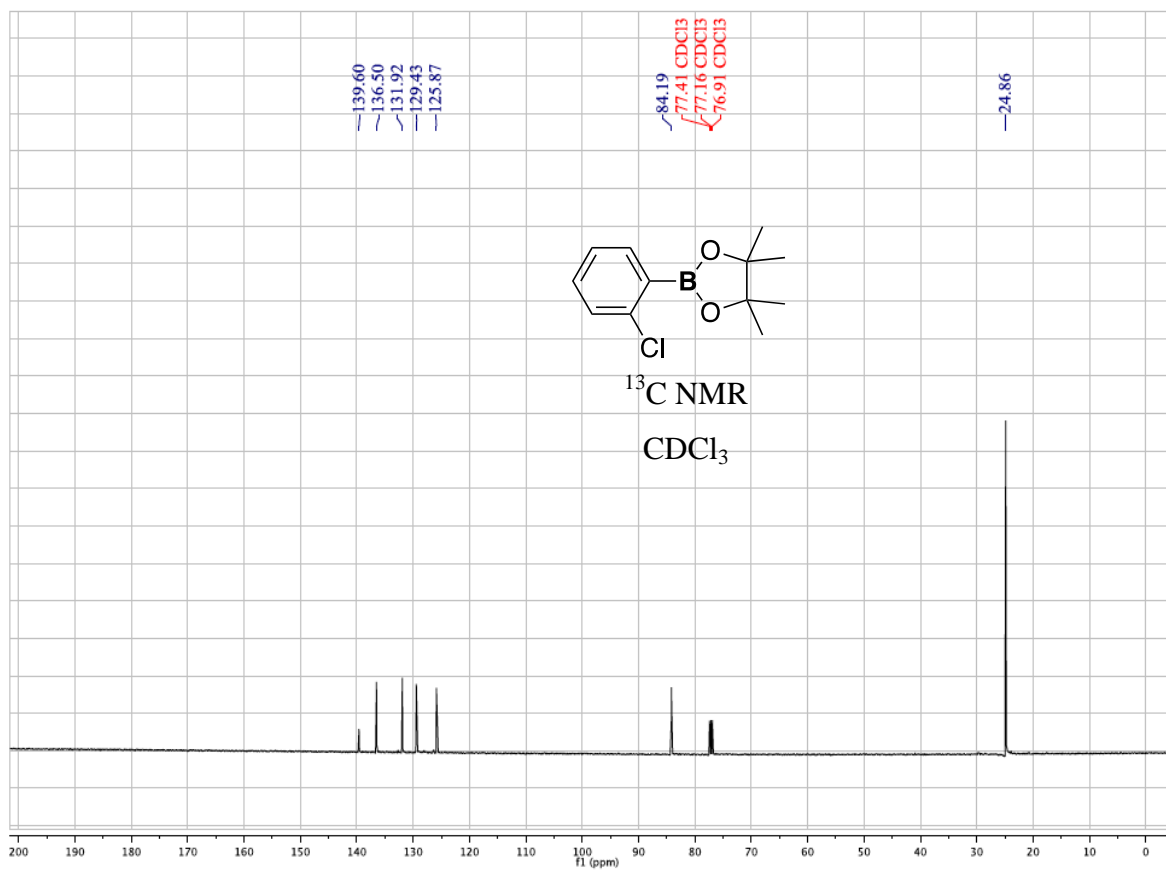


4,4,5,5-tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (**3j**):

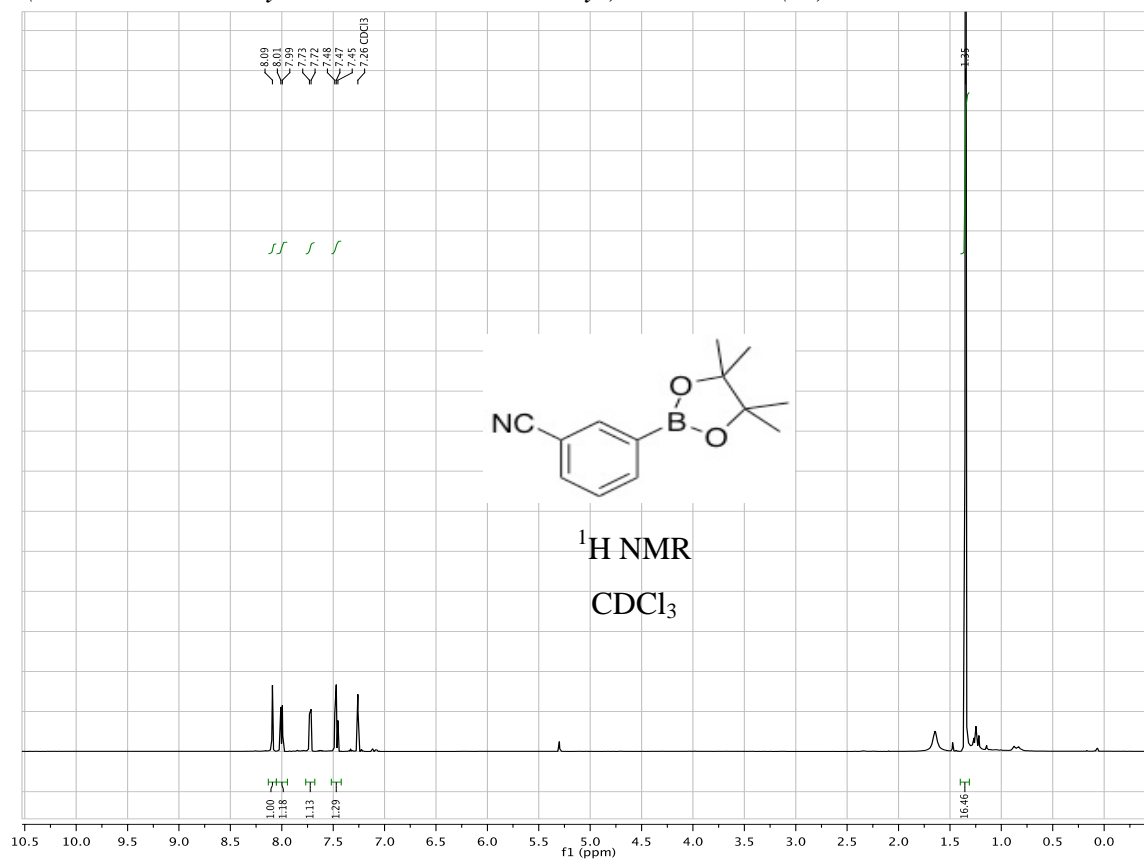


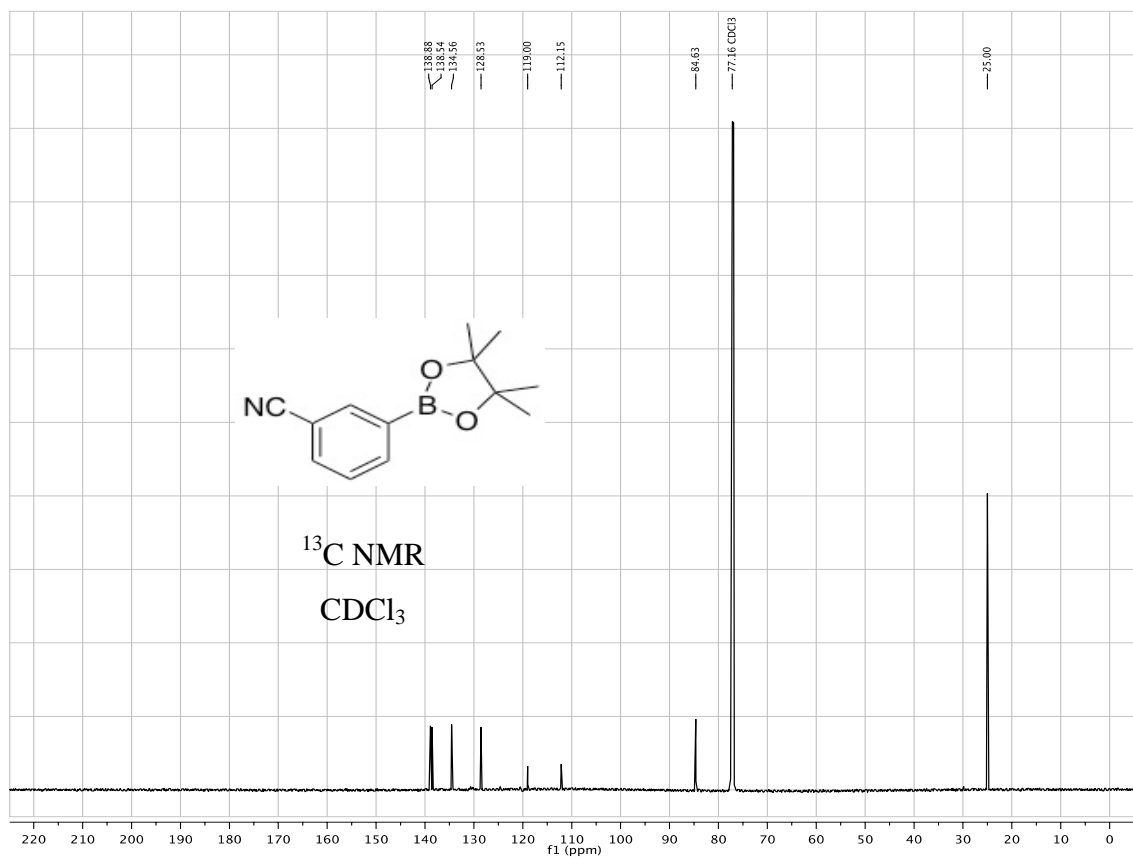
2-(2-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3k**):



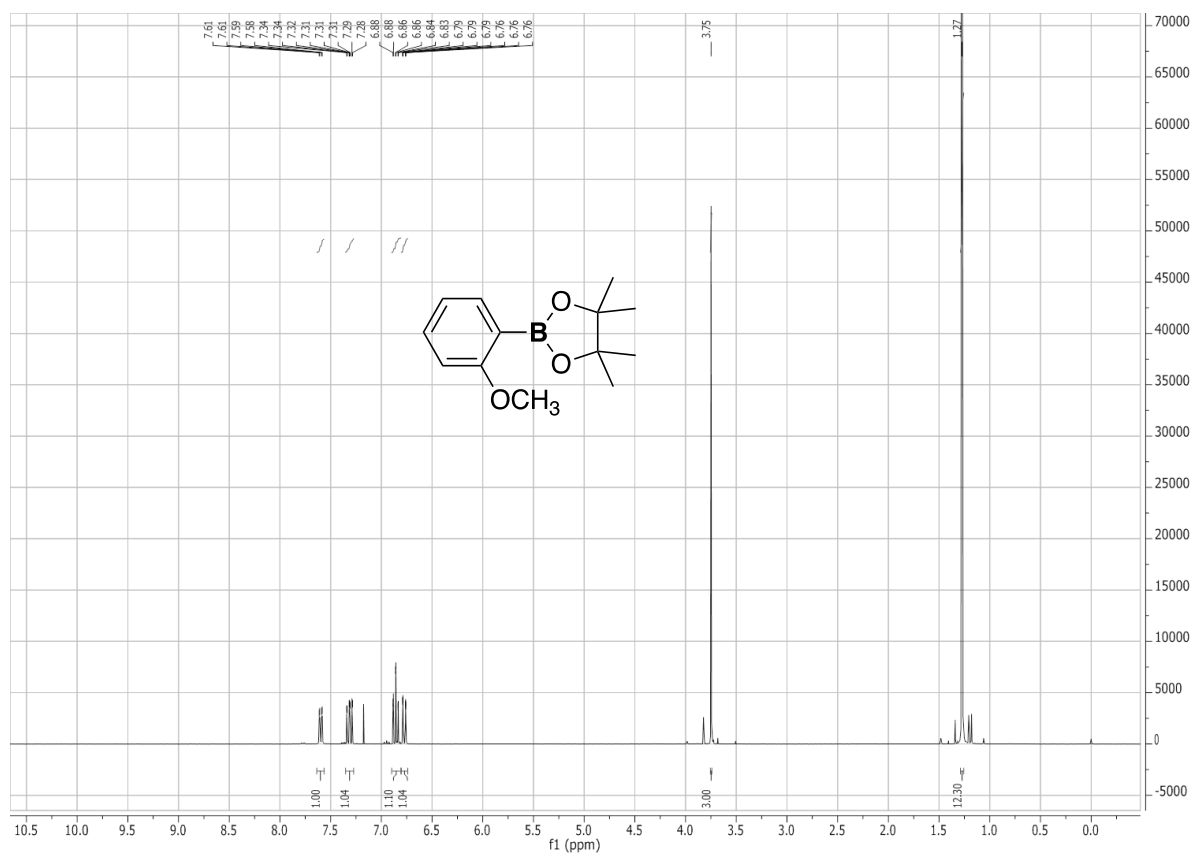


3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl nitrile (**3l**):

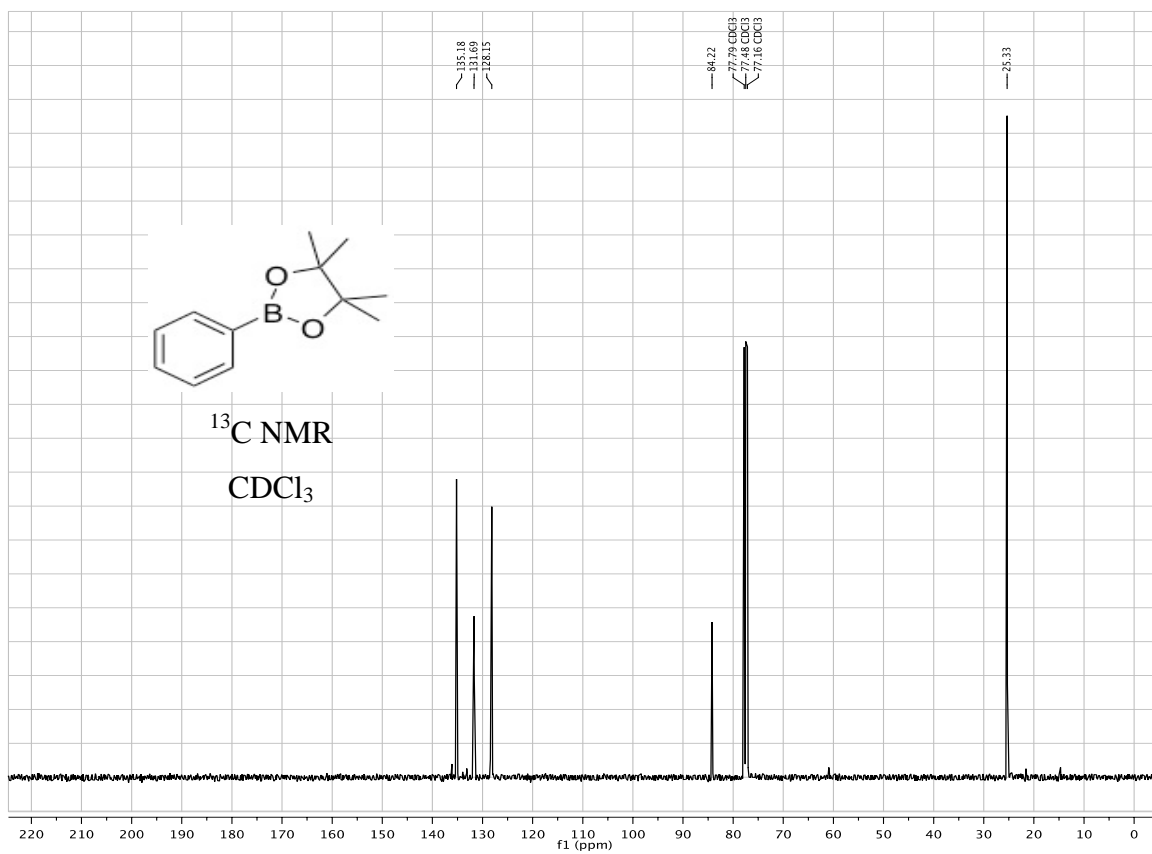
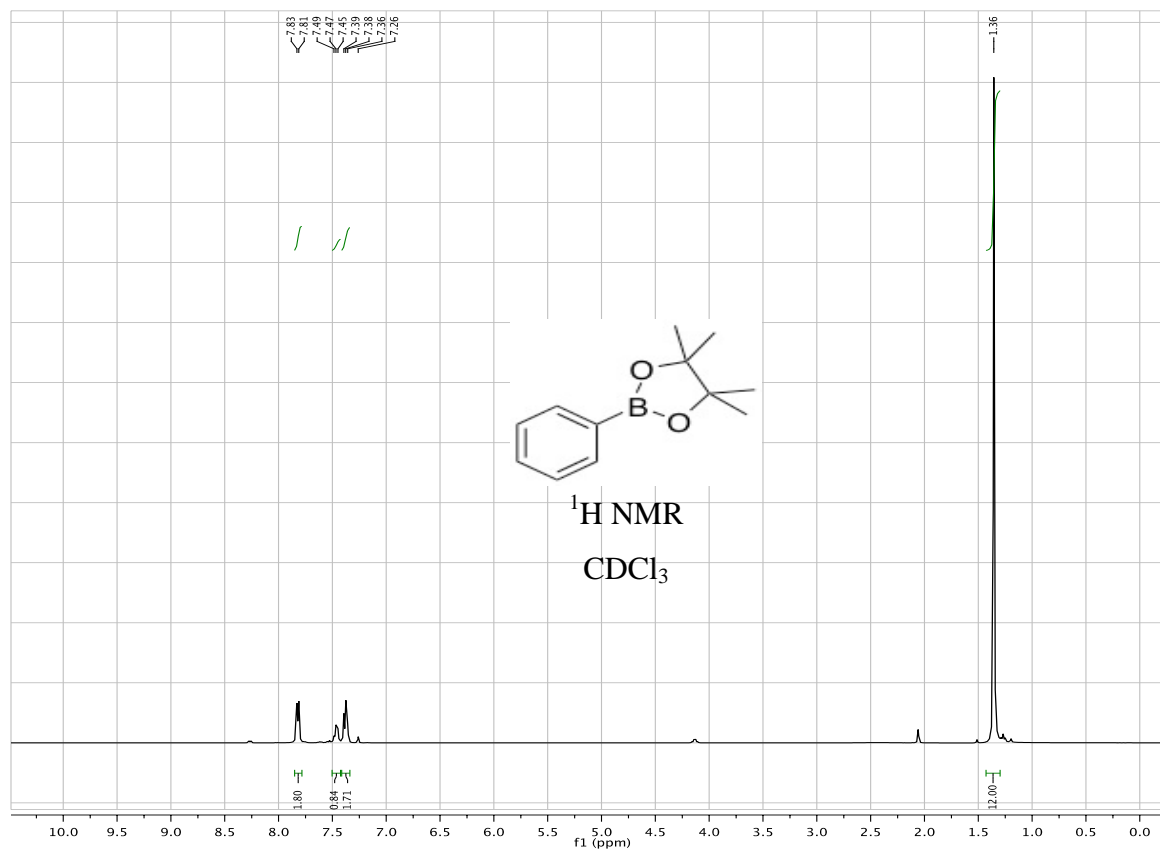




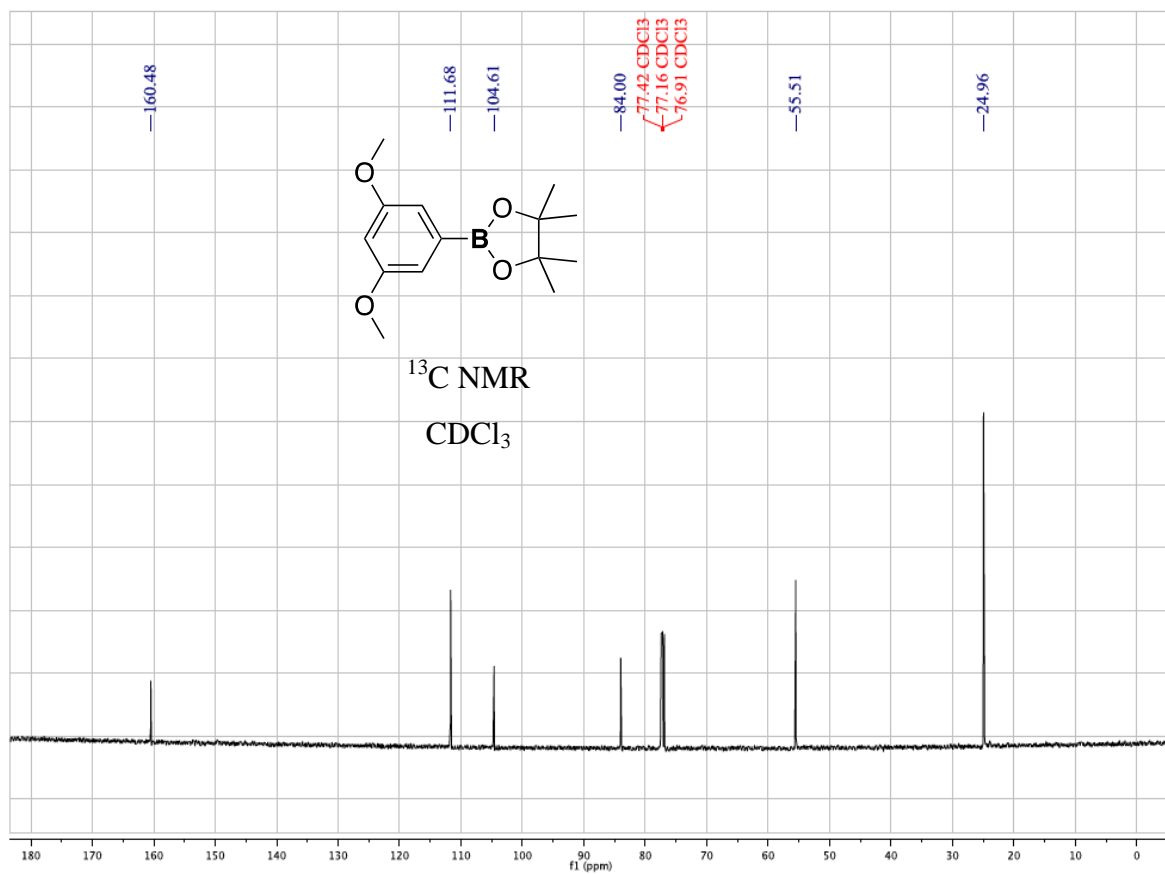
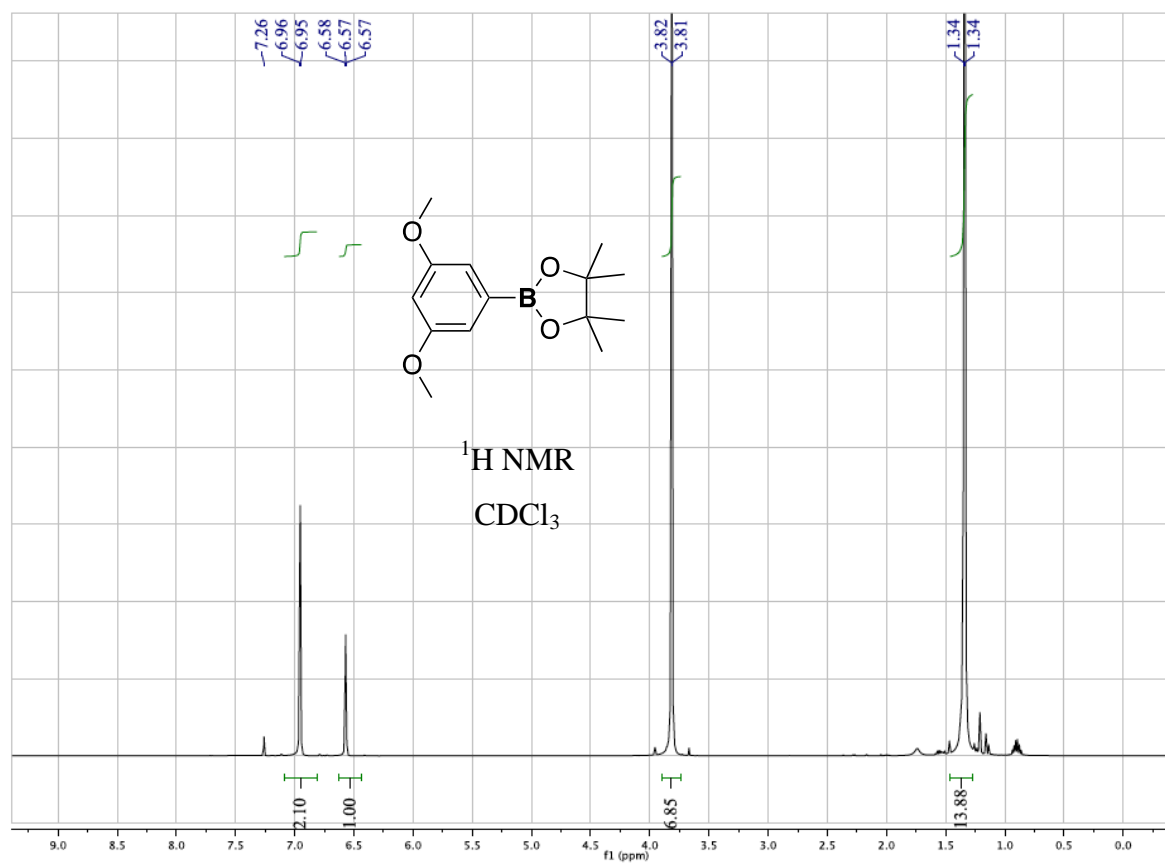
2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3m**)



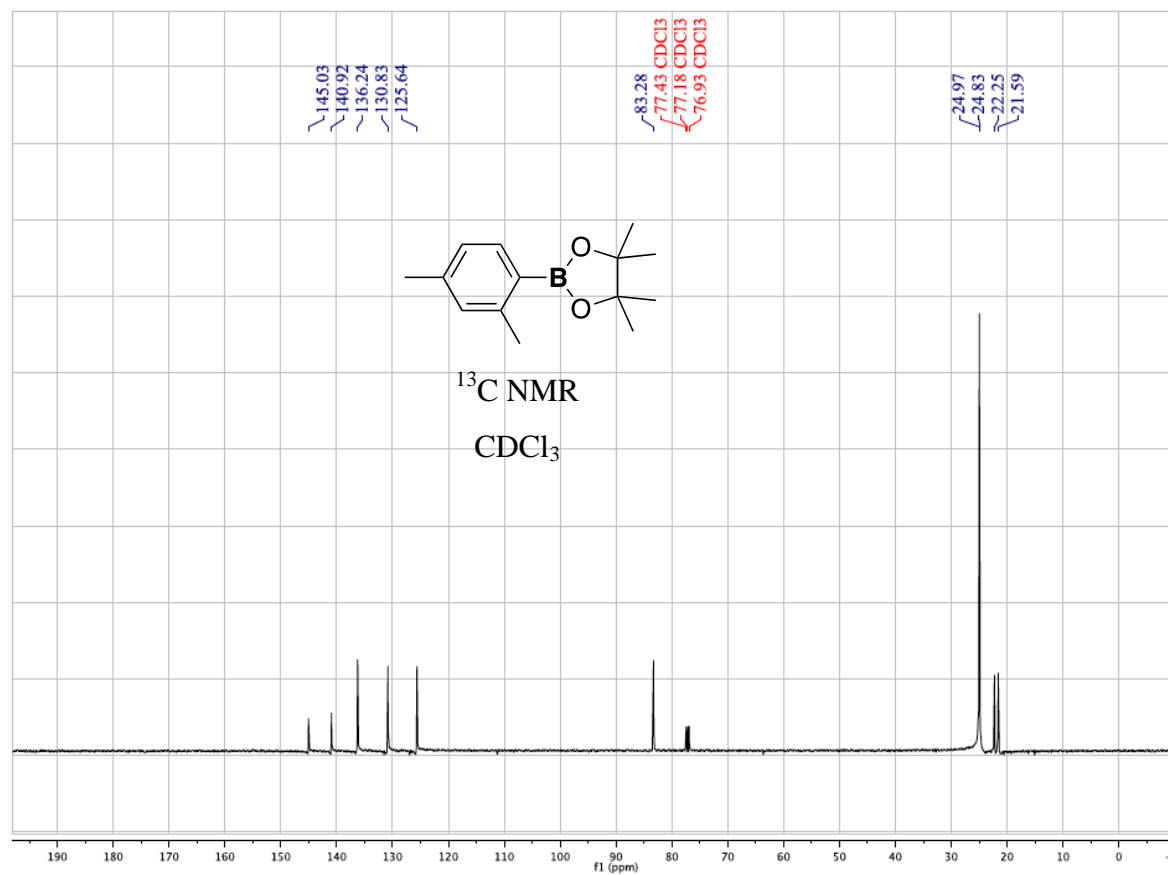
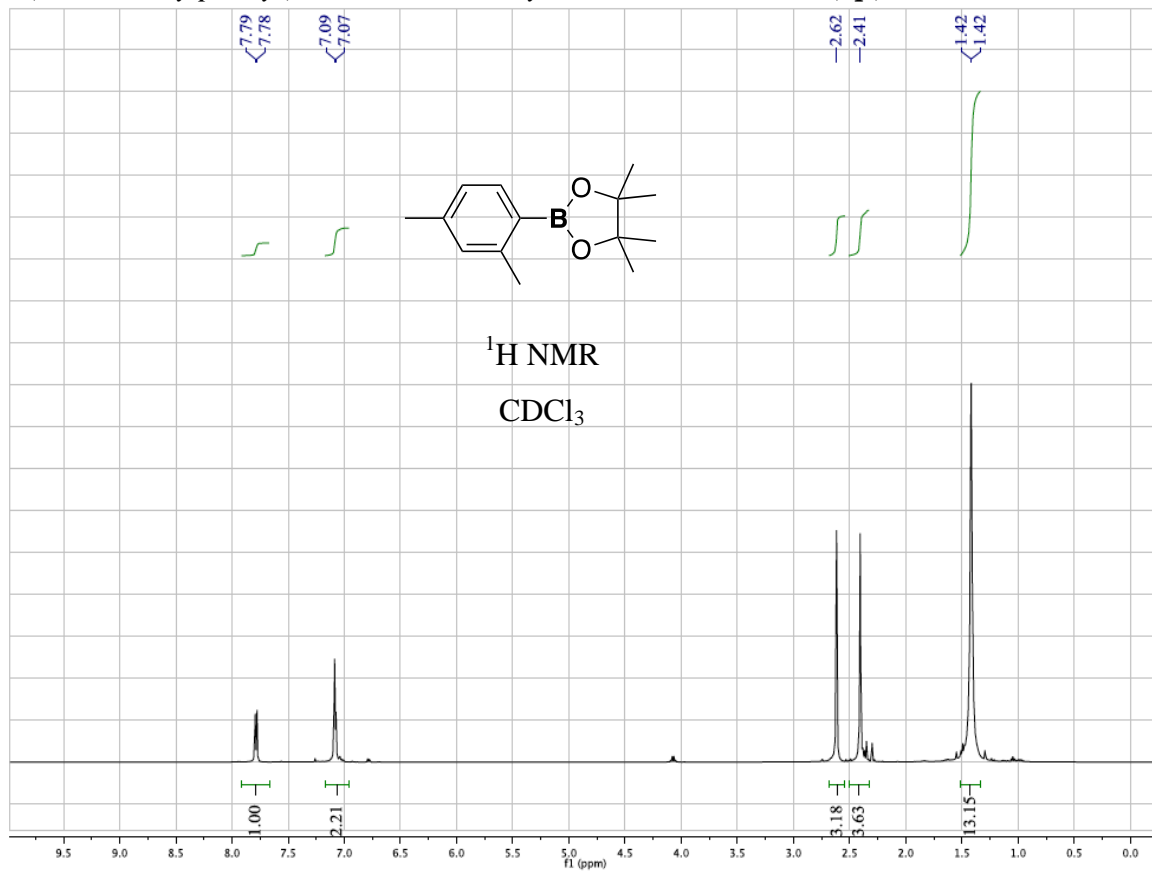
4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane (**3n**):



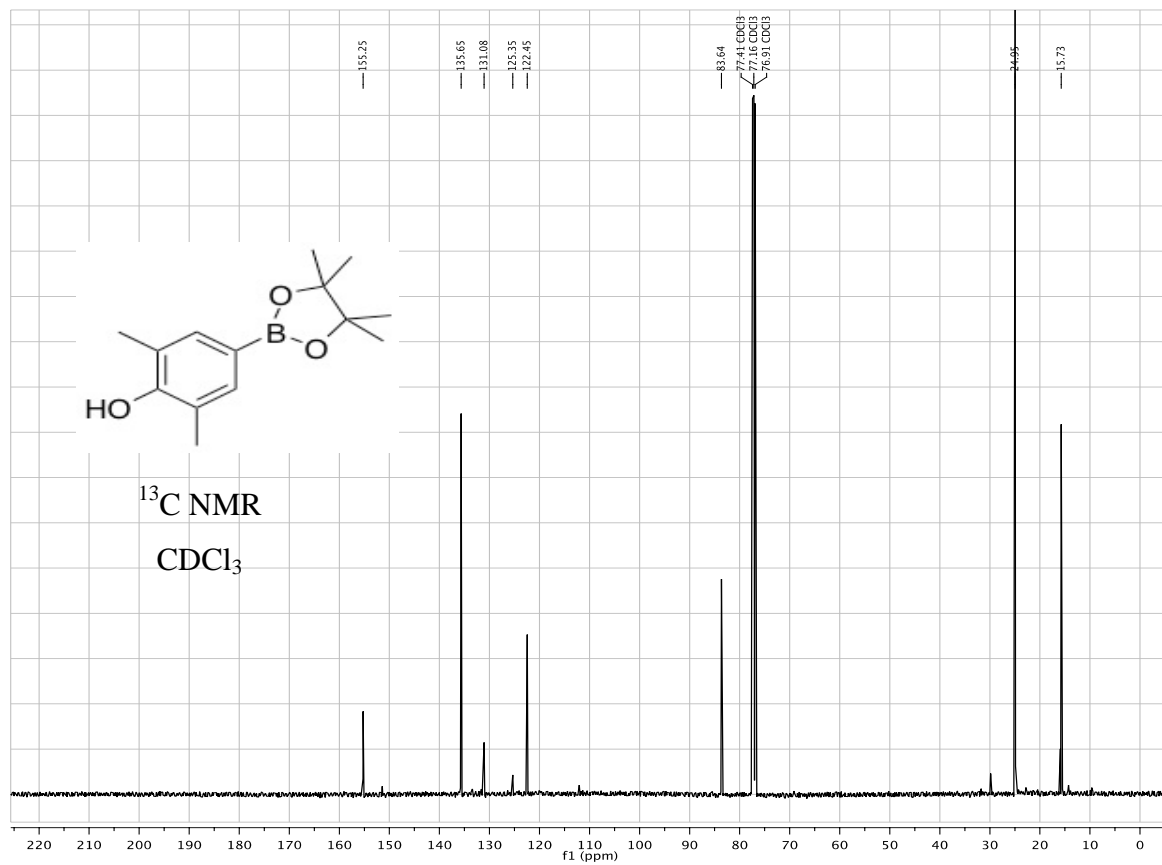
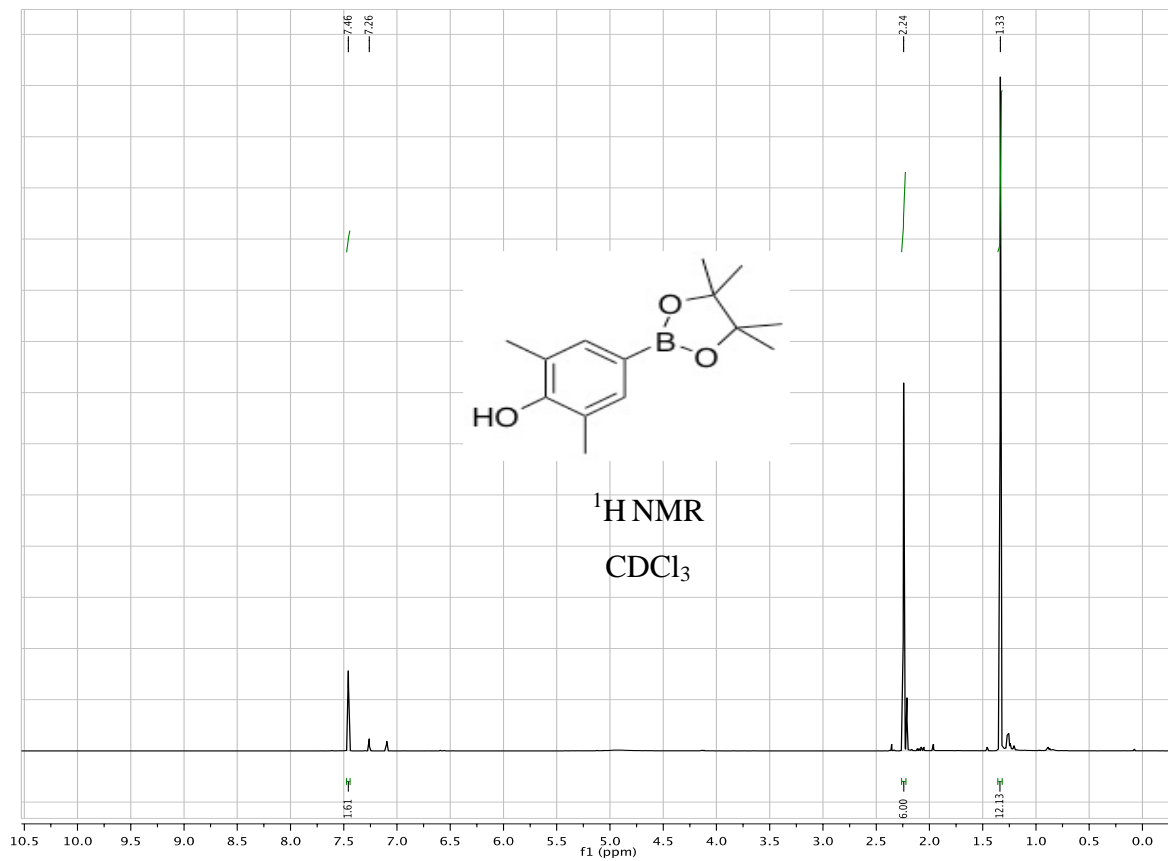
2-(3,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3o**):



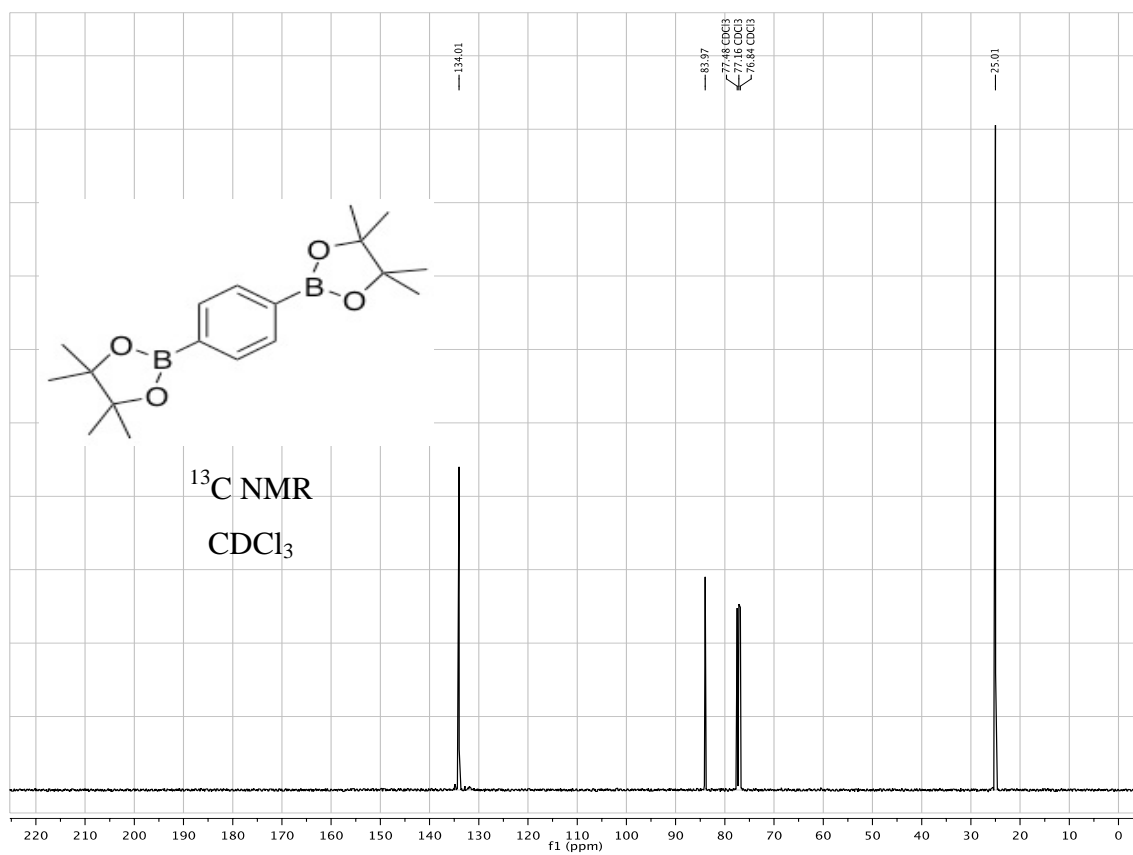
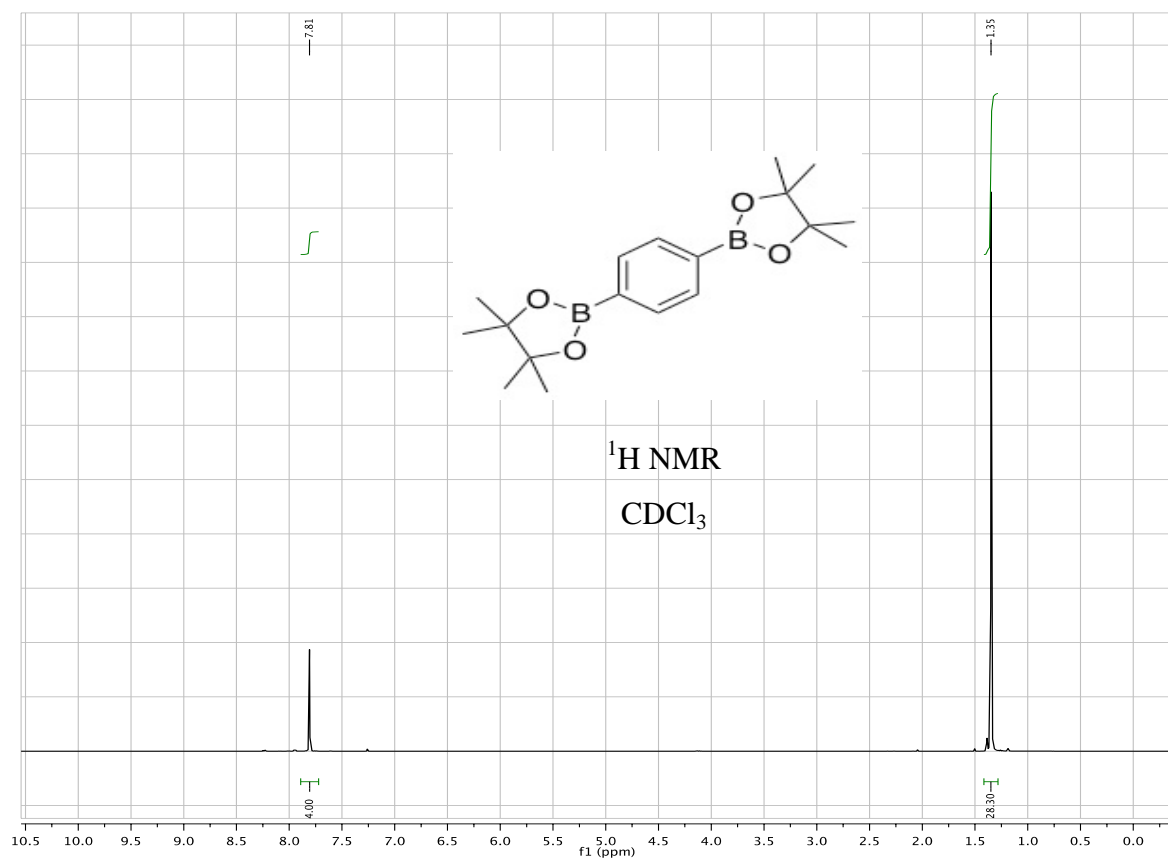
2-(2,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3p**)



2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3q**):



1,4-bis(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3r**)



1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3s**)

