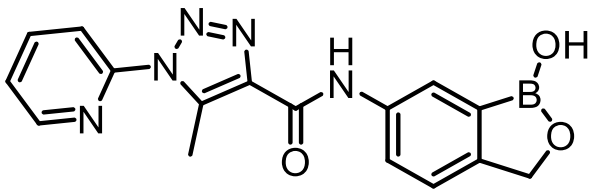
Medicines for All Institute

Summary of Synthetic Route Scouting Work on the Regulatory Starting Material of DNDI-6148



Contact:

Medicines for All (M4ALL) Institute

Virginia Commonwealth University

Richmond, VA 23219

M4ALL@vcu.edu

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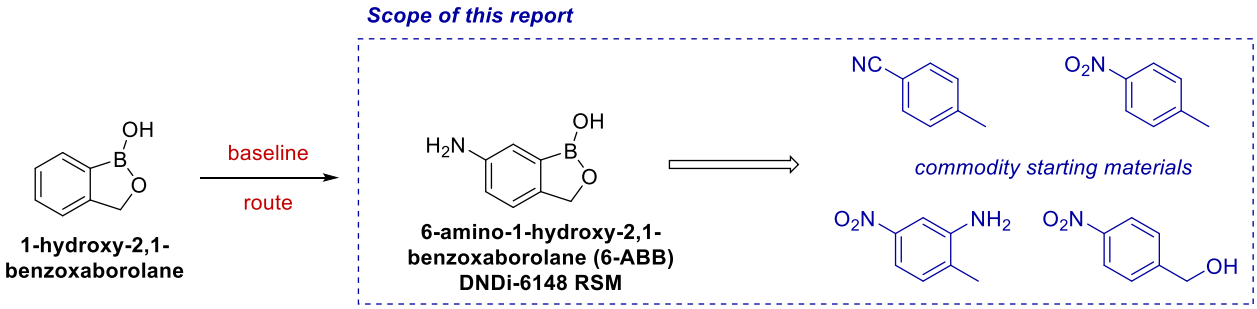
Executive Summary

This report describes the results of synthetic route scouting (SRS) efforts at the Medicines For All (M4ALL) Institute to discover new, low-cost synthetic strategies to make 6-amino-1-hydroxy-2,1-benzoxaborolane (6-ABB), which is a key intermediate and cost-driver in the synthesis of the Visceral Leishmaniasis (VL) drug candidate DNDI-6148.[1–3] The current baseline route for synthesis of 6-ABB involves a nitration of 1-hydroxy-2,1-benzoxaborolane and subsequent nitro-reduction, which results in the cost of 6-ABB being unnecessarily high due to cost of 1-hydroxy-2,1-benzoxaborolane as a starting material and the use of palladium. Safety concerns are also present as risks are introduced during the nitration and hydrogenation steps.[4] Herein, we report the development of several commodity-centric synthetic approaches to make 6-ABB which may offer alternative low-cost processes to make this regulatory starting material (RSM) of DNDI-6148. Of these routes that we explored, one promising route afforded 6-ABB in 5 steps from 4-methylbenzonitrile in a 40% overall yield (Key idea I) and the other route afforded 6-ABB in 4 steps with an overall yield of up to 45% from 2-methyl-5-nitroaniline (Key idea II). Techno-economic (TE) cost analysis suggests that, compared to the known baseline route starting from 1-hydroxy-2,1-benzoxaborolane, the overall raw material cost (RMC) of the API for Key idea I could offer a reduction of up to 80%, and for Key idea II, the RMC could be reduced by up to 90%.



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Medicines for All – Contributors to the Research and Report

Contributor	Title / Role
Dr. Charles S. Shanahan	Director of Research
Dr. Limei Jin	Sr. Research Scientist (Project Lead)
Dr. John Saathoff	Research Scientist
Dr. Pankaj Khairnar	Postdoctoral Researcher
Dr. Daniel W. Cook	Senior Analytical chemist
Sam Hochstetler	Analytical chemist

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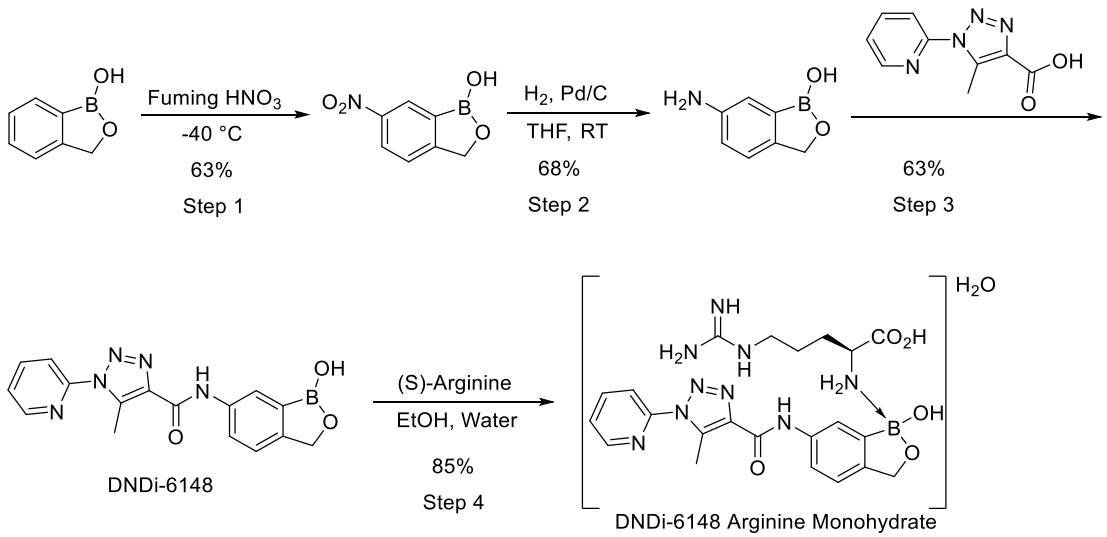
Project Background

DNDI-6148, with a core structure of 1-hydroxy-2,1-benzoxaborolane, is currently in clinical trial phase IIb. This drug candidate showed effective initial results in Visceral Leishmaniasis (VL) treatment both in various *in vitro* and *in vivo* studies, as well as an improved activity and toxicity profiles compared to many of the current VL treatments.[1–3] The current route (Scheme **0**) for synthesis of DNDI-6148 is a 4-step sequence with a 21 % overall yield.[4] The synthetic strategy breaks the molecule into two halves: a carboxylic acid functionalized triazole and 6-ABB. The triazole was synthesized in a one-pot reaction between tetrazolo[1,5-a]pyridine and ethyl acetoacetate under basic conditions, which set the triazole ring, and a subsequent hydrolysis of the intermediate ethyl ester generated the desired carboxylic acid. The 6-ABB was prepared in two steps from 1-hydroxy-2,1-benzoxaborolane. After nitration of the aromatic ring under cold conditions, the nitro group was reduced to an amine with H_2 and catalytic Pd/C. An amide bond formation, facilitated by the carbodiimide EDCI and HOBt, coupled these two halves into DNDI-6148 free acid, and in the final step, a dative complex was formed between DNDI-6148 and arginine, which was isolated as a crystalline monohydrate. This synthetic route provided a concise and convergent way to make DNDI-6148, however, it provides room for improvements, including replacement of expensive raw materials and bypassing dangerous nitration processes. Particularly, our TE analysis indicates that 1-hydroxy-2,1-benzoxaborolane in this baseline route is the main cost driver (raw material cost (RMC) contribution was > 60%)[1] and also not readily available. Furthermore, utilizing H_2 gas and Pd/C in the nitro group reduction increases cost and safety concerns for this transformation. Thereby the dangerous and toxic reagents in the synthesis as well as the accessibility of the starting material might greatly impede the supply of regulatory starting material for the large-scale manufacturing of DNDI-6148.

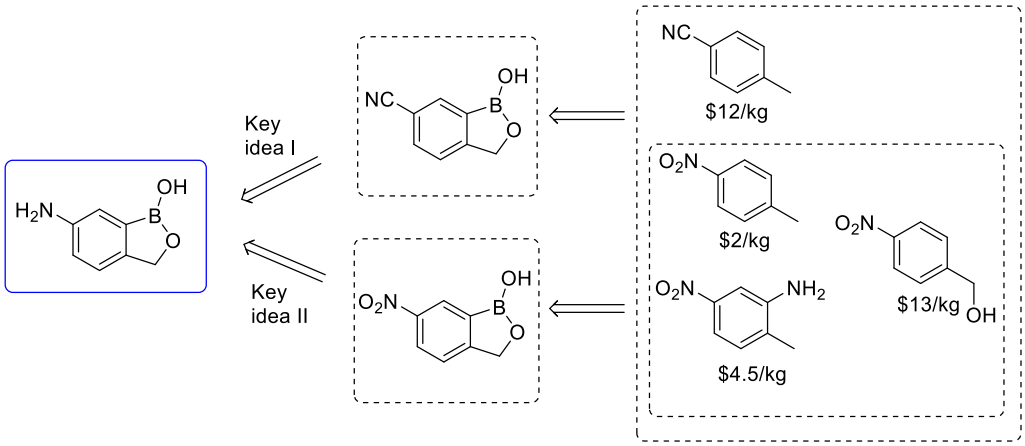
[1] Raw material prices were obtained from direct vendor quotes, available catalog prices, and/or bills of lading from import/export databases such as Zauba and Datamyne.

Scheme 0. Current 6-ABB synthesis and the baseline route to DNDI-6148



To address the supply issues and hazardous chemistry in the baseline chemistry, M4ALL has explored two main Key ideas, including 6 different routes from low-cost readily available commodities (Fig 1).

Fig 1. Two key ideas for synthesis of 6-ABB from readily commodities.

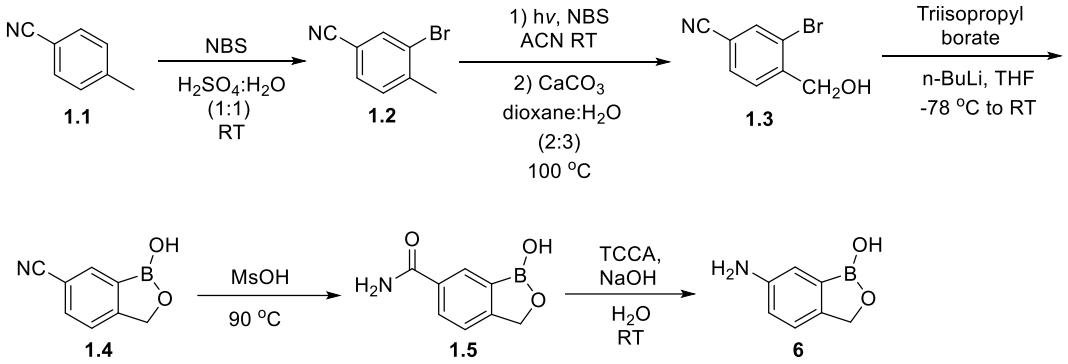


Two distinct routes were emerged the most promising to bypass the expensive starting material, 1-hydroxy-2,1-benzoxaborolane, used in the baseline, as well as hazardous nitration and/or reduction process. Particularly, the route from 2-methyl-5-nitroaniline provides a scalable method for the synthesis of 6-ABB, which might have the potential to become a candidate for further scale-up development.

Results and Discussion

1. Synthesis of 6-ABB from *p*-tolunitrile[2]

Scheme 1.



In efforts to make 6-ABB from a nitrile-containing commodity, a synthetic route was developed as shown in Scheme 2. Most transformations were precedented when we began route development, but the final Hofmann transformation was unprecedented and is key to the success of the route. In order to quickly obtain the key precursor **1.5** for investigating the Hofmann rearrangement, we planned to utilize the commercially available **1.4**. Unfortunately, the reported yield of this amide formation was exceptionally low. Moreover, the high market cost - presumably due to low production volume - of compound **1.4** impeded our plan. Therefore, we developed an efficient three-step protocol to prepare the key intermediate **1.4** and then utilized it for the synthesis of 6-ABB via **1.5** (Scheme 2).

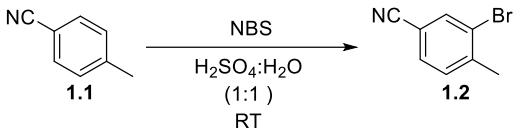
1.1 Electrophilic bromination

The bromination of *p*-tolunitrile (**1.1**) with NBS has been previously reported on a multi-gram scale to afford 3-bromo-4-methylbenzonitrile (**1.2**) in 90 % yield.[5] In our hands, this heterogenous reaction progressed smoothly on a small scale (1 g and 5g) to give **1.2** in high yield

[2] This route was the Key Idea 2F in our previous Tech-review report.

(up to 96 %) with up to 95 % *q*NMR purity after a simple aqueous workup (**Table 1.1**). The batch of 50 g scale reaction gave **1.2** in excellent yield (> 84 %) with *q*NMR purity up to 93 %.

Table 1.1: Bromination of **1.1** with NBS.

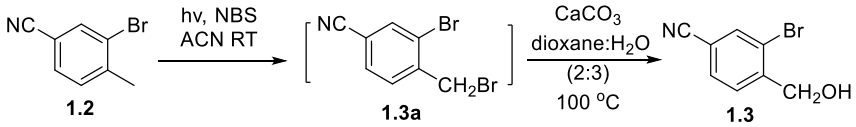


Entry	Scale	Yield	Purity (qNMR)	Major impurities[a]
1	1 g	96 %	94 %	**1.3a** (~ 5 %)
2	5 g	93 %	99 %	**1.3a** (< 1 %)
3	50 g	84 %	93 %	**1.3a** (~ 6 %)

[a] *The main impurity was 3-bromo-4-(bromomethyl)benzonitrile (**1.3a**) confirmed by GC/MS and NMR analysis, which was an intermediate in Step 2*

1.2 Hydrolysis

Scheme 1.1.



A second radical bromination followed by hydrolysis that gives **1.3** in high yield has already been reported.[6] However, the second bromination requires a free-radical initiator (i.e., azobisisobutyronitrile (AIBN)). We found that incandescent light could promote this bromination without the need of radical initiator. Initially, a small scale (0.1 g) reaction was conducted on **1.2** with NBS (1.5 eq) and acetonitrile (CH_3CN) in the presence of an incandescent light (60 W) for 12 h. GC/MS analysis indicated the formation of 61 % of 3-bromo-4-(bromomethyl)benzonitrile (**1.3a**) (Scheme 1.1). This led to a scale-up (1 g) reaction under the same condition that gave the desired material a good yield (77 %) with >95 % purity (*q*NMR) after column purification.

Upon purification, **1.3a** was hydrolyzed in 1,4-dioxane:H_2O (2:3) mixture in the presence of calcium carbonate ($CaCO_3$) at 100 °C. For instance, 1.1 g of **1.3a** was heated (100 °C) with

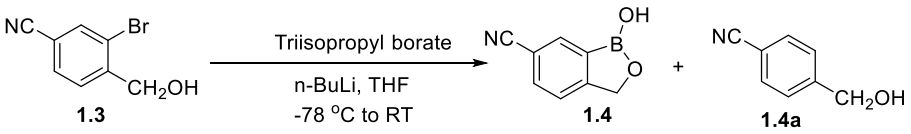
$CaCO_3$ in 1,4-dioxane:H_2O (2:3) mixture for 16 h, and after evaporation of solvents the resulting crude reaction mixture was recrystallized with CH_2Cl_2/MeOH (80:10, v/v) to afford 0.5 g (yield: 60 %) of **1.3** as a white powder with >95 % purity (*q*NMR). A final study showed that 10 g of **1.2** could be brominated and then subsequently hydrolyzed under the previous conditions in a telescoped fashion to give **1.3** in 83 % overall yield with 94 % purity (wt % HPLC).

1.3 Lithium-halogen exchange borylation

A lithium-halogen exchange reaction with 3-bromo-4-(hydroxymethyl)benzonitrile (**1.3**), triisopropyl borate, and *n*-BuLi at -78 °C has previously been reported to form the 6-cyano-1-hydroxy-2,1-benzoxaborolane (**1.4**) in moderate yield (69 %).[6] We sought to increase the overall yield and simplify the work-up protocol to ensure better scalability.

First, to validate the reported chemistry, a trial reaction (0.5 g of **1.3**) was run, which afforded the desired product in 64 % yield. While this yield is comparable, one major improvement we sought was the use of trituration for purification instead of column chromatography. Thus, we scaled-up reactions with triisopropyl borate to 10 g leveraging our improved purification protocol to provide **1.4** in up to 95 % yield and up to 96 % purity (**Table 1.2**). Unfortunately, while triisopropyl borate is reactive under these conditions, it's worth noting that the cheaper trimethyl borate does not work.

Table 1.2: Yield and purity for the borylation of **1.3** with *n*-BuLi.

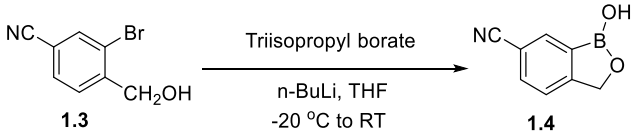


Entry	Scale	Yield	Purity (qNMR)	Major impurities
1	2 g	95 %	96 %	**1.4a** (~ 3 %)
2	5 g	86 %	86 %	**1.4a** (> 10 %)
3	10 g	91 %	95 %	**1.4a** (~ 4 %)

While these results are promising, the use of -78 °C temperatures in large-scale batch reactors is challenging. To overcome this problem, three paths were evaluated; 1) utilizing

Grignard reagents,[7,8] 2) increasing reaction temperature, and 3) employing flow chemistry.[9] We first tried the reaction of *i*PrMgCl with **1.3** followed by triisopropyl borate at -20 °C. Unfortunately, no product was formed, and only unreacted **1.3** remained. While it would be worthwhile to screen more Grignard reagents (i.e., Turbo Grignard or PhMgBr), this was not addressed, thus this route was abandoned, and our attention turned to other avenues. Then we revisited the reaction of n-BuLi at elevated temperatures (i.e., -20 °C, -40 °C). Unfortunately, the reaction became slow and often messy due to competitive side-reactions (i.e., nucleophilic addition and proton transfer) (Table 1.3).

Table 1.3: Comparison of stirring time at -20 °C for the cyclization of **1.3** with *n*-BuLi.



Entry	Scale	Stirring time at -20 °C	A%[b] 1.3	A%[b] 1.4
1	0.42 g	0 h	48 %	17 %
2	0.5 g	1 h	36 %	36 %
3	0.25 g	8 h	32 %	36 %
4[a]	0.25 g	--	57 %	9 %

[a]Reaction was done in flow. [b]HPLC area percentage at 210 nm, with unknown impurities.

We were also intrigued by the possibility of avoiding cryogenic cooling in this reaction, and decided to test this reaction under flow conditions (Vapourtec E series) at -20 °C. Unfortunately, these conditions did not prove effective at increasing the amount of **1.4** and resulted in less pure reaction profiles. But it should be noted that the flow condition was not optimized due to the limited time of the project.

1.4 Amide formation from hydrolysis of cyano group

Due to the intrinsic challenge of transforming a cyano group to a corresponding amide, an efficient conversion of 6-cyano-1-hydroxy-2,1-benzoxaborolane (**1.4**) to 6-amido-1-hydroxy-2,1-benzoxaborolane (**1.5**) was key to the success of this route. Fortuitously, this conversion is already

reported with concentrated H_2SO_4 at 90 °C for 1 h, albeit in extremely low yield (15 %).[10] Interestingly, our first two trial reactions run on small-scale (0.25 g) gave **1.5** as a white solid in moderate yields of 48 % and 53 % with excellent purity (>95%,by qNMR) after preparative reverse phase chromatography. Purification by preparative chromatography limits the scale of reaction, but no significant effort was made during this project to investigate chromatography-free isolation conditions. This would certainly be the subject of further optimization if this route is chosen for scale-up investigations. Dangerous workup conditions related to the concentrated H_2SO_4 (diluting and neutralizing the reaction mixture) was another drawback for this transformation. Attempts to extract into a suitable organic solvent (i.e., EtOAc, DCM, and/or 2-MeTHF) provided poor yields. As these conditions are not amenable to scale-up, new conditions are needed to be explored.

Then effort was focused on the basic conditions, including sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH)[11], and potassium *tert*-butoxide (KO*t*Bu).[12] Among these screened bases, KOH gave very promising results (**Table 1.4**). KOH (30 eq) afforded 62 % (by LC/MS analysis) of **1.5**. Therefore, we chose to further optimize these conditions, first by varying the equivalents of KOH. Decreasing the equivalents by half (from 30 eq to 15 eq) showed no effect on the conversion of **1.4** to **1.5**, with the percentage of **1.5** staying the same. In contrast, when the equivalents of KOH were decreased further (i.e., 5-10 eq), the conversion was significantly lower. Furthermore, it was found that a critical time point (**Figure 1**) between 6-16 hours was identified to minimize the over-hydrolyzed acid formation. Next, we looked at reducing the temperature, with hopes of stopping the hydrolysis of **1.5** to the acid impurity. Unfortunately, reduction in temperature only seemed to reduce the conversion of **1.4** to **1.5**. We believed that 15 eq KOH at 90 °C for 16 hours were the best conditions to give us the greatest possible outcome for this reaction. Unfortunately, the purification was problematic. The further hydrolysis of the product to generate acid impurity was inevitable during the workup. Therefore, basic hydrolysis of **1.4** to **1.5** was discontinued.

Figure 1: Formation of acid impurity with respect to time (by HPLC).

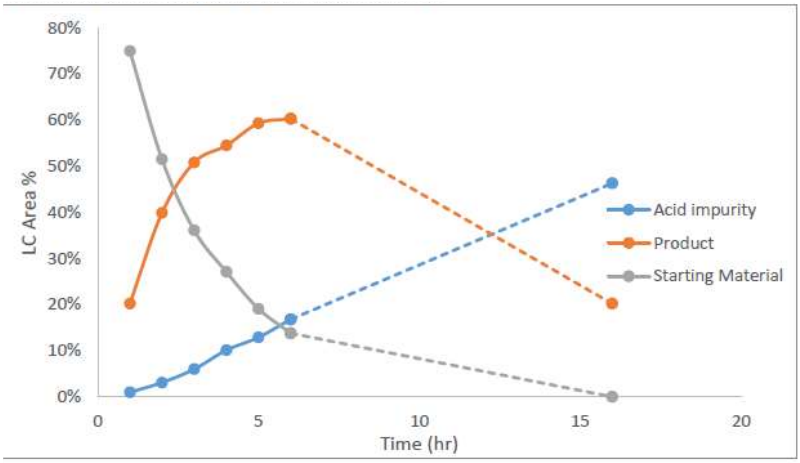


Table 1.4: Synthesis of amide **1.5** by hydrolysis of nitrile **1.4**.

1.4 **1.5**

Entry	Conditions	Isolated yield of 1.5
1 (**1.4**: 1 g)	NaOH, iPrOH, 90 °C, 16h	~18 A%[a]
2 (**1.4**: 1 g)	LiOH, iPrOH, 90 °C, 16h	NR
3 (**1.4**: 1 g)	KOH, iPrOH, 90 °C, 16h	~60 A%[a] (failed to isolate)
4 (**1.4**: 1 g)	H_2SO_4, 90 °C, 1h	49%
5 (**1.4**: 10 g)	H_2SO_4, 90 °C, 1h	53%
6 (**1.4**: 1 g)	MsOH, 90 °C, 16h	72%
7 (**1.4**: 10 g)	MsOH, 90 °C, 16h	78%
8 (**1.4**: 1 g)	TFA, 90 °C, 16h	31%
9 (**1.4**: 1 g)	TfOH, 90 °C, 16h	5 A%[ab]
10 (**1.4**: 1 g)	H_2SO_4, 90 °C, 16h	0[b]
11 (**1.4**: 1 g)	HCl, 90 °C, 16h	12 A%[ac]
11 (**1.4**: 1 g)	$NaHSO_4$, 90 °C, 16h	NR
11 (**1.4**: 1 g)	$NaHSO_3$, 90 °C, 16h	NR

[a]HPLC area percentage at 210 nm. [b]SM was consumed. Decomposition occurred. [c]76 A% carboxylic acid was formed.

Then the acidic hydrolysis was revisited. A variety of acids were screened, including hydrochloric acid (HCl), trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), methanesulfonic acid (MsOH), sodium hydrogen sulfate ($NaHSO_4$), and sodium bisulfite ($NaHSO_3$) (**Table 1.4)**. It's clear to see that MsOH outperformed in this transformation with good yield of amide and minimal amount of acid impurity. Since MsOH showed great promise in the nitrile conversion two scaled reaction were conducted: 1 g and 6.65 g. Both reactions showed high formation of **1.5** (>75 A%), the most impressive aspect is that no acid impurity was formed. After purification, these reactions gave similar yields, 72 % and 74 %, thus showing that this reaction gave good replicable results. While these acidic conditions are promising, direct removal of the acid by distillation is challenging due to its high boiling point. Neutralization with NaOHaq is still needed during the workup. Attempt to using a TFA- or AcOH-MsOH co-reagent system for the transformation, regrettably, led to only 13 A% (210 nm) of **1.5** and 71 A% (210 nm) of unreacted starting material.

In addition to strong acids and bases, enzymes are also used to convert a variety of nitriles to amides.[13] Since, we were gifted a nitrile hydratase enzyme we tried the nitrile conversion under enzymatic conditions (Prozomix Limited company, Northumberland, UK). However, no desired product was observed, but it should be noted that these conditions were only tried twice without optimization because the acidic and basic conditions gave the **1.5**.

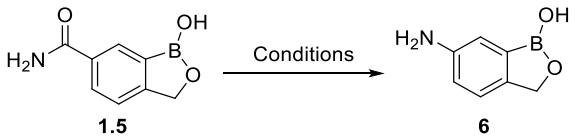
Finally, it's a reasonable assumption to make, that the 6-cyano-1-hydroxy-2,1-benzoxaborolane (**1.4**) could be telescoped directly into the Hofmann rearrangement from the nitrile hydration step, thus removing the need for purification by preparative chromatography. Therefore, crude **1.5** (38 A%) was used in the Hofmann reaction with trichloroisocyanuric acid (TCCA). However, this reaction yielded no product, and it is most likely due to the salts which formed during the acid-base workup of the hydrolysis reaction, interfering with the Hofmann reaction.

1.5 Hofmann rearrangement

The Hofmann rearrangement involves the conversion of a primary amide to a primary amine, via an isocyanate intermediate. Several novel reagents have been developed for this transformation and can be categorized into two groups: halogen reagents and hypervalent iodine species.[14] Halogen reagents were the first activating species to be employed in the Hofmann reaction, and are oxidants (i.e., sodium hypochlorite,[15,16] bromine, lead tetraacetate,[17,18] and trichloroisocyanuric acid[19]). Thus, this final Hofmann rearrangement is extremely challenging and it is essentially our primary focus for this route.

Generally, the amide is first reacted with the oxidizing agent to afford an *N*-halogenated amide, which contains an electron-deficient nitrogen atom, that can be deprotonated with different bases leading to a formal α-elimination and a nitrene as a formal intermediate. Next, rearrangement is accomplished after heating to generate an isocyanate that commonly undergoes solvolysis in protic solvents to afford the free amine.[14] This process is usually done with sodium hypochlorite (NaOCl) or bromine (Br_2) as the oxidizing agent in the presence of a base (i.e., NaOH), due to their inexpensive nature and ease of use. When 6-amido-1-hydroxy-2,1-benzoxaborolane (**1.5**) was reacted with NaOCl or Br_2 (**Table 1.5**) under standard conditions (i.e., 0-100 °C for 16 hours) the LC/MS data was inconclusive, showing no starting material, isocyanate intermediate, or 6-ABB (**6**). A closer look at the reaction with **1.5** in the presence of Br_2 and NaOH at lower temperatures and short time points showed that the desired product **6** was slowly being created, albeit in minimal amounts. Therefore, we believe that NaOCl and Br_2 were incapable of transforming **1.5** to **6**, and alternative reagents needed to be employed.

Table 1.5: Study on condition for the Hofmann Rearrangement of **1.5** to **6**[a].



1.5 **6**

Entry	Conditions	A% (yield)[b] of **6**
1 (**1.5**: 50 mg)	NaOH, NaOCl, 100 °C, 16h	ND

2 (**1.5**: 50 mg)	NaOH, Br_2, 75 °C, 2h	16 (--[c])
3 (**1.5**: 50 mg)	NaOH, Br_2, 75 °C, 12h	8 (--[c])
4 (**1.5**: 50 mg)	NaOH, TCCA, 75 °C, 12h	55 (--[c])
5 (**1.5:** 50 mg)	NaOH, TCCA, 55 °C, 12h	57 (--[c])
6 (**1.5**: 50 mg)	NaOH, TCCA, 25 °C, 12h	60 (--[c])
7 (**1.5:** 100 mg)	NaOH, TCCA, 25 °C, 12h	78 (58)
8 (**1.5**: 2 g)	NaOH, TCCA, 25 °C, 12h	96 (81)

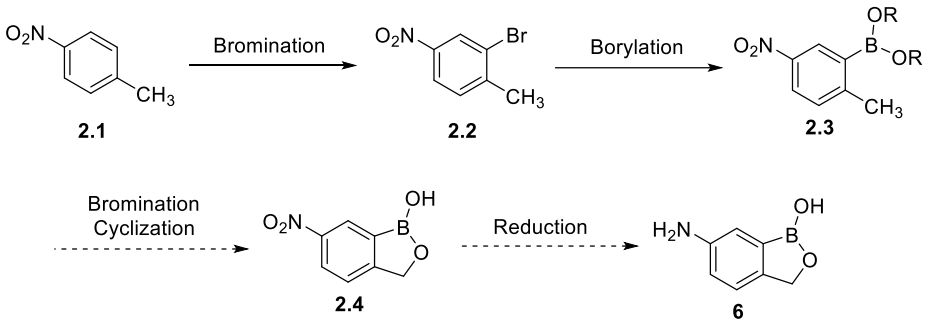
[a]All reactions were performed with **5** (50 mg, 1 eq), oxidant (1 eq), temperature, and reaction time as shown in the table unless otherwise stated; for TCCA, 0.35 eq was used. [b]Area percentage (210 nm) unless otherwise stated and isolated yield in parenthesis. [c]No isolation.

Fortunately, when **1.5** reacted with TCCA and NaOH at various temperatures and time points affording **6** in a decent amount (>55 A%, 210 nm), however as the temperature was increased the product decreased over time with the highest amount of **6** being seen at 25 °C (**Table 1.5**). Thus, **1.5** was reacted at 25 °C for 12 hours with TCCA and NaOH without heating, to yield 59 A% of **6**. A 100 mg reaction was run to determine yield, which gave **6** in 78 % isolated yield with 75 % purity (corrected yield = 58 %). Finally, a 2 g reaction was conducted giving **6** in 83.8 % isolated yield with 96.3 wt% a purity by HPLC (main impurities were residual solvents, i.e., water). This corresponds to a corrected yield of 81 %.

Overall, this 5-step sequence from 4-methylbenzonitrile affords 6-ABB **6** with an overall yield of ~40%. Further optimizations, e.g., to get rid of the preparative chromatography and cold reaction condition, are needed for scale-up.

2. Synthesis of 6-ABB from *p*-nitrotoluene[3]

Scheme 2.



In order to obtain a more efficient and effective route for synthesis of the 6-ABB, we then focused on utilizing nitroaromatic commodity as the starting material. At the outset, we first investigated a route based on *para*-nitrotoluene **2.1**. As shown in Scheme 2, this route includes electrophilic bromination, borylation, radical bromination/hydrolysis/cyclization and nitro-reduction.

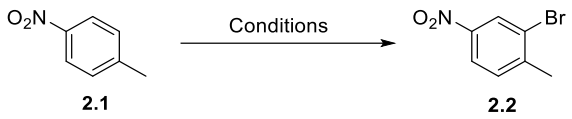
2.1 Electrophilic bromination of *p*-nitrotoluene

Similar to *p*-tolunitrile, the electrophilic bromination of *p*-nitrotoluene **2.1** also went smoothly, affording the bromide **2.2** in an excellent yield. Both Br_2 and the easier to handle NBS worked well for the bromination[20,21]. We validated both conditions on 10g scale. With NBS, the bromination occurred at room temperature with H_2SO_4/H_2O as the solvent. The isolation was straightforward, and simple trituration afforded the product up to 93% yield with 99% purity (by qNMR). The only drawback under this condition was that the reaction was slow and needed 24 h to reach a full conversion. While with Br_2, the reaction was fast and the melted *p*-nitrotoluene (70 °C) was stirred in the presence of catalytic amount of iron under neat condition to afford the product within 3h. The workup was also simple and the isolated yield was up to 92% with 97%

[3] It was the key idea 1A in our previous tech-review report.

purity by qNMR (**Table 2.1**). Considered the limitation of the Br_2 for scaleup, bromination with NBS was chosen for this transformation.

Table 2.1 Electrophilic bromination of **2.1**.



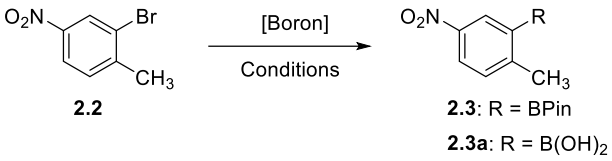
2.1 **2.2**

Entry	Scale	Conditions	Yield (qNMR purity)
1	10 g	NBS (1.0 eq), H_2SO_4/H_2O (1/1, v/v), rt, 24 h	93% (99%)
2	10 g	Br_2, Fe (cat.), neat, 75 °C, 3h	92% (97%)

2.2 Borylation

Traditional lithium-halogen exchange promoted borylation provides a cost-effective way for synthesis of boron-containing compound.[22] Initial borylation of compound **2.2** began with lithium-halogen exchange, followed by reacting with a borate. Unfortunately, the desired product was not detected. Replacement of organolithium with Grignard reagents also failed.[23] It is probably due to the incompatible of the nitro group with organometal reagents. The Pd-catalyzed borylation occurred well.[24] A variety of Pd-catalysts were screened for this borylation. $Pd(dppf)Cl_2$ was found to be the optimal catalyst. Treatment of bromide **8** with B_2Pin_2 produced the borylated product **9** in an excellent yield albeit with 5 mol% of $Pd(dppf)Cl_2$. It should be noted that 5 mol% of Pd-catalyst loading would hardly make the route cost-effective. Attempts to diminish the catalyst loading in this transformation resulted in a very low conversion. Switching the diboron resource to $B_2(OH)_4$ failed to give any better results (**Table 2.2**). Due to pricey borylation this route was abandoned in favor of a more cost effective deaminative borylation of arylamines (vide infra).[25,26,27]

Table 2.2 Borylation of **2.2**[a]



2.2

2.3: R = BPin

2.3a: R = $B(OH)_2$

Entry	[Boron]	Conditions	A%[c]
1[b]	$B(OMe)_3$	iPrMgCl-LiCl, THF, -78 °C	ND
2[b]	$B(OiPr)_3$	iPrMgCl-LiCl, THF, -78 °C	ND
3[b]	$B(OiPr)_3$	n-BuLi, THF, -78 °C	ND
4[b]	iPrO-BPin	n-BuLi, THF, -78 °C	ND
5[b]	BH_3-$NH(iPr)_2$	Mg, PhLi, THF, 70 °C	ND
6[b]	$B(OiPr)_3$	Mg, THF, rt - 70 °C	NR
7	B_2Pin_2	5 mol% $Pd(PPh_3)Cl_2$, PPh_3, KOAc, 1,4-dioxane, 100 °C	20
8	B_2Pin_2	5 mol% $Pd(OAc)_2$, PPh_3, KOAc, 1,4-dioxane, 100 °C	ND
9	B_2Pin_2	5 mol% $Pd(OAc)_2$, Xphos,, KOAc, EtOH, 80 °C	10
10	B_2Pin_2	5 mol% $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 100 °C	>90
11	B_2Pin_2	1% $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 100 °C	~30
12	B_2Pin_2	1% $Pd(OAc)_2$, dppf, KOAc, 1,4-dioxane, 100 °C	~56
13	B_2Pin_2	0.1% $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 100 °C	~7
14	B_2Pin_2	10 mol% $Pd(OAc)_2$, 1,4-dioxane, 100 °C	ND
15	B_2Pin_2	10 mol% $PdCl_2$, 1,4-dioxane, 100 °C	ND
16	B_2Pin_2	10 mol% Pd/C, 1,4-dioxane, 100 °C	ND
17	$B_2(OH)_4$	5 mol% $Pd(PPh_3)Cl_2$, PPh_3, KOAc, EtOH, 80 °C	ND
18	$B_2(OH)_4$	5 mol/% $Pd(OAc)_2$, Xphos,, KOAc, EtOH, 80 °C	20
19	$B_2(OH)_4$	5 mol% $Pd(dppf)Cl_2$, KOAc, EtOH, 80 °C	ND
20	$B_2(OH)_4$	5 mol% Xphos-Pd-G_2, KOAc, EtOH, 80 °C	ND

[a]Reaction conditions: 2-bromo-1-methyl-4-nitrobenzene (1.0 eq.), [Boron] (1.1 eq.), Pd-Catalyst (X mol%), potassium acetate (2.0 eq.), Solvent (10V), until otherwise stated. [b]2-bromo-1-methyl-4-nitrobenzene (1.0 eq.), [Boron] (2 eq.), organometal reagent (1.5eq). [c]HPLC A% at 210 nm. ND: desired product was not detected.

3. Synthesis of 6-ABB from *p*-nitrobenzylic alcohol[4]

Another route based on *para*-nitrobenzylic alcohol **3.1** was also investigated (Scheme 3). The starting benzylic alcohol **3.1** is cheap and readily available. The preinstalled alcohol functionality is expected to facilitate the latter ring closure step. However, the aforementioned bromination conditions didn't work. Thus, three different O-protecting compounds **3.2** (R: -MOM, -Ac, -Piv) were synthesized and subjected to the bromination. Neither Br_2/Fe nor NBS/H_2SO_4 yielded any desired product. Fortunately, when using TFA as a co-acid with H_2SO_4, both 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and NBS gave the desired bromide isolated as free alcohol **3.3** after a basic workup. Analysis of ^{1}HNMR of the crude reaction mixture before workup found that a TFA ester was the intermediate. The swap of O-protecting group with TFA was found to be responsible for the success of the transformation. Later, unprotected alcohol **3.1** reacting with NBS in the presence of TFA/H_2SO_4 also afforded the **3.3** with a similar yield. It is believed that the O-TFA was generated in-situ in the bromination.

Scheme 3.

[4] This route was the Key idea 1B in our previous Tech-review report.

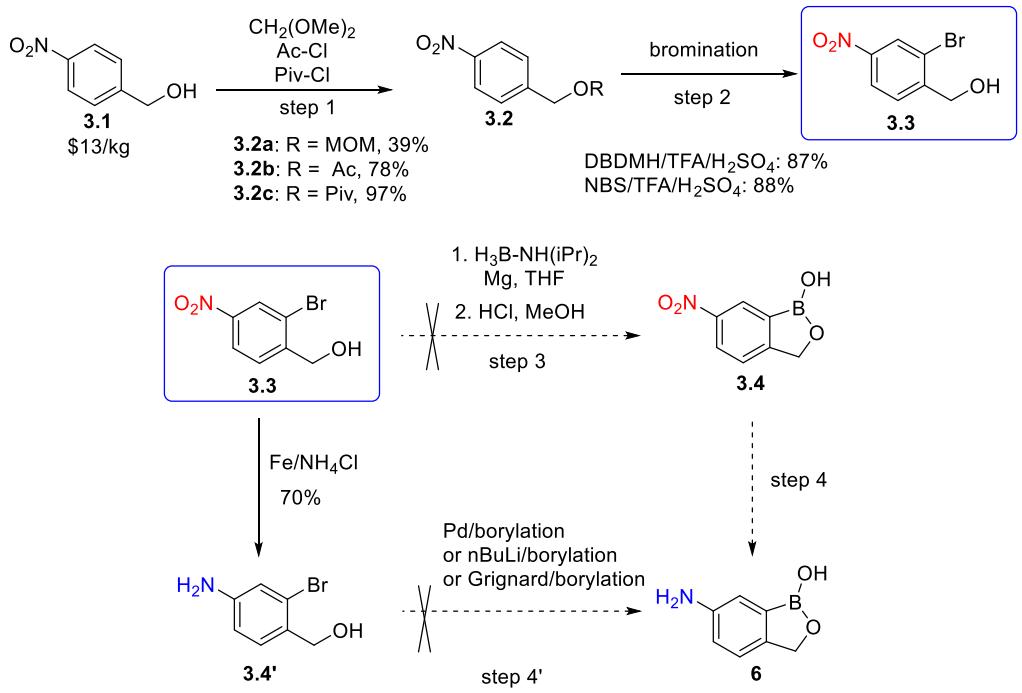


Table 3.1 Attempts of borylation of **3.3** and **3.4′** through Li-Br exchange or metal catalyzed transformation[a]

Entry	Conditions	Results
1	n-BuLi (4eq), $B(OMe)_3$, -70 °C	NR
2	i-PrMgCl (3eq) n-BuLi (2eq), $B(OiPr)_3$, -70 °C	ND
3	n-BuLi/TMEDA, then $(MeO)_3B$	ND
4	LDA/TMEDA, then $(MeO)_3B$	ND
5	Mg, I_2, TMSCl, LiCl, $B(OiPr)_3$, 60 °C	NR
6	Pd/L, B_2Pin_2	ND
7	Pd/L, $B_2(OH)_4$	ND
8	$NiCl_2$/L, $B_2(OH)_4$	ND
9	$[Ir(COD)(OMe)]_2$/L, B_2Pin_2, 80 °C	NR

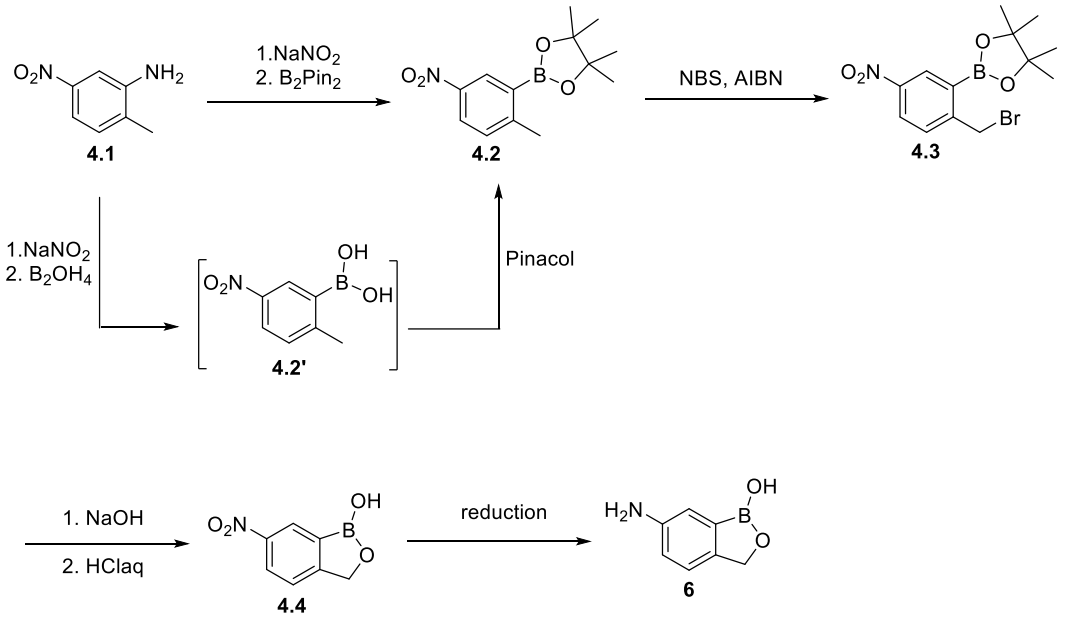
Unfortunately, borylation of compound **3.3** with organometal reagent, followed by borate didn't generate any desired product but debromination. Additionally, attempts of utilizing transition metals, such Pd, Ni, and Ir-catalyst failed to deliver the borylated product (Table 3.1). We assumed that the nitro-group may interfere the borylation. Then **3.3** was converted to **3.4** with Fe/NH_4Cl in a good yield. Regrettably, the borylation of **3.4** under similar conditions failed to give any desired product. As a result, this route was terminated and an alternative route (vide infra) was developed.

4. Synthesis of 6-ABB from 2-methyl-5-nitroaniline[5]

Synthesis of the compound **4.2** was described in the literature from commercially available 2-methyl-5-nitroaniline **4.1**, with an excess of B_2Pin_2, but only on small scale and with a chromatographic purification.[25] We thus focused on the optimization of this transformation for the synthesis of the intermediate **4.2**, by addressing three major issues: 1) minimize the amount of expensive diboron compound needed thus reducing the raw material cost; 2) remove column purification to minimize the processing cost; and 3) diminish the process mass intensity (PMI) with another diboron source, e.g. $B_2(OH)_4$.

Scheme 4.

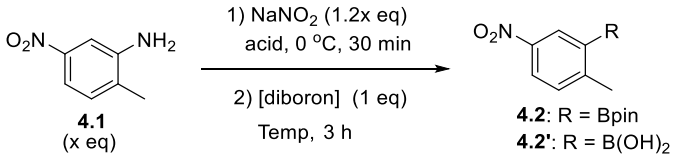
[5] This route was the Key idea 1C in our previous Tech-review report.



4.1 Borylation of aniline

As shown in Table 4.1, our first try was to utilize the pricey B_2Pin_2 as the limiting reagent. Diazotization of 2.0 equivalents of aniline **4.1** in the presence of HCl (6M) and borylation with B_2Pin_2 at 25 ^oC afforded the desired product **4.2** in a good isolated yield. Interestingly, lowering the equivalents of aniline (1.2 eq) worked similarly well in this transformation. Unfortunately, extractive workup and subsequential trituration were needed for purification under this condition (Entries 1-3). Carrying out the borylation with B_2Pin_2 at 0 ^oC resulted in a yellowish precipitate, which dramatically simplified the workup process. The precipitate was collected by simple filtration to afford the product in a 60% yield with > 97% purity by qNMR (Entry 4). Contrary to this, borylation at 40 ^oC resulted in a low yield (Entry 5). Furthermore, it was found that diazotization with H_2SO_4 provided a superior outcome (Entries 6-9). The optimized conditions afforded the borylated product **4.2** in a 61% isolated yield on decagram scale (Entry 10). Surprisingly, no reaction occurred with $B_2(OH)_4$ under the same conditions (Entry 11), but required a slightly higher temperature for the borylation to occur. At this enhanced reaction temperature, all screened acids (i.e., HCl, HBr, and H_2SO_4) worked similarly to afford the corresponding boronic acid **4.2′**. H_2SO_4 was chosen as the optimial acid for the transformation based on the price consideration (Entries 10, 15).

Table 4.1 Borylation of **4.1**



Entry	eq of **4.1**	[diboron]	Acid	Temp/°C	Isolated yield /%
1	2 eq	B_2Pin_2	HCl (6M)	0 - 25	60
2	1.5 eq	B_2Pin_2	HCl (6M)	0 - 25	61
3	1.2 eq	B_2Pin_2	HCl (6M)	0 - 25	56
4	1.2 eq	B_2Pin_2	HCl (6M)	0	60
5	1.2 eq	B_2Pin_2	HCl (6M)	0 – 40	26
6	1.2 eq	B_2Pin_2	HBr (6M)	0	48
7	1.2 eq	B_2Pin_2	H_2SO_4 (6M)	0	77[b]
8	1.2 eq	B_2Pin_2	HBF_4	0	NR
9	1.2 eq	B_2Pin_2	H_3PO_4 (6M)	0	NR
10[e]	**1.2 eq (40g)**	**B_2Pin_2**	**H_2SO_4 (6M)**	**0**	**61**
11	1.2 eq	$B_2(OH)_4$	H_2SO_4 (6M)	0	NR[c]
12	1.2 eq	$B_2(OH)_4$	H_2SO_4 (6M)	0 - 25	43[d]
13	1.2 eq	$B_2(OH)_4$	HCl (6M)	0 - 25	39[d]
14	1.2 eq (10g)	$B_2(OH)_4$	HBr (6M)	0 - 25	48[d]
15[f]	**1.2 eq (20g)**	**$B_2(OH)_4$**	**H_2SO_4 (6M)**	**0 - 25**	**44**[d]

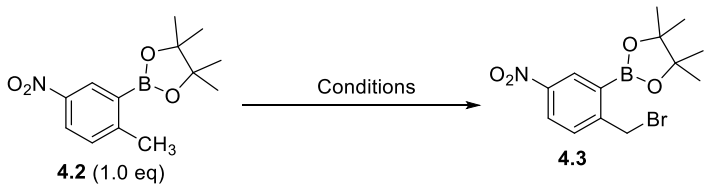
*[a]All reactions were performed with **4.1** (1g, x eq), $NaNO_2$ (1.2x eq), 0 °C, 30 min, then [diboron] (1 eq), 3h, temperature as shown in the table, unless otherwise stated; [b]Assay yield based on [1]HNMR; [c] NR: no reaction; [d] 24 h, Isolated yield of boronic acid **4.2'**; [e] 40 g of aniline was used; [f] 20 g of aniline was used.*

Diazonium salt was the intermediate of this deaminative borylation. Because the diazonium salt possesses the potential thermal instability and sensitivity to friction and shock, this borylation brought safety concerns, especially when scaling up of the chemistry. Thus, thermal data and runaway temperature of the reaction were studied. By carrying out the reaction in an EasyMax chemical synthesis reactor, an exothermic reaction with the heat generated equaling to 155 kJ/mol was observed. The DSC data of the isolated diazonium salt indicated that an exotherm (257 J/g) at 100 °C with an onset at 95 °C and TGA data exhibited a decomposition with a 51% mass loss from 95 – 240 °C. Notably, the DSC/TGA of the solution of the diazonium salt of the reaction mixture presented negligible heat bumps. All these results indicated that the runaway temp might be greater than 90 °C and this diazotization is safe to handle under the current mild reaction condition (See Appendix 1).

4.2.1 Radical bromination

Bromination of the boronic acid pinacol ester **4.2** with NBS has previously been reported.[25] With the boronic acid pinacol ester **4.2** in hand, the radical bromination with NBS went smoothly to yield the bromide **4.3** as the major product (**Table 4.2.1**). It is worthy of mentioning that both radical initiators such as AIBN and BPO (benzoyl peroxide) worked well for the bromination and the undesired dibromide was negligible, less than 5 A% detected by LCMS. However, the purification of the bromides by flash column resulted in unknown impurities. Thus, the crude mixture of the bromides was treated by a simple trituration and telescoped to the next step.

Table 4.2.1 Radical bromination of **4.2**[a]



4.2 (1.0 eq) **4.3**

Entry	4.2	Conditions	Isolated yield/% [b]
1[c]	1 g	NBS (1.5 eq), BPO (0.25 eq), CH_3CN, reflux, 2h	80
2[c]	1 g	NBS (1.5 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	90
3	16 g	NBS (1.5 eq), BPO (0.1 eq), CH_3CN, reflux, 2h	>90
4	6 g	NBS (1.5 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	81
5[c]	200 mg	NBS (1.5 eq), CH_3CN, reflux, 12h	NR
6[c]	200 mg	NaBr:$NaBrO_3$:NaCl, Mercury lamp, DCE:H_2O, 80 °C, 12h	NR
7[c]	200 mg	Pyridinium perbromide, THF, 80 °C, 12h	NR
8[c]	200 mg	$[N(C_4H_9)_4]Br_3$, DCM, 50 °C, 12h	NR

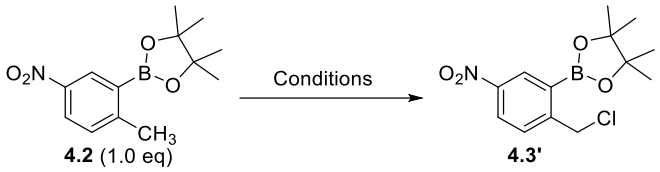
[a]Reaction conditions: 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (1.0 eq.), NBS (1.5 eq), solvent (20V), conditions as shown in table. [b]Isolated yields after trituration from water, used for next step without further purification. [c]Commercial SM was used for condition screening. NR = no reaction.

Notably, in order to avoid radical initiator, bromination under oxidative condition was investigated. Several oxidants, such as $NaBrO_3$, pyridinium perbromide and $N(C_4H_9)_4Br_3$ were tested for the bromination. Unfortunately, none of these conditions gave any bromide but recovery of the starting material **4.2**.

4.2.2 Radical chlorination

In addition to bromination, the synthesis of the related chloride analogue **4.3′** was investigated as well, with the hope to be used as the intermediate for the following ring closure reaction, and to lower the cost of the whole sequence. Unfortunately, radical chlorination with NCS /AIBN or NCS/BPO in refluxing CH_3CN afforded the desired chloride only in 30-35 A%. When utilizing TCCA/$Cu(OAc)_2$, the chlorination yielded the desired product in 50 A%. Further optimization by screening solvent and radical initiators maximized the yield up to 65 A%. And two optimized conditions were identified: 1) NCS/DDQ/NHPI (N-Hydroxyphthalimide); and 2) NCS/BPO/AcOH. However, the chlorination didn't outperform the bromination in terms of yield. Therefore, the investigation of chlorination was discontinued and bromination was chosen for the Scheme 4.

Table 4.2.2 Radical chlorination of **4.2**[a]



4.2 (1.0 eq) **4.3'**

Entry	Conditions	A% of 4.3′ [b]
1	TCCA (1.5 eq), DDQ (0.005 eq), NHPI (0. 1 eq), CH_3CN, reflux	30
2	TCCA (0.5 eq), $Cu(OAc)_2.H_2O$(0.02 eq) NHPI(0.1 eq), CBr4 (0.1 eq), DCM, 25 °C	50
3	**NCS (1.5 eq), DDQ (0.005 eq) NHPI (0. 1 eq), CH_3CN, reflux**	**65**
4	NCS (1.5 eq), AIBN (0.1 eq), CH_3CN, reflux	35
5	NCS (1.5 eq), BPO (0.1 eq), CH_3CN, reflux	30
6	TCCA (0.5 eq), BPO (0.1 eq), CH_3CN, reflux	30
7	TCCA (0.5 eq), BPO (0.1 eq), CH_3CN, reflux	40
8	**NCS (3.0 eq), BPO (0.1 eq), AcOH, 80** °C	**65**
9	TCCA (1.0 eq), BPO (0.1 eq), AcOH, 80 °C	30
10	NCS (3.0 eq), BPO (0.1 eq), H_2SO_4, 50 °C	0
11	NCS (3.0 eq), BPO (0.1 eq), TFA, 50 °C	NR

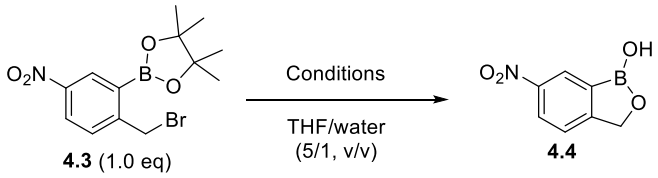
[a]Reaction conditions: 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (0.5g, 1.0 eq), solvent (20V), conditions as shown in table. [b]HPLC A% at 210 nm. NR = no reaction.

4.3 Hydrolysis/ring closure

The conversion of bromide **4.3** to ring closed product **4.4** has previously been reported.[25] According to the Fuscaldo et al., treatment with 10 equivalents of NaOH at 50 °C the bromides yielded the intermediate of benzylic alcohol. Notably, bases other than NaOH, such as KOH, LiOH

worked in this reaction as well under the similar condition, but $CaCO_3$ didn't work for this transformation. The hydrolysis occurred at 25 °C with NaOH, KOH or LiOH, albeit with slightly low yields. The purification of the benzylic alcohol was problematic and the resulting crude reaction mixture was telescoped to the next ring closure. The resulting mixture was treated with 30 equivalents of aqueous HCl affording the ring closure product **4.4** as the major product. In order to develop a scalable process for this transformation, the amounts of base and acid were investigated. Utilizing NaOH as the base, it was found that the hydrolysis occurred well with 3 equivalents of NaOH, and the following ring closure proceeded in the presence of 9 equivalents of aq HCl. Parenthetically, the compound **4.4** was stable for column purification. Fortunately, after solvent screening, a good solvent was found being able to precipitate the product without the need for column purification. For instance, slurring the crude reaction mixture in ethyl acetate afforded the product **4.4** in 82% overall yield with > 97% purity by qNMR on a 20 g scale (Table 4.3).

Table 4.3 Hydrolysis and ring closure of **4.3**[a]



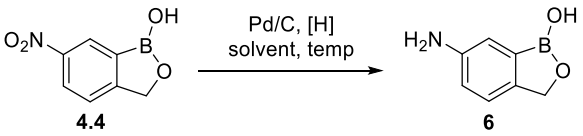
Entry	Scale	Conditions	A% of 4.4[b]
1	1.4 g	1) NaOH, 10 eq, 50 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8h	82[c]
3	0.5 g	1) KOH, 10 eq, 50 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	79
4	0.5 g	1) LiOH, 10 eq, 50 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	92
8	0.5 g	1) $CaCO_3$, 10 eq, 50 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	NR
5	0.5 g	1) NaOH, 10 eq, 20 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	76
6	0.5 g	1) KOH, 10 eq, 20 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	68
7	0.5 g	1) LiOH, 10 eq, 20 °C, 2 h; 2) 6 M HCl, 30 eq, 50 °C, 8 h	73
9	**2.5 g**	**1) NaOH, 5 eq, 50 °C, 2 h; 2) 6 M HCl, 10 eq, 50 °C, 8 h**	**86**[c]
10	0.5 g	1) NaOH, 2 eq, 50 °C, 2 h; 2) 6 M HCl, 9 eq, 50 °C, 8 h	80
11	0.5 g	1) NaOH, 1 eq, 50 °C, 2 h; 2) 6 M HCl, 9 eq, 50 °C, 8 h	55
12	**20 g**	**1) NaOH, 5 eq, 50 °C, 2 h; 2) 6 M HCl, 10 eq, 50 °C, 8 h**	**82**[c]

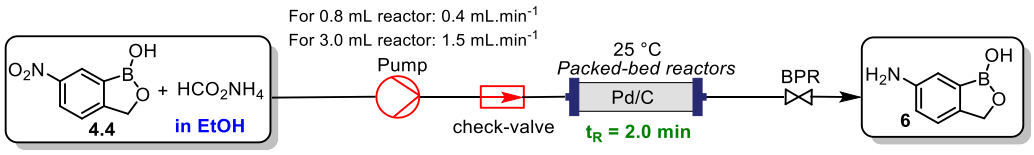
[a]Reaction conditions: 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (1.0 eq), THF:H_2O (20V, 5:1), conditions as shown in table. [b]Yields were calculated using HPLC A% at 210 nm. [c]Isolated yield. NR = no reaction.

4.4 Hydrogenation

With the compound **4.4** in hand, hydrogenation to afford 6-ABB **6** was investigated. Considered the possible heterogeneous catalyst recovery, we focused on the reduction with Pd/C as the catalyst. Initial screening under batch condition with hydrogen gas as the reducing reagent showed that 0.34 mol% of catalyst loading afforded the amine product in an excellent yield when performing the reaction at 25 °C (Entries 1-5). Unfortunately, the reaction was slow and needed 36 h to obtain a full conversion. To address this problem, effort was focused on the continuous flow hydrogenation with a packed bed reactor. It is known that flow hydrogenation outperforms the related batch condition due to a significantly higher effective molarity of the catalyst/reagent, thus dramatically reduces the reaction time. Another advantage of the packed bed reactor is to provide a more convenient way to recover the palladium catalyst.[28] As shown in Table 4.4 (Entry 6), the initial hydrogenation was carried out in a 0.8 mL of packed bed reactor with HCO_2H as reducing reagent, and significant amount of the desired amine was obtained albeit in a relatively low yield. ^{1}H NMR of the crude reaction mixture indicated the formation of amide from the product **6** and formic acid. The unwanted side reaction was completely eliminated when utilizing HCO_2NH_4 as the hydrogen source. For instance, an excellent isolated yield was obtained by feeding the solution of the mixture of HCO_2NH_4 and compound **4.4** with a flow rate of 0.1 ml/min. When increasing the flow rate to 0.4 mL/min, the same result was obtained (Entries 6-9). The efficiency of this flow transfer-hydrogenation was demonstrated by a sub-decagram scale reaction. In a 3 mL of reactor charged with 0.34 mol% of Pd/C (10 wt%), a 5-gram scale reaction under flow rate of 1.5 mL/min produced the product in > 95% of isolated yield within 2.5 h (Entry 10). It is worth mentioning that the purification process was straightforward. A simple trituration of the crude reaction mixture afforded the product in > 95% yield with > 97% purity by qNMR.

Table 4.4 Hydrogenation of **4.4**[a]



Entry	Pd/C (/mol %)	[H]	Temp (/°C)	Time (/h)	Yield (/%)
Under batch condition					
1	1.7	H_2 (90 psi)	50	24	ND[b]
2	1.7	H_2 (90 psi)	25	12	50[c]
3	1.7	H_2 (60 psi)	25	36	> 90[c]
4	0.34	H_2 (60 psi)	25	36	> 90[c]
5	0.34	H_2 (15 psi)	25	36	20[c]
Under continuous flow condition					
					
6[d]	0.34	HCO_2H (3 eq)	25	4	20[e]
7[d]	0.34	HCO_2NH_4 (3 eq)	25	4	90[f]
8[g]	0.34	HCO_2NH_4 (3 eq)	25	1	93[f]
9[g]	0.17	HCO_2NH_4 (3 eq)	25	1	45[h]

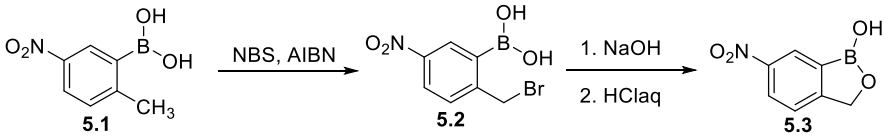
10[i]	0.34	HCO_2NH_4 (3 eq)	25	2.5	95[f]

*[a]All reactions were performed with **4.4** (0.5 g, 2.8 mmol, 1.0 eq), 10 wt% Pd/C, H_2 or other reducing reagents as shown in the table in EtOH (20 mL, 40 V), 25 °C, unless otherwise stated; [b] Starting material consumed without any major peaks/spots by LCMS/TLC; [c]Assay yield based on [1]HNMR; [d] In 0.8 mL of reactor, flow rate: 0.1 mL/min; [e] 20% desired product, 20% of corresponding amide, and 60% of **4.4** by [1]HNMR; [e] Isolated yield; [f] Isolated yield; [g] In 0.8 mL of reactor, flow rate: 0.4 mL/min; [h]Assay yield based on [1]HNMR, 55% of **4.4** remained; [i] In 3 mL of reactor, flow rate: 1.5 mL/min, 5g of **4.4** was used.*

5. Synthesis of 6-ABB via bromination of boronic acid[6]

With these exciting results in hand, we were then curious to see if boronic acid **5.1** could afford **5.3** in a telescoped manner. The advantage of the directly using boronic acid **5.1** in this transformation is the generation of a more benign byproduct (i.e., $B(OH)_3$) during the cyclization, which as a result, generates less PMI for the route.

Scheme 5.



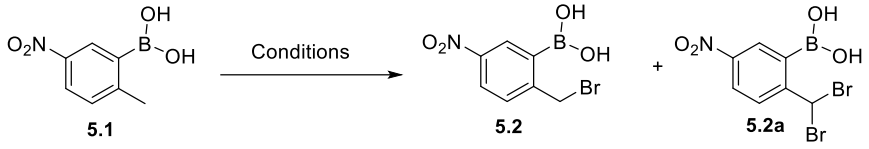
5.1 Bromination of the boronic acid

Towards this endeavor, boronic acid **5.1** was subjected to bromination with NBS (Table 5.1). Using the same condition as that for boronic acid pinacol ester, the desired bromide **5.2** was obtained, however concurrently with the formation of dibromide **5.2a** as the major side-product. For example, treatment of **5.1** with NBS (1.5 eq) and AIBN (0.1 eq) afforded **5.2** in 77 A%, while dibromide **5.2a** was up to 17 A% (Entry 1). Intriguingly, decrease of the amount NBS to 1.1 equivalents increased the yield of the bromide **5.2** up to 85 A% while the dibromide was reduced

[6] This route was the Key idea 1E in our previous Tech-review report.

to 8 A% (Entry 4). However, decrease of the amount of initiator, e.g. utilizing 0.05 eq of AIBN generated more side-product dibromide (Entry 6). Surprisingly, unlike the reaction of pinacol ester **4.1**, switching radical initiator to BPO yielded more dibromide side-product (Entry 7). Interestingly, ambient light also promoted the bromination enabling bromide **5.2** formation in the absence of the radical initiator (Entry 8). As a control reaction, refluxing **5.1** with NBS in acetonitrile resulted in recovery of all the starting materials. Furthermore, solvent screen of this transformation gave no preference of the mono-bromide formation (Entries 9 – 12). With the optimized condition, a 10 g scale reaction of **5.1** with NBS (1.1 eq) and AIBN (0.1 eq) afforded the desired bromide **5.2** in an 80% isolated yield after trituration from water (Entry 13).

Table 5.1 Radical bromination of boronic acid **5.1**[a]



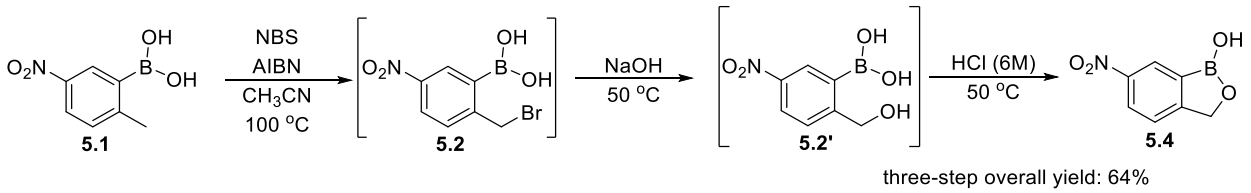
Entry	Scale of 5.1	Conditions	A% (210 nm)	
			5.2	5.2a
1	0.5 g	NBS (1.5 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	77	17
2	0.5 g	NBS (1.2 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	78	4
3	0.5 g	NBS (1.2 eq), AIBN (0.1 eq), CH_3CN, reflux, 12h	70	23
4	0.5 g	NBS (1.1 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	84	8
5	0.5 g	NBS (1.1 eq), AIBN (0.15 eq), CH_3CN, reflux, 2h	80	12
6	0.5 g	NBS (1.1 eq), AIBN (0.05 eq), CH_3CN, reflux, 2h	55	27
7	0.5 g	NBS (1.2 eq), BPO (0.1 eq), CH_3CN, reflux, 2h	55	20
8	0.5 g	NBS (1.2 eq), Room Light, CH_3CN, rt, 8h	80	5
9	0.5 g	NBS (1.2 eq), CH_3CN, reflux, 12h	NR	
10	0.5 g	AIBN (0.1 eq), THF, reflux, 12h	NR	
11	0.5 g	AIBN (0.1 eq), EtOAc, reflux, 12h	56	--[c]
12	0.5 g	AIBN (0.1 eq), CH_3CN/H_2O (90/10), reflux, 12h	30	--[c]
13	10 g	NBS (1.1 eq), AIBN (0.1 eq), CH_3CN, reflux, 2h	80[b]	

[a]Reaction conditions: 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (1.0 eq.), solvent (20V), conditions as shown in table. [b]Isolated yields. [c]Data not collected. NR = no reaction.

5.2 Synthesis of 6-nitro-1-hydroxy-2,1-benzoxaborolane

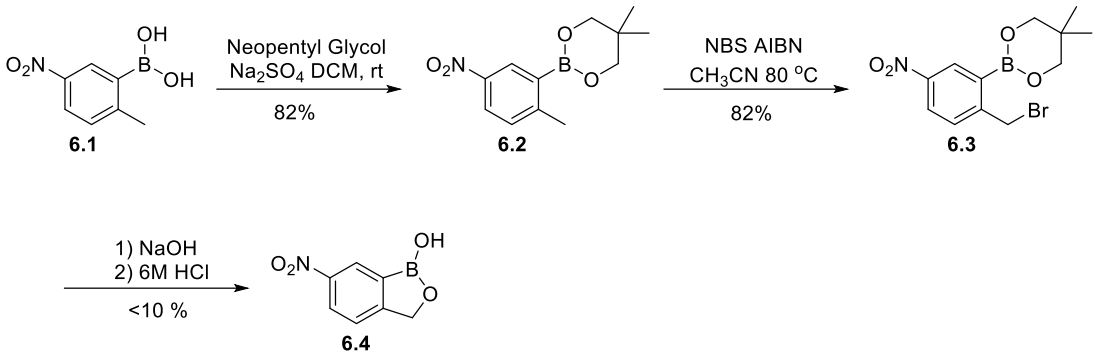
The conversion of bromide **5.2** to ring closed product **5.3** went smoothly like its analogue bromide **4.2**. Treatment of **5.2** with 3 equivalents of NaOH at 50 °C for 2 h, followed by treating with 9 equivalents of aqHCl afforded the 6-nitro-1-hydroxy-2,1-benzoxaborolane **5.3** in a good overall yield (Scheme 5.1). Notably, the same solvent system worked for this purification, i.e. slurring the crude reaction mixture in ethyl acetate afforded the product **5.3** in 70% overall yield with > 97% (by qNMR) purity. Similarly, this process was also successfully demonstrated with decagram scale reactions and no column purification is needed for the whole process. It provides an alternative way to access the valuable 6-ABB **6**.

Scheme 5.1 Converting boronic acid **5.1** to 6-nitro-1-hydroxy-2,1-benzoxaborolane **5.3**.



6. Synthesis of borate neopentyl glycol ester for 6-ABB[7]

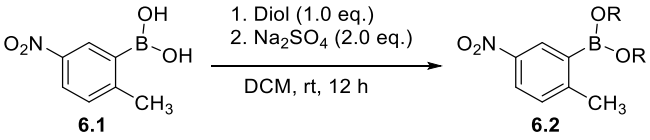
Scheme 6.



6.1 Synthesis of borate neopentyl glycol ester

With the boronic acid in hand, we also synthesized new boronic acid ester with cheap diols. First, the reaction of boronic acid **6.1** with pinacol was carried out and the corresponding pinacol ester **6.2a** was obtained in an 88% yield. And neopentyl glycol reacting with boronic acid **6.1** afforded boronic ester **6.2b** in an 91% isolated yield. However, the ethylene glycol ester was not formed under a similar condition (Table 6.1).

Table 6.1 Radical bromination of boronic acid **6.1** *a*



Entry	Diol (cost)	6.2 (Isolated yield)
1	Pinacol (~$30/kg)	**6.2a** (88%)
2	Neopentyl Glycol (~$1/kg)	**6.2b** (91%)
3	Ethylene Glycol (< $1/kg)	**6.2c** (NR)

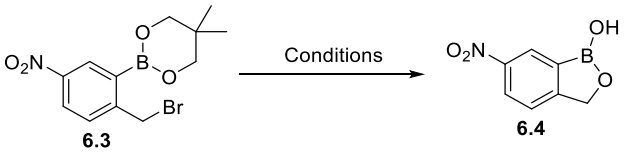
[7] The route was the Key idea 1D in our previous Tech-review report.

[a]Reaction conditions: (2-methyl-5-nitrophenyl)boronic acid (1.0 eq), diol (1.0 eq.), $NaSO_4$ (2.0 eq.), DCM (10V). NR = No reaction.

6.2 Bromination/hydrolysis/ring closure

With the new ester **6.2b** in hand, the radical bromination reaction under previously established condition (NBS (1.2 eq), AINB (0.1 eq), CH_3CN, reflux, 2h) went smoothly to afford the bromide **6.3** in an 82% isolated yield. Notably, the bromide **6.3** was purified by trituration to give a satisfactory ^{1}HNMR. Unfortunately, the hydrolysis of **6.3** and the following ring closure afforded the product **6.4** in a very low yield. As summarized in Table 6.2, when treating the bromide **6.3** with the standard hydrolysis/ring closure condition (NaOH then aq. HCl, vide supra), surprisingly no desired ring-closure product was observed while all starting material was consumed. ^{1}H NMR analysis of the crude reaction mixture after treatment with NaOH showed no alcohol product. This negative result might be due to the labile neopentyl glycol moiety compared to pinacol group. And it encouraged us to screen other bases, i.e. $CaCO_3$, LiOH, and KOH. Interestingly, KOH gave a ~30% assay yield of the desired product after acid treatment and $CaCO_3$ resulted in no reaction. We then ran a 2 g scale reaction with KOH. After column chromatography purification, the desired product was isolated, however in a very low yield (~9 %). As a result, this route was abandoned because of the low yield of hydrolysis and cyclization.

Table 6.2 Hydrolysis and cyclization of **6.3**[a]



6.3 **6.4**

Entry	Scale of 6.3	Conditions	Results
1	0.5 g	NaOH (10 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 30 eq), 50 °C, 8h	ND
2	0.5 g	KOH (10 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 30 eq), 50 °C, 8h	30% (crude NMR)

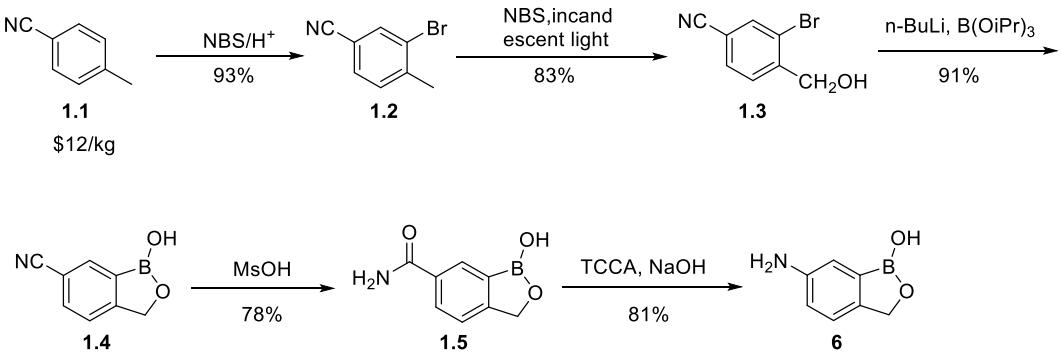
3	0.5 g	LiOH (5 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 10 eq), 50 °C, 8h	ND
4	0.5 g	$CaCO_3$ (5 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 10 eq), 50 °C, 8h	NR
5	0.5 g	KOH (5 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 10 eq), 50 °C, 8h	29% (crude NMR)
6	2 g	KOH (5 eq), THF/water (5/1), 50 °C, 2h, then HCl (6M, 10 eq), 50 °C, 8h	9[b]

[a]*Reaction conditions: 2-(2-(bromomethyl)-5-nitrophenyl)-5,5-dimethyl-1,3,2-dioxaborinane* ***13*** *(1.0 eq), Base (X eq.), 6M HCl (30 eq.), THF:H_2O (10V, 5:1).* [b]*Isolated yields based on Biotage isolera flash column purification. ND: not detected, but starting material was consumed; NR: no reaction and the starting material remained.*

Conclusion

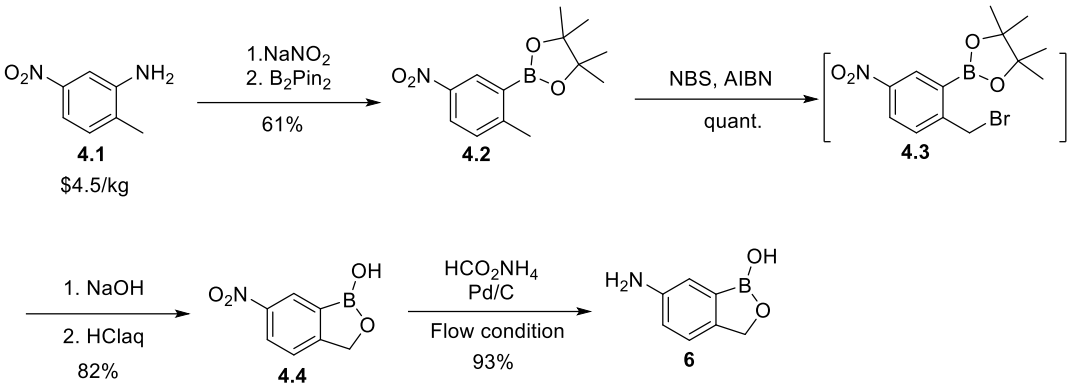
In conclusion, DNDI-6148 holds promising initial treatment results for visceral leishmaniasis in addition to several other advantages over the current treatment options. However, the high cost of 1-hydroxy-2,1-benzoxaborolane - the starting material of 6-ABB - and dangerous nitration process impede the possible large-scale manufacturing of DNDI-6148. To reduce the cost of 6-ABB and to avoid dangerous nitration reaction, we developed several approaches for synthesis of the 6-ABB from cheap and readily available commodities. Among the six routes that we explored, two emerged as the most promising 1) a 5-step sequence from 4-methylbenzonitrile (Scheme 1), and 2) a 4-step sequence from 2-methyl-5-nitroaniline (Scheme 4). The first sequence based on 4-methylbenzonitrile utilized the Hofmann rearrangement as the key transformation with an overall yield of ~40%. While pitfalls still exist in this process that need further optimization, e.g., to get rid of the preparative chromatography for amide purification, but no significant effort was made during this project to investigate chromatography-free isolation conditions. This would certainly be the subject of further optimization if this route is chosen for scale-up investigations.

Scheme 1.



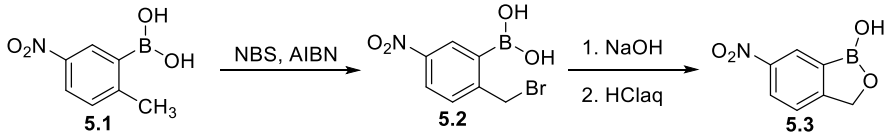
The second approach employed 2-methyl-5-nitroaniline as the starting material, featured with the key steps of borylation of aniline with B_2Pin_2 and continuous flow nitro reduction with an overall yield of ~45% without the need of chromatographic purification (Scheme 4).

Scheme 4.



In addition, directly utilizing the corresponding boronic acid **5.1** to furnish the 6-nitro-1-hydroxy-2,1-benzoxaborolane **5.4** has also been demonstrated, providing an alternative route to 6-ABB (Scheme 5).

Scheme 5.



All routes have been demonstrated on several decagram scale and bypass the nitration step and avoid utilizing the expensive starting material. Furthermore, our techno-economic analysis (TE) of the baseline and M4ALL routes suggest that overall raw material cost of the new routes is reduced up to 80% for the first approach (Scheme 1, with 4-tolunitrile) and up to 90% for the second approach (Scheme 4, with 2-methyl-5-nitroaniline/B_2Pin_2). It's our hope that the synthetic routes developed here will find its practical application in the commercial-scale synthesis of DNDI-6148 to help combat Visceral Leishmaniasis.

Experimental Procedures

I. General Methods

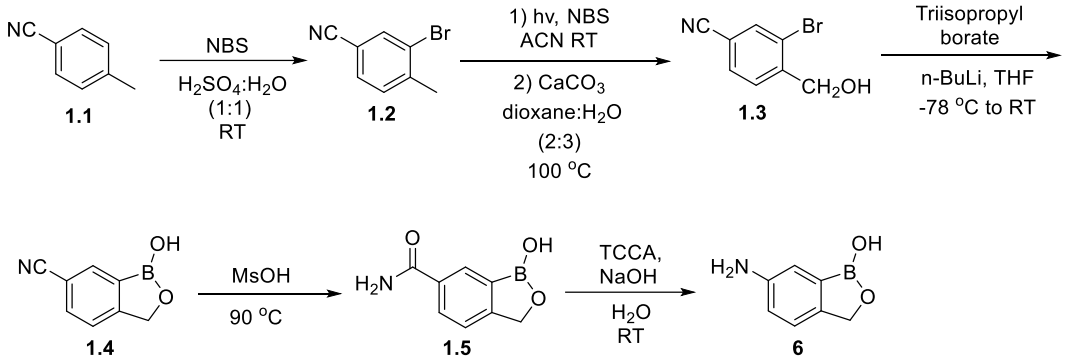
Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Reactions were carried out in oven-dried (120 °C) glassware, that was assembled while hot, and cooled to ambient temperature under an inert atmosphere. All reactions were carried out under inert atmosphere (N_2) unless otherwise noted. Reactions were monitored by TLC (precoated silica gel 60 F_{254} plates, EMD Chemicals), HPLC or LC/MS using various methods as described below. TLC was visualized with UV light or by treatment with Phosphomolybdic acid (PMA), ninhydrin, and/or $KMnO_4$. Flash chromatography was performed on a Teledyne ISCO Combi-Flash NEXTGEN 300+ and/or a Biotage Isolera using solvents as indicated. HRMS was recorded using Perkin Elmer Axion 2 ToF MS, ionization mode: positive with scan range: 100 - 1000 m/z, flight tube voltage: 8 kV, spray voltage: 3.5 kV, solvent: methanol. Melting point was measured using Stuart™ melting point apparatus SMP10. ^{1}HNMR and ^{13}CNMR spectra were routinely recorded on Bruker Avance III HD Ascend 600 MHz spectrometer. The NMR solvents used were $CDCl_3$, CD_3OD or DMSO-d_6 as indicated. Tetramethylsilane (TMS) was used as an internal standard. Coupling constants J are reported in hertz (Hz). The following abbreviations were used to designate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet, p, pentet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, double of triplets; ddt, doublet of doublet of triplets; m, multiplet; br, broad. 1,3,5-trimethoxybenzene and/or triphenylmethane, were used as internal standards for quantitative 1H-NMR.

II. Chromatographic Methods

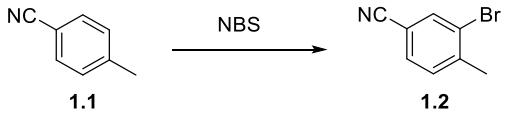
The reactions outlined in Scheme 1 (cyano route) were monitored by a combination of LC-MS and GC-MS. LC-MS analysis was performed with an Agilent Zorbax SB-C18 (3 × 150 mm; 5µm) column with a gradient of 5% to 95% acetonitrile in water over 10 minutes. 0.1% formic acid was used in both solvents. GC-MS was used to analyze the bromination steps of Scheme 1 utilizing an HP-5MS (30 M × 0.25 mm; 5 µm film) column and a heat ramp of 25 °C/min from 50 °C to 225 °C. Reactions outlined in Scheme 2 - 6 (nitro route) were monitored with LC-UV method employing a Phenomenex Kinetix Phenyl Hexyl (150 × 4.6 mm; 5 µm) column. For analysis of

all reaction steps with the exception of the final step a gradient was used consisting of 20% to 80% methanol against 0.1% H_3PO_4 in water over 9 min followed by an isocratic hold for 3 min. Analysis of the final compound was performed with an identical gradient program with 10 mM potassium phosphate buffer at pH 6.0 rather than the 0.1% H_3PO_4.

Scheme 1.



Synthesis of 3-bromo-4-methylbenzonitrile (1.2) from *p*-tolunitrile (1.1)



To a 500 mL round-bottom flask equipped with a magnetic stir bar, was added 4-methylbenzonitrile (50.0 g, 1.0 eq, 427 mmol) and 200 mL of aqueous sulfuric acid (50:50 ratio by volume of conc. H_2SO_4 and water). The flask was wrapped with aluminum foil to prevent competitive free-radical reactions. The mixture was stirred for 10 min, whereupon *N*-bromosuccinimide (83 g, 1.1 eq, 469 mmol) was added to the flask slowly over 20 min via a solid addition funnel. The mixture was then stirred at 25 °C for 24 h and then analyzed via GC/MS. After completion, the reaction mixture was then extracted with DCM (100 mL x 3). The combined organics were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 8.54 g of crude material. This material was passed through a SiO_2 plug and washed thrice with 5% EtOAc in Hexanes (100 mL each) to give 75.7 g of 3-bromo-4-methylbenzonitrile as a white solid (386 mmol, 84%) with 93% purity via qNMR.

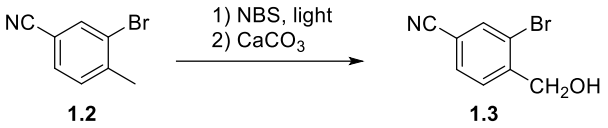
^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.11 (d, *J* = 1.5 Hz, 1H), 7.76 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 2.41 (s, 3H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 143.8, 135.2, 131.8, 131.4, 124.5, 117.5, 110.5, 22.8

MS (m/z) (M+H): calcd. for C_8H_7BrN 195, found 195

Melting Point (uncorrected): 43 - 45 °C.

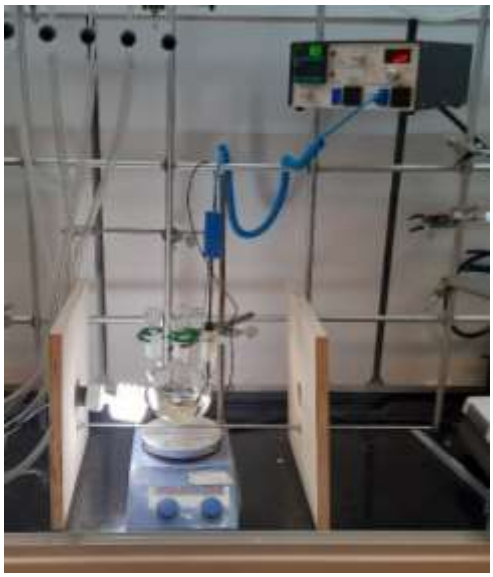
Synthesis of 3-bromo-4-(hydroxymethyl)benzonitrile (1.3) from 3-bromo-4-methylbenzonitrile (1.2)



1.2 1.3

To a 500 mL three-neck round-bottom flask equipped with a magnetic stir bar, was added 3-bromo-4-methylbenzonitrile (10.0 g, 1.0 eq, 51.0 mmol) and acetonitrile (150 mL). *N*-bromosuccinimide (13.6 g, 1.5 eq, 76.5 mmol) was then added to the mixture and stirred at 25 °C for 12 h in the presence of an incandescent light bulb (see picture below). The reaction mixture was then analyzed via GC/MS, upon confirmed consumption of the **2**, the reaction was concentrated *in vacuo*. The crude material was partitioned between DCM (100 mL) and DI H_2O (100 mL) and the aqueous layer was extracted twice with DCM (100 mL each). The organic layers were combined and washed with DI H_2O (100 mL), and brine (100 mL) before being dried over Na_2SO_4. The material was then filtered and concentrated *in vacuo* to give crude 3-bromo-4-(bromomethyl)benzonitrile (14.63 g) as a yellow solid (NMR confirmed). To the crude material was added 1,4-dioxane (80 mL), water (120 mL), and calcium carbonate (23. 5 g, 4.6 eq, 234.6 mmol). This mixture was heated at 100 °C for 16 h and then analyzed via LC/MS for starting material consumption. Upon confirmation, the mixture was cooled to room temperature, and filtered through celite. The filtrate was partitioned between water (100 mL), and EtOAc (100 mL). The aqueous layer was extracted twice with EtOAc (100 mL each). The combined organics were washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 12.22 g of

crude **3** as a tan solid. This resulting solid was recrystallized with 100 mL of DCM:MeOH (80:10, v/v) to obtain 8.97 g of 3-bromo-4-(hydroxymethyl)benzonitrile (**1.3**) as a white powder (42.3 mmol, 82.9%) with 94% purity via weight % analysis. This corresponds to a corrected yield of 77.9 %.



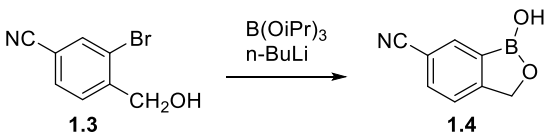
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.12 (d, *J* = 1.5 Hz, 1H), 7.88 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 5.71 (s, 1H), 4.55 (br. s., 2H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 147.2, 135.1, 131.6, 128.3, 121.0, 117.6, 111.1, 62.5

MS (m/z) (M+H): calcd. for C_8H_7BrNO 212, found 212

Melting Point (uncorrected): 135 - 137 °C

Synthesis of 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonitrile (1.4) from 3-bromo-4-(hydroxymethyl)benzonitrile (1.3)



1.3 **1.4**

A 1000 mL three-necked round-bottomed flask was charged with a stir-bar, and then 3-bromo-4-(hydroxymethyl)benzonitrile (10.0 g, 1 eq, 47.2 mmol) and tetrahydrofuran (300 mL, Sigma-Aldrich, Anhydrous) was added under N_2. The reaction vessel was cooled at -78 °C, and then triisopropyl borate (17.7 g, 21.8 mL, 2 eq, 94.3 mmol) was added. The mixture was stirred for 20 minutes, before the addition of 2.5 M *n*-butyllithium in hexanes (7.55 g, 47.2 mL, 2.50 M, 2.5 eq, 117.9 mmol) dropwise in three separate portions at -78 °C. The mixture was removed from the cooling bath and allowed to warm to room temperature and stirred for 16 hours under an N_2 atmosphere. After which, the mixture was quenched with 1N HCl (100 mL) and extracted thrice with ethyl acetate (100 mL each). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and then concentrated *in vacuo* to afford 12.9 g of a yellow solid. This solid was triturated with 100 mL of a suitable solvent (i.e., Et_2O, MTBE, DCM, and/or hexanes) to give 6.67 g of 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonitrile (**1.4**) as a pale-yellow solid (42.0 mmol, 88.9 % yield) with 96% purity via qNMR. This corresponds to a corrected yield of 85.4 %.

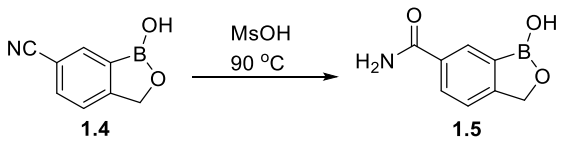
^{1}H NMR (600 MHz, DMSO-d_6): δ 9.51 (s, 1H), 8.10 (s, 1H), 7.91 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.64 (dd, *J* = 0.6, 7.9 Hz, 1H), 5.08 (s, 2H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 158.7, 134.6, 133.9, 122.9, 119.2, 110.0, 70.2

MS (m/z) (M+H): calcd. for $C_8H_7BNO_2$ 160, found 160

Melting Point (uncorrected): 198 - 201 °C

Synthesis of 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (1.5) from 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonitrile (1.4)



1.4 **1.5**

To a 500 mL round-bottom flask, charged with a stir-bar, was added 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonitrile (6.65 g, 1 eq, 41.8 mmol) and methanesulfonic acid (120.6 g, 81.4 mL, 30 eq, 1.26 mol). The reaction mixture was heated at 90 °C for 16 hours under N_2 atmosphere. After this, the reaction was analyzed via LC/MS to confirm consumption of starting material. The reaction mixture was then neutralized (pH 6-7) with 6 M NaOH (30 mL), concentrated *in vacuo* onto C18 silica gel, and purified via reverse-phase chromatography with 5% CH_3CN in H_2O plus 0.1 % formic acid to give 5.48 g of 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (**1.5**) as a white solid (31.0 mmol, 74.0 % yield) with a 96% purity via qNMR. This corresponds to a corrected yield of 71.0 %.

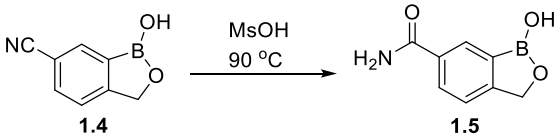
^{1}H NMR (600 MHz, DMSO-d_6): δ 9.30 (br. s., 1H), 8.24 (d, J = 0.73 Hz, 1H), 7.98 (br. s., 1H), 7.95 (dd, J = 1.65, 7.89 Hz, 1H), 7.46 (dd, J = 0.55, 7.89 Hz, 1H), 7.33 (br. s., 1H), 5.03 (s, 2H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 168.3, 156.8, 133.3, 130.0, 129.8, 121.1, 69.9

MS (m/z) (M+H): calcd. for $C_8H_9BNO_3$ 178, found 178

Melting Point (uncorrected): 209 – 211 °C

Enzymatic hydrolysis of 1.4 by nitrile hydratase[8]



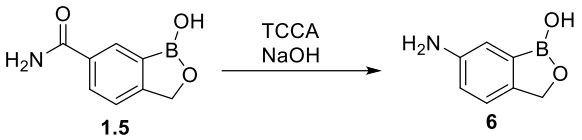
1.4 **1.5**

To a solution of 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonitrile (50.0 mg, 1 eq, 314.56 µmol) in DMSO (1 mL) was added phophate buffer (pH= 7) (10.0 mL, 1 eq, 314.56 µmol), and cloudy yellowish suspension was formed. To this suspension was added enzyme pro-nhase

[8] Nitrile hydratase was gifted by Prozomix Limited company, Northumberland, UK

(001) (1.0 mL, 1 eq, 314.56 µmol) at rt. The mixture was shaked at 30 °C for 36 h and monitored by LCMS every 12 h. The LCMS results indicated that no any reaction occurred.

Synthesis of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (6) from 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (1.5)



1.5 6

To a solution of the 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (2.00 g, 1 eq, 11.3 mmol) and Sodium hydroxide, ultra-dry (2.49 g, 5.5 eq, 62.2 mmol) in H_2O (50 mL) was added Trichloroisocyanuric Acid (880 mg, 0.335 eq, 3.79 mmol) at 0 °C. This solution was stirred for 2 hours, then allowed to warm to 25 °C and stirred for an additional 12 hours. The reaction was then neutralized (pH 6-7) with 1M HCl (40 mL) and extracted thrice with EtOAc (100 mL each). The organics were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*, to afford a yellow solid. This solid was recrystallized from MTBE (20 mL) to afford 1.41 g of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (**6**) as a light-yellow solid (9.47 mmol, 83.7 %) with 96% purity via weight % analysis. This corresponds to a corrected yield of 80.4 %.

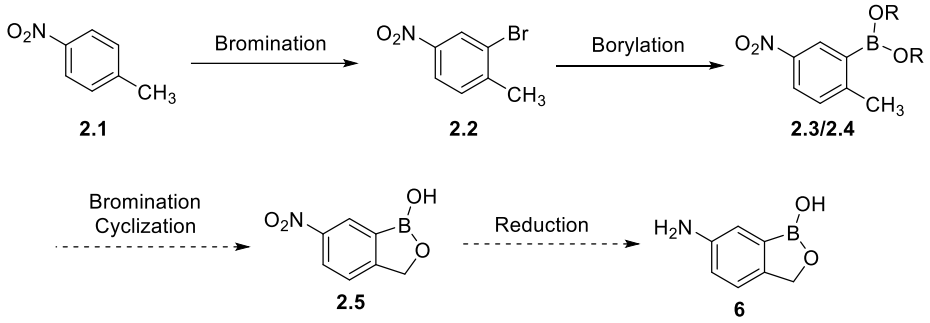
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.03 (d, J = 8.07 Hz, 1H), 6.89 (d, J = 2.02 Hz, 1H), 6.70 (dd, J = 2.20, 8.07 Hz, 1H), 4.98 (br. S., 2H), 4.81 (s, 2H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 147.5, 141.4, 131.0 (C-B), 121.4, 117.6, 114.6, 69.6

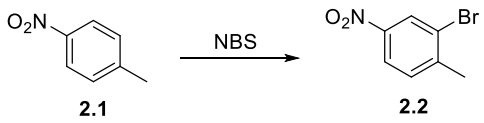
HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_7H_8BNO_2$ 150.0721; Found 150.0723

Melting Point (uncorrected): 147 – 150 °C

Scheme 2.



Synthesis of 2-bromo-4-nitrotoluene (2.2) from *p*-nitrotoluene (2.1)



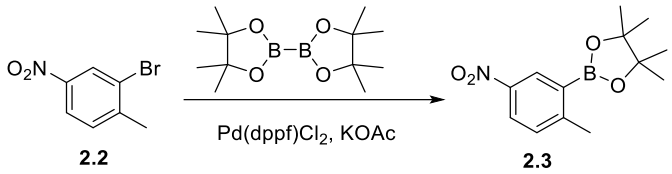
To a round bottom flask equipped with a magnetic stir bar, a mixture of *p*-nitrotoluene (10.0 g, 1.0 eq. 72.9 mmol) and 80 mL of aqueous sulfuric acid (50:50 ratio by volume of conc. H_2SO_4 and water) were added. The flask was wrapped with aluminum foil so that darkness might prevent competitive radical reactions. The mixture was stirred for 10 minutes, then *N*-bromosuccinimide (15.5 g, 1.2 eq. 87.5 mmol) was added slowly (portion wise, over 20 minutes). The mixture was stirred at room temperature for 24 h. After completion (monitored by HPLC), the product was extracted by EtOAc (50 mL x 3). The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. Solvent was removed to afford 14.4 g of 2-bromo-4-nitrotoluene (**2.2**) as a yellow solid (66.7mmol, 92%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 2.49 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm: 146.7, 146.0, 131.2, 127.5, 125.1, 122.3, 23.4

Melting Point (uncorrected): 74 -76 °C

Synthesis of 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (2.3) from 2-bromo-4-nitrotoluene (2.2)



2.2 **2.3**

A mixture of $Pd(dppf)Cl_2$ (0.34 g, 5 mol%, 462.9 µmol), 2-bromo-4-nitrotoluene (2.0 g, 1.0 eq, 9.2 mmol), bis(pinacolato)diboron (2.58 g, 1.1 eq, 10.2 mmol), and potassium acetate (1.82 g, 2.0 eq, 18.5 mmol) in 1,4-dioxane (20 mL) was degassed with N_2 at rt for 5 min, then the mixture was refluxed under nitrogen for 8 h. After completion (monitored by HPLC), the mixture was extracted with EtOAc (20 mL x 3). The organic layers were combined and washed sequentially with water and brine. The organic phase was separated and dried over anhydrous Na_2SO_4, and evaporated to dryness by rotary evaporation. The residue was stirred in hexanes (20 mL) for 30 min at rt, then the solid was collected by filtration and washed with hexanes (10 mL x 3) to afford a 2.1 g of pure 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (**2.3**) (8mmol, 86%).

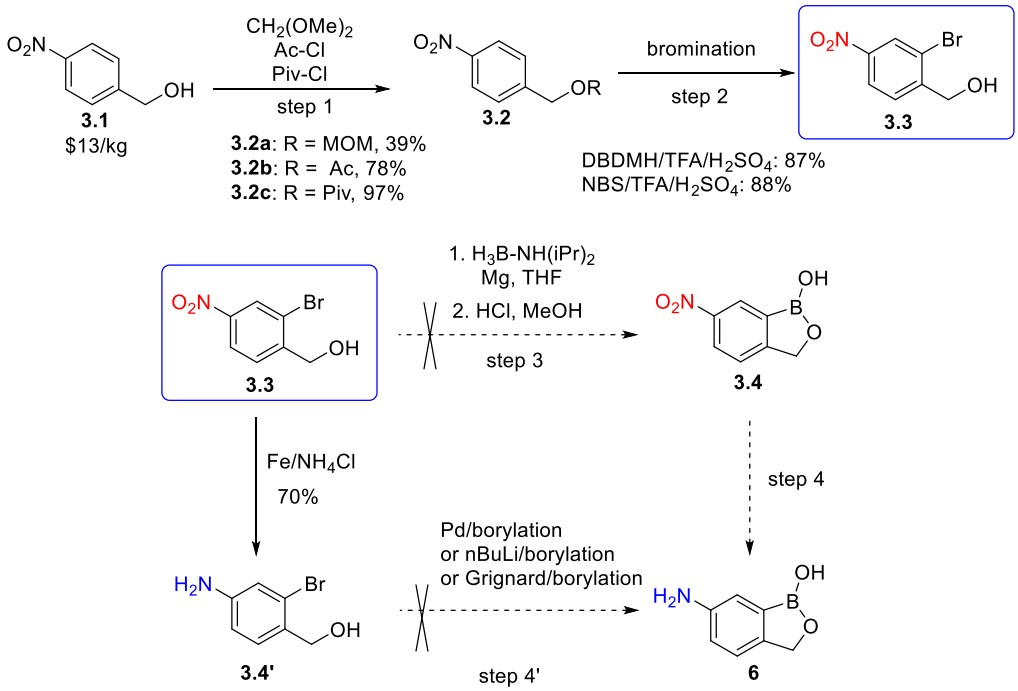
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.6 Hz, 1H), 8.12 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.62 (s, 3H), 1.35 (s, 12H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.9, 145.8, 130.8, 125.5, 84.4, 25.0, 22.6

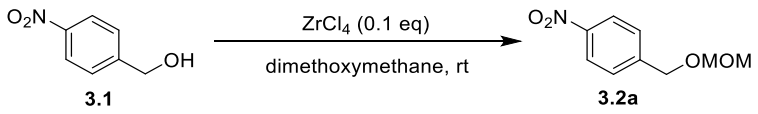
MS (m/z) (M+H): calc. for $C_{13}H_{19}BNO_4$ 264, found 264

Melting Point (uncorrected): 89 – 92 °C

Scheme 3.



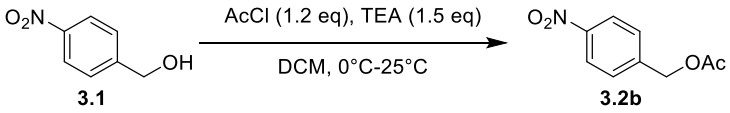
Synthesis of 3.2a (-MOM)



A mixture of (4-nitrophenyl)methanol (10 g, 65.30 mmol, 1 eq) and $ZrCl_4$ (1.52 g, 6.53 mmol, 0.1 *eq*) in dimethoxymethane (30 mL) was stirred at 20 °C for 12 hr. The mixture was concentrated under vacuum. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 10/1) to give **3.2a** (3.5 g, 17.75 mmol, 27% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.70 (s, 2H), 3.42 (s, 3H).

Synthesis of 3.2b (-Ac)

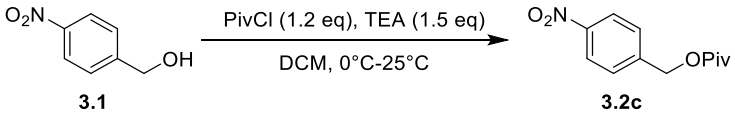


3.1 3.2b

To a solution of (4-nitrophenyl)methanol (**3.1**, 20 g, 130.60 mmol, 1 eq) in DCM (100 mL) was added Ac-Cl (12.30 g, 156.72 mmol, 11.18 mL, 1.2 eq) at 0°C, then the reaction mixture was stirred at 25°C for 5h. TLC showed **3.1** was consumed completely. The reaction solution was washed the saturated $NaHCO_3$ (40 mL), and the organic phase was separated, dried over Na_2SO_4, filtered and concentrated to give **3.2b** (24 g, crude) as a white solid (yield: 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 5.2 (s, 2H), 2.15 (s, 3H).

Synthesis of 3.2c (-Piv)

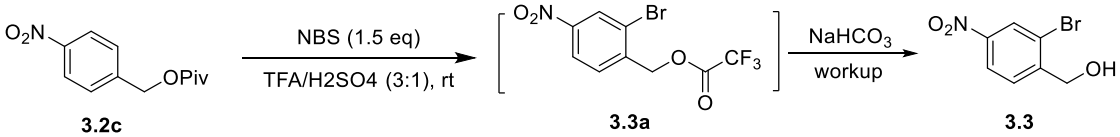


3.1 3.2c

To a solution of (4-nitrophenyl)methanol (**3.1**, 5 g, 32.65 mmol, 1 eq) and TEA (4.96 g, 48.98 mmol, 6.82 mL, 1.5 eq) in DCM (50 mL) was added PivCl (4.72 g, 39.18 mmol, 4.82 mL, 1.2 eq) at 0°C, then the reaction mixture was stirred at 25°C for 8h. TLC showed **3.1** was consumed completely. The reaction mixture was poured into water (30 mL), extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated to give **3.2c** (7.5 g, 31.61 mmol, 97% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 5.2 (s, 2H), 1.25 (s, 9H).

Typical procedure for synthesis of 3.3 from 3.2 (exemplified by using 3.2c)



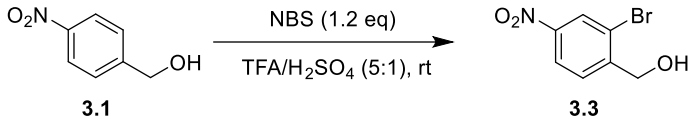
3.2c 3.3a 3.3

To a solution of (4-nitrophenyl)methyl 2,2-dimethylpropanoate (200 mg, 842.99 umol, 1 eq) in H_2SO_4 (1.5 mL, 98% purity) and TFA (5 mL) was added NBS (225.05 mg, 1.26 mmol, 1.5 eq), and the reaction mixture was stirred at 25°C for 8h. And crude ^{1}HNMR indicated the formation of **3.3a**. The reaction was quenched by saturated $NaHCO_3$ solution and **3.3** was isolated by column (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3:1) (170 mg, 0.73 mmol, 87%).

.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 2.4 Hz, 1H), 8.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 4.8 (s, 2H), 2.25 (s, 1H).

Synthesis of 3.3 from 3.1

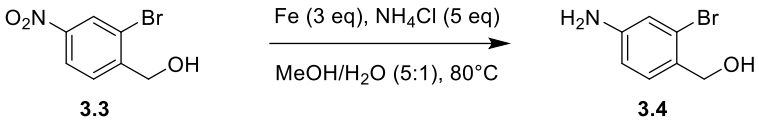


3.1 **3.3**

To a solution of (4-nitrophenyl)methanol (**3.1**, 20 g, 130.60 mmol, 1 eq) in TFA (100 mL) and H_2SO_4 (20 mL) was added NBS (27.89 g, 156.72 mmol, 1.2 eq), and the reaction mixture was stirred at 25 °C for 8h. ^{1}HNMR showed the start material was consumed completely. The reaction was quenched by NaOH solution (4N, 400 mL) followed by saturated Na_2SO_3 solution (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (500 mL×2). The organic phase was combined and washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3:1) to give a desired compound (26 g, 115 mmol, 88% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 2.4 Hz, 1H), 8.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 4.8 (s, 2H), 2.25 (s, 1H).

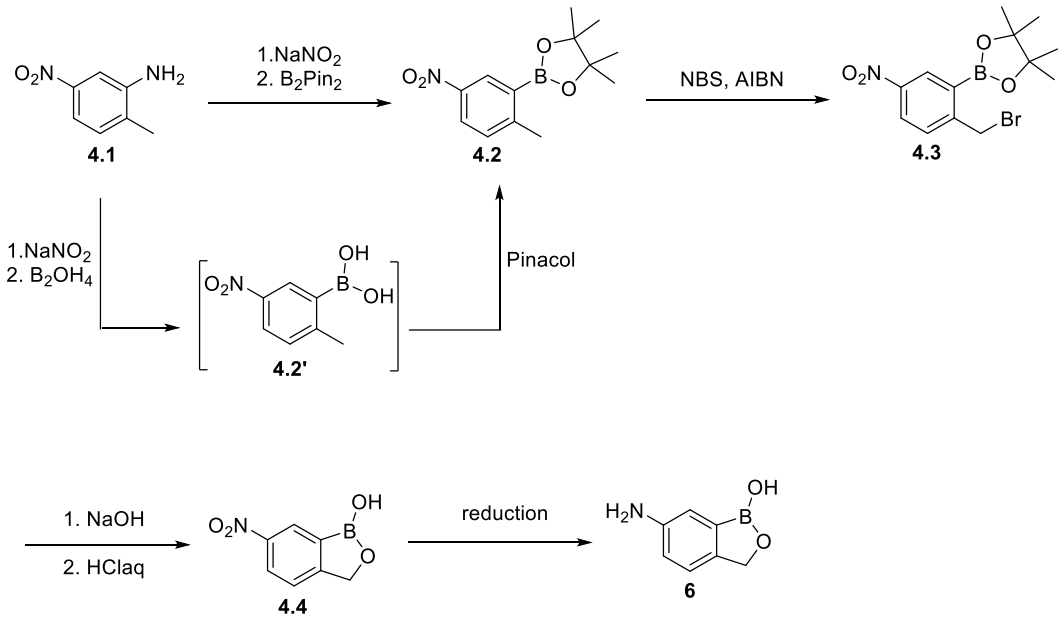
Synthesis of 3.4



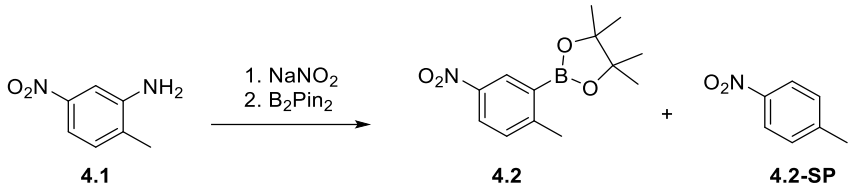
To a solution of (2-bromo-4-nitro-phenyl)methanol (**3.3**, 2 g, 8.62 mmol, 1 eq) and NH_4Cl (2.31 g, 43.10 mmol, 5 eq) in MeOH (30 mL) and H_2O (5 mL) was added Fe (1.44 g, 25.86 mmol, 3 eq), and the reaction mixture was stirred at 80 °C for 2h. TLC showed **3.3** was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to dryness under vacuum. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1 to 2:1) to give **3.4** (1.2 g, 5.94 mmol, 70% yield) as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.64 (s, 2H), 3.73 (s, 2H), 1.90 (s, 1H).

Scheme 4.



Synthesis of 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (4.2) from 2-methyl-5-nitroaniline (4.1)



4.1 4.2 4.2-SP

To an ice-cold suspension of 2-methyl-5-nitroaniline (7.19 g, 1.2 eq, 47.2 mmol) and MeOH (60 mL) was added H_2SO_4 (59.0 mL, 6.0 molar, 9.3 eq, 354.1 mmol). The internal temperature was monitored by J-Kem. The resulting mixture was cooled to 0 °C and a solution of sodium nitrite (4.1 g, 1.5 q, 59.0 mmol) in water (60 mL) was added dropwise using addition funnel, the care being taken not to raise the internal temperature above 10 °C. The mixture was stirred at 0 °C for 30 min at this time the suspension became a clear solution. After consumption of the starting material aniline (monitored by TLC and HPLC), a solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (10 g, 1.0 eq, 39.4 mmol) in methanol (60 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 3 h at rt and the precipitated solid was collected by filtration to give 6.3 g of pure 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane **(4.3)** (61%) as a yellow solid. The filtrate contained mainly deamination side-product **4.2-SP** (1.3 g, 24%).

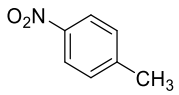
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.6 Hz, 1H), 8.12 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.62 (s, 3H), 1.35 (s, 12H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.9, 145.8, 130.8, 125.5, 84.4, 25.0, 22.6

MS (m/z) (M+H): calc. for $C_{13}H_{19}BNO_4$ 264, found 264

Melting Point (uncorrected): 89 – 92 °C

1-methyl-4-nitrobenzene (4.2-SP)

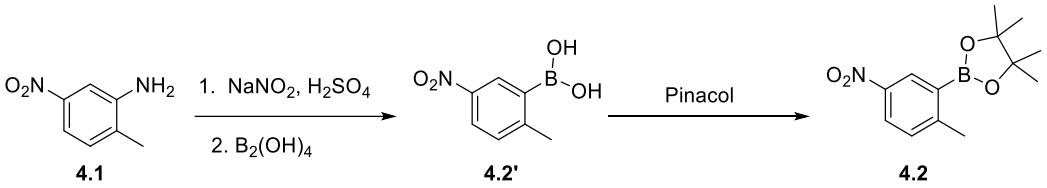


4.2-SP

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.29 (dd, *J* = 8.6 Hz, 1H), 2.44 (s, 3H)

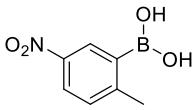
^{13}C NMR (150 MHz, $CDCl_3$) δ 146.1, 129.9, 133.6, 21.7

Synthesis of 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (4.2) from 2-methyl-5-nitroaniline (4.1)



4.1 4.2' 4.2

To an ice-cold suspension of 2-methyl-5-nitroaniline (40.73 g, 1.2 eq, 267.7 mmol) and MeOH (200 mL) was added H_2SO_4 (346 mL, 6.0 molar, 9.3 eq, 2.0 mol). The resulting mixture was cooled to 0 °C and a solution of sodium nitrite (23.1 g, 1.5 eq, 334.6 mmol) in water (60 mL) was added dropwise using addition funnel, the care being taken not to raise the internal temperature above 10 °C. The resulting mixture was stirred at 0 °C for 30 min at this time the suspension became a clear solution. After consumption of the starting material aniline (monitored by TLC and HPLC), a solid of tetrahydroxy diborane (20 g, 1.0 eq, 223.1 mmol) was added in portion-wise within 10 min at 0 °C. The resulting mixture was stirred for 24 h at rt. After the reaction was completed (Checked by TLC and HPLC), the MeOH was removed by rotovap, and the resulting aqueous solution was extracted with ethyl acetate (3 x 200 mL). The combined organic layer was rotavapped to dryness to get a crude mixture of the desired boronic acid and the *p*-nitrotoluene. The solid crude mixture was then washed with hexanes (3 x 50 mL) to completely remove the non-polar side product *p*-nitrotoluene and the resulting residue was triturated from ethyl acetate (50 mL) to afford the pure boronic acid **4.2′** as a yellow solid (18 g, 100 mmol, yield: 45%, 98% qNMR purity). To a solution of pure boronic acid (2 g, 1.0 eq, 11 mmol) in dry DCM (20 mL) was added pinacol (1.32 g, 1.0 eq, 11.1 mmol) and sodium sulfate (3.17 g, 2.0 eq, 22.3 mmol). The resulting mixture was stirred at rt for overnight. After completion (monitored by TLC and HPLC), the inorganic salts were filtered off and washed with DCM. The combined organic phase was evaporated to dryness to get **4.2** (2.3 g, 78%) as a pale-yellow solid with the 96% of qNMR purity, the characterization data from this two-step protocol is the same as previously synthesized **4.2**.



4.2'

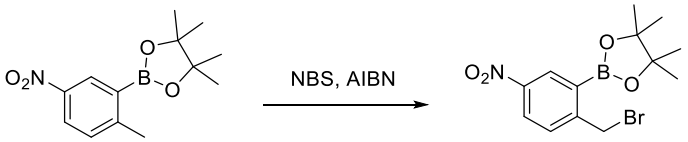
^{1}H NMR (600 MHz, DMSO): δ 8.27 (d, *J* = 2.6 Hz, 1H), 8.08 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 2.52 (s, 3H)

^{13}C NMR (150 MHz, DMSO): δ 152.0, 144.9, 130.6, 127.7, 123.5, 22.2

MS (m/z) (M+H): calc. for $C_7H_9BNO_4$ 182, found 182

Melting Point (uncorrected): 56 – 57 °C

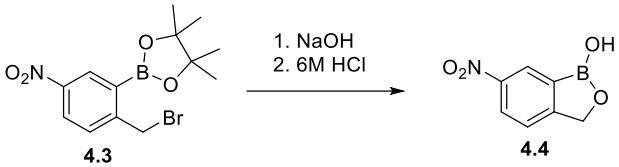
Synthesis of 2-(2-(bromomethyl)-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3) from 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (4.2)



4.2 4.3

A solution of 4,4,5,5-tetramethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborolane (1 g, 1.0 eq, 3.8 mmol), in CH_3CN (20 mL) was degassed with N_2 for 5 min at rt, then AIBN (62.4 mg, 0.1 eq, 380.0 µmol) and *N*-bromosuccinimide (0.81 g, 1.2 eq, 4.5 mmol) were added. The reaction mixture was then stirred at 80°C for 12h. After HPLC and LCMS showed the starting material was consumed completely the reaction mixture was cooled to 25°C, and concentrated under reduced pressure to give a crude residue. The residue was quenched by the saturated Na_2SO_3 (15 mL) and Na_2CO_3 (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude product in quantitative yield. The crude mixture was triturated from water for the next step without further purification.

Synthesis of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (4.4) from 2-(2-(bromomethyl)-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3)



4.3 4.4

To a solution of 2-(2-(bromomethyl)-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16 g, 1.0 eq, 47.8 mmol) in THF (100 mL) and H_2O (30 mL) was added sodium hydroxide (8.2 g, 5.0 eq, 205 mmol), and the reaction mixture was stirred at 50°C for 2h. Once completed (monitored by TLC, and LCMS), the mixture was cooled down to 25°C. To this was added hydrogen chloride (67 mL, 6.0 molar, 10.0 eq, 41.0 mmol) at 25°C, and the reaction mixture was stirred at 50°C for additional 8h. TLC showed that the starting material was consumed completely. The reaction mixture was cooled to rt and the volatiles was removed by rotovap and the resulting precipitates were collected by filtration. The filter cake was washed with water (20 mL), dried under vacuum to give the crude solid. The solid was triturated from EtOAc (14 mL) to afford the pure **4.4** as a yellow solid (7 g, 39 mmol, yield: 82%, 95% qNMR purity).

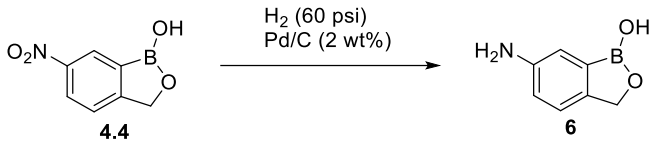
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52-8.45 (m, 1H), 8.27-8.19 (m, 1H), 7.65-7.58 (m, 1H), 5.07 (s, 2H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.6, 147.1, 132.3 (C-B), 125.6, 125.5, 122.9, 70.1

MS (m/z) (M+H): calc. for $C_7H_7BNO_4$ 180, found 180

Melting Point (uncorrected): 175 – 177 °C

Synthesis of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (6) from 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (4.4) under batch conditions



In a Parr reactor containing a solution of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (0.5 g, 1.0 eq, 2.8 mmol) in THF (12.0 mL) was added 10 wt% of palladium on carbon (0.1 g, 2 wt%). The resulting mixture was degassed with N_2 four times, followed by H_2 two times. The mixture was stirred under H_2 atmosphere (60 psi) at 25°C for 36 h. During the course, the reaction was monitored by ^{1}H NMR. After completion (about 36 h), the reaction solution was filtered through a short pad of celite. The filter cake was washed with methanol, and all filtrates were combined and evaporated to afford 0.37 g of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (**6**) as a foamy orange solid (2.4 mmol, 86%, purity 97% by HPLC area percentage). Analytical data is the same as the one prepared from **1.5** (as shown in step 5, Scheme 1).

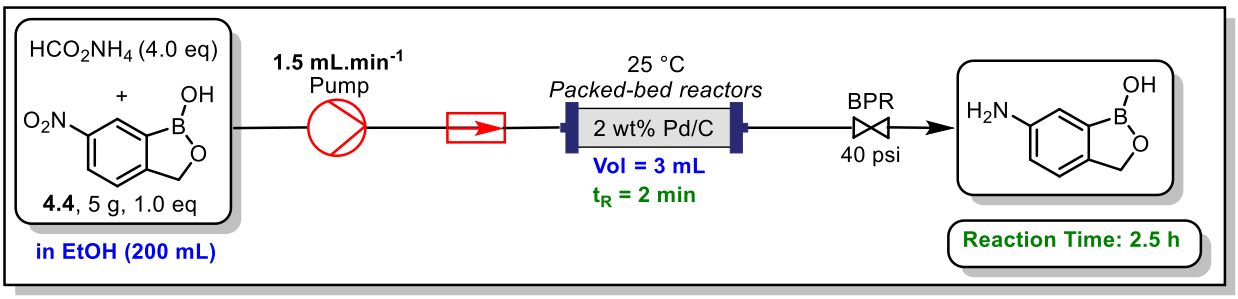
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.03 (d, J = 8.07 Hz, 1H), 6.89 (d, J = 2.02 Hz, 1H), 6.70 (dd, J = 2.20, 8.07 Hz, 1H), 4.98 (brs, 2H), 4.81 (s, 2H)

^{13}C NMR (150 MHz, DMSO-d_6): δ 147.5, 141.4, 131.0 (C-B), 121.4, 117.6, 114.6, 69.6

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_7H_8BNO_2$ 150.0721; Found 150.0723

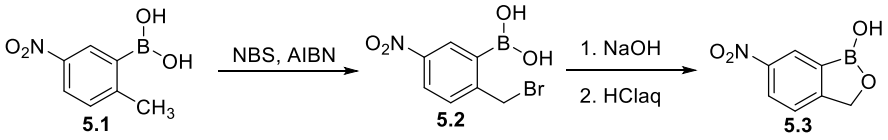
Melting Point (uncorrected): 147 – 150 °C

Synthesis of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (6) from 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (4.4) continuous flow conditions

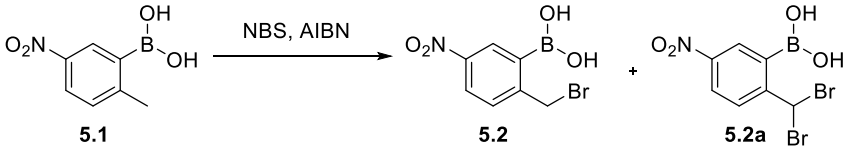


A pre-mixed solution of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (5.0 g, 1.0 eq, 28 mmol), and ammonium formate (7.0 g, 4.0 eq, 112 mmol) in EtOH (200 mL) was pumped using a Vapourtec-E series flow reactor to a prepacked Pd/C (1 g, 2 wt%) Omnifit-reactor (3 mL) at a flow rate of 1.5 mL/min. After 2.5 h the completed reaction mixture was collected at the end port. The resulting solution was evaporated to dryness. The residue was triturated from ethyl acetate to afford 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (**6**) as a pale yellowish solid (3.96 g, 26.4 mmol, yield: 92%, 99.4 wt%). Analytical data is the same as above.

Scheme 5.

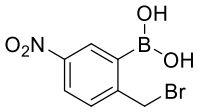


Synthesis of bromide 5.2 from (2-methyl-5-nitrophenyl)boronic acid 5.1



A mixture of (2-methyl-5-nitrophenyl)boronic acid (10.0 g, 1.0 eq, 55.3 mmol), AIBN (1.1 g, 0.1 eq, 5.52 mmol) and *N*-bromosuccinimide (10.8 g, 1.1 eq, 60.8 mmol) in CH_3CN (200 mL) was stirred at 25°C for 10 min. The resulting clear solution was then stirred at 80°C for 1h. After completion (monitored by HPLC), the reaction mixture was cooled to 25 °C, and concentrated to dryness under reduced pressure. The residue was then triturated with H_2O (30 mL x 2) to give a

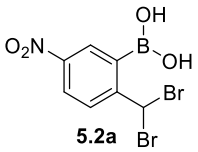
crude solid product (11.9 g, 83% yield) as a mixture of 80% mono-bromo (**5.2**) and 10% di-bromo (**5.2a**). The crude mixture was as such used for the next step without further purification. For analytic data, the mixture was purified by prep-HPLC.



5.2

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.36 (d, *J* = 2.51 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 4.99 (s, 2H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 160.7, 147.3, 132.5, 125.9, 125.8, 123.3, 70.3.

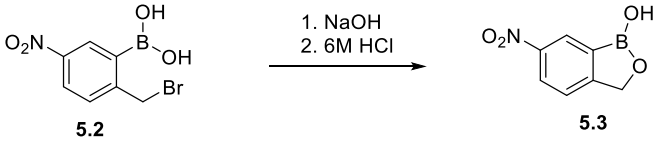


5.2a

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.38 (d, *J* = 2.5 Hz, 1H), 8.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 152.9, 147.3, 132.6, 131.5, 129.1, 125.9, 40.4.

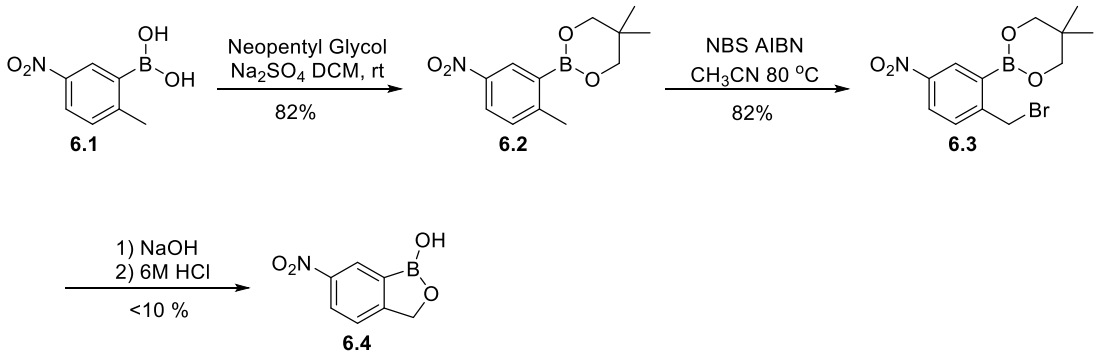
Synthesis of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (5.3) from (2-(bromomethyl)-5-nitrophenyl)boronic acid (5.2)



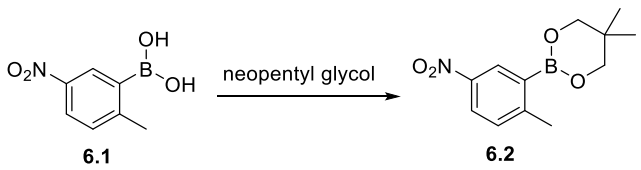
5.2 **5.3**

To a solution of the mixture of (2-(bromomethyl)-5-nitrophenyl)boronic acid (10.0 g, 1.0 eq, 38.5 mmol) in THF (170 mL) and H_2O (30 mL) was added sodium hydroxide (4.6 g, 3.0 eq, 115.4 mmol). The reaction mixture was stirred at 50 °C for 2h during this time a lot of solid will precipitate out. After the reaction was completed (checked by LCMS and HPLC), the mixture was cooled to 25 °C, and then aq HCl (32 mL, 6 molar, 5.0 eq, 192.4 mmol) was added at this time the reaction mixture will become completely homogeneous. The resulting mixture was stirred at 50 °C for 8h. After the starting material was consumed completely (monitored by TLC), the reaction mixture was cooled to rt and concentrated under reduced pressure to about 50 mL volume. The resulting suspension was filtered and the filter cake was rinsed with ~30 mL of water, then dried under a high vacuum to give a crude brown solid. Titration with EtOAc (12 mL) gave 5.23 g of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (**5.3**) as a yellowish solid (29.2 mmol, yield: 72%, 95% qNMR purity).

Scheme 6.



Synthesis of 5,5-dimethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborinane (6.2)



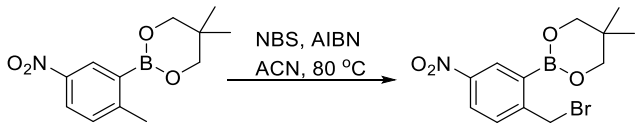
To a solution of boronic acid (**6.1**, 4.89 g, 1.0 eq, 27.0 mmol) in dry DCM (100 mL) was added neopentyl glycol (2.8 g, 1.0 eq, 27.0 mmol) and sodium sulfate (7.7 g, 2.0 eq, 55.3 mmol). The resulting mixture was stirred at rt for overnight, after the completion of reaction (monitored by TLC and HPLC), the inorganic salts were filtered off and washed with DCM. The combined organic phase was evaporated to dryness to give 5.6 g of 5,5-dimethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborinane (**6.2**) as an off-white solid (22.4 mmol, yield: 82%, 98% qNMR purity).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.57 (d, *J* = 2.6 Hz, 1H), 8.07 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 4H), 2.59 (s, 3H), 1.03 (s, 6H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.3, 145.8, 131.0, 130.0, 124.8, 72.6, 31.8, 22.7, 21.9

Melting Point (uncorrected): 95 – 96 °C

Synthesis of 2-(2-(bromomethyl)-5-nitrophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (6.3) from 5,5-dimethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborinane (6.2)

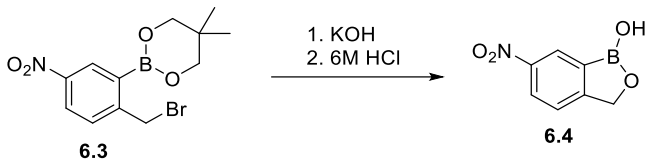


6.2 **6.3**

To a solution of 5,5-dimethyl-2-(2-methyl-5-nitrophenyl)-1,3,2-dioxaborinane (2 g, 1.0 eq, 8.0 mmol) and AIBN (0.13 g, 0.1 eq, 803 μmol) in CH_3CN (40 mL) was added *N*-bromosuccinimide (1.71 g, 1.2 eq, 9.6 mmol) at 25°C. The reaction mixture was degassed with N_2 for 5 min and then heated to 80°C, and stirred at 80°C for 8h. LCMS showed that the starting material was consumed completely and the desired bromide was formed. The reaction mixture was cooled to 25°C, and concentrated under reduced pressure to give a residue. The residue was quenched by the saturated Na_2SO_3 (15 mL) and Na_2CO_3 (15 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced

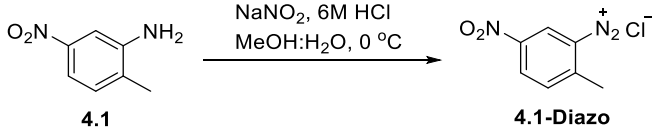
pressure to give crude mono-bromo (**6.3**) in a quantitative yield. The crude mixture was used for the next step without further purification.

Synthesis of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (6.4) from 2-(2-(bromomethyl)-5-nitrophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (6.3)



To a solution of the mixture of 2-(2-(bromomethyl)-5-nitrophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (1 g, 1.0 eq, 6.4 mmol) in THF (20 mL) and H_2O (5 mL) was added potassium hydroxide (1.8 g, 5.0 eq, 32.3 mmol) and the reaction mixture was stirred at 50°C for 2h, once the reaction is completed (monitored by TLC, and LCMS), the mixture was cooled down to 25°C and to this was added aq HCl (32 mL, 6 molar, 30.0 eq, 193.9 mmol) at 25°C, and the reaction mixture was stirred at 50°C for additional 8h. TLC showed the starting material was consumed completely. The reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude was material purified via combi-flash chromatography (25 g SiO_2 cartridge, 0-10% ethyl acetate in hexanes) twice to get 0.1 g of 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol (**6.4**) as an yellowish solid (0.56 mmol, yield: 9%). Analytical data are the same as **4.4**.

Synthesis of 2-methyl-5-nitrobenzenediazonium salt (4.1-Diazo) from 2-methyl-5-nitroaniline (4.1)



To an ice-cold solution of 2-methyl-5-nitroaniline (1.0 g, 1.0 eq, 6.8 mmol) in methanol (20 mL) was added aq. HCl (10.2 mL, 6. 0 M, 9.3 eq, 61.1 mmol). To this mixture was added a solution of sodium nitrite (0.59 g, 1.3 eq, 8.5 mmol) in water (10 mL) dropwise using addition funnel. The

resulting mixture was stirred at 0 °C for 1h (Monitored by TLC, HPLC). After completion, the solid was collected by filtration and washed with methanol to afford 1.29 g of 2-methyl-5-nitrobenzenediazonium salt (**4.1-Diazo**) as a brown solid (yield: 98%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.64 (d, *J* = 2.3 Hz, 1H), 8.93 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 2.98 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.9, 138.1, 126.1, 125.9, 119.4, 109.3, 9.6

HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_6N_3O_2^+$ 164.0455; Found 164.0456

Acknowledgements

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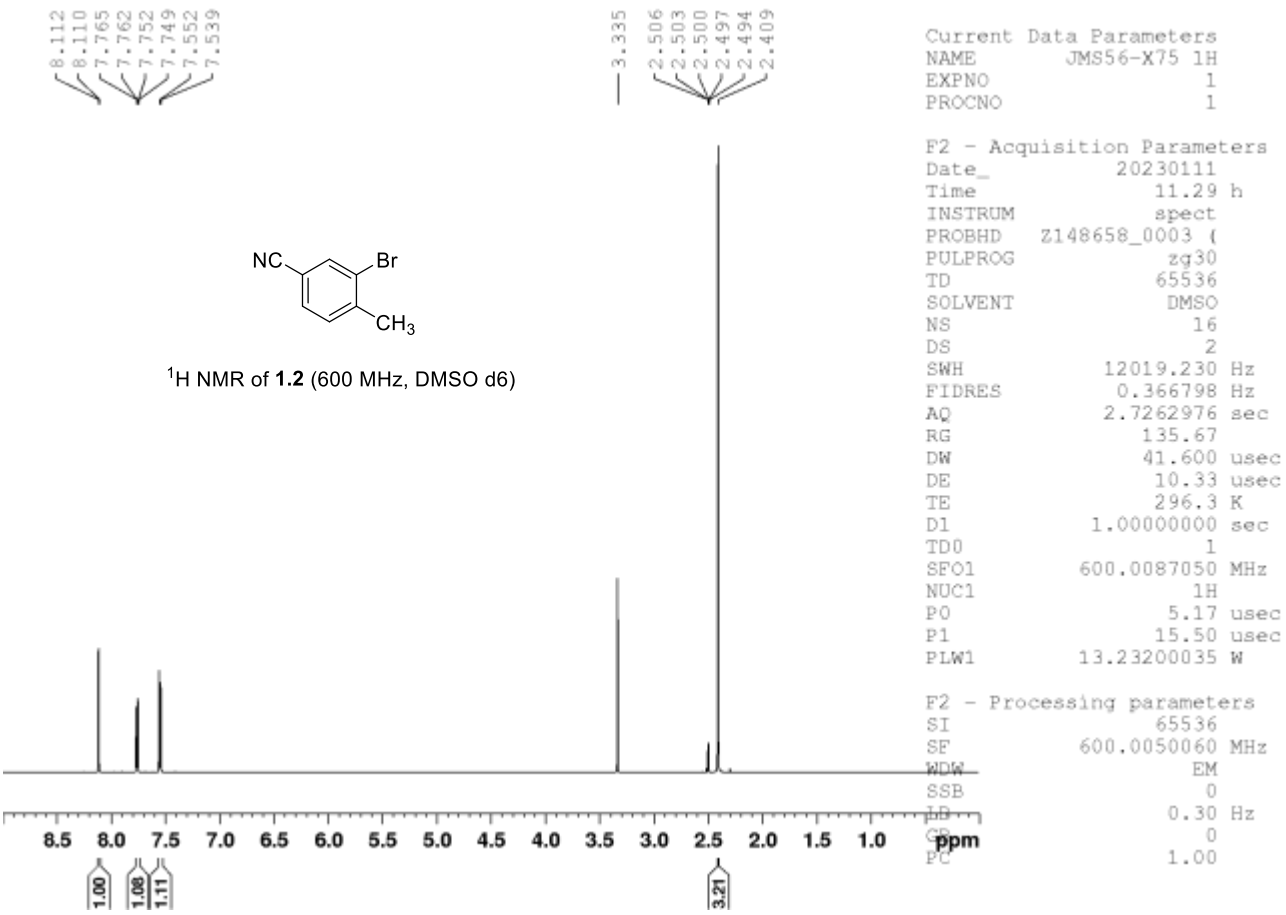
^{1}H and ^{13}C NMR Spectra



^{1}H NMR of **1.2** (600 MHz, DMSO d6)

```
Current Data Parameters
NAME        JMS56-X75 1H
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230111
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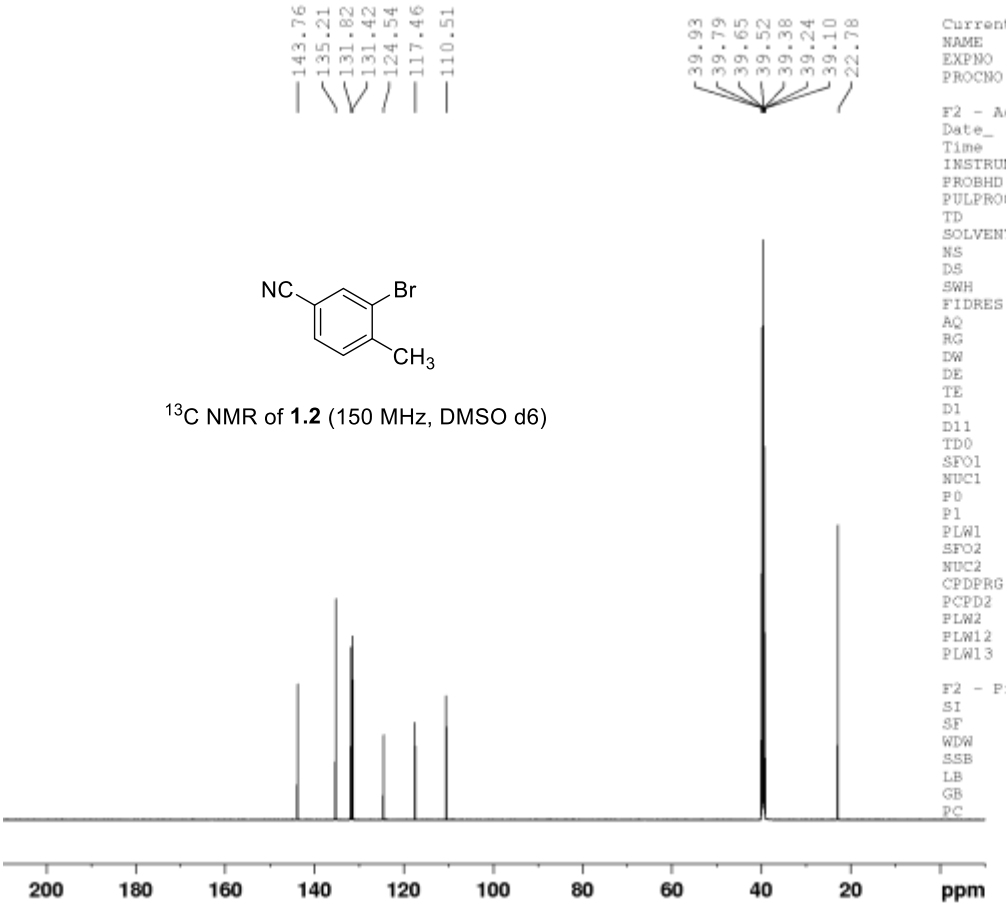
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT           DMSO
NS                  16
DS                   2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG               135.67
DW               41.600 usec
DE               10.33 usec
TE               296.3 K
D1            1.00000000 sec
TD0                  1
SFO1         600.0087050 MHz
NUC1                1H
P0                5.17 usec
P1               15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050060 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```



^{13}C NMR of **1.2** (150 MHz, DMSO d6)

```
Current Data Parameters
NAME       JMS56-X75 13C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230112
Time               5.29 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 5000
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 usec
DE                 6.50 usec
TE                298.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1         150.8864644 MHz
NUC1                 13C
P0                 4.00 usec
P1                12.00 usec
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                 1H
CPDPRG[2         waltz65
PCPD2             70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF           150.8714518 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
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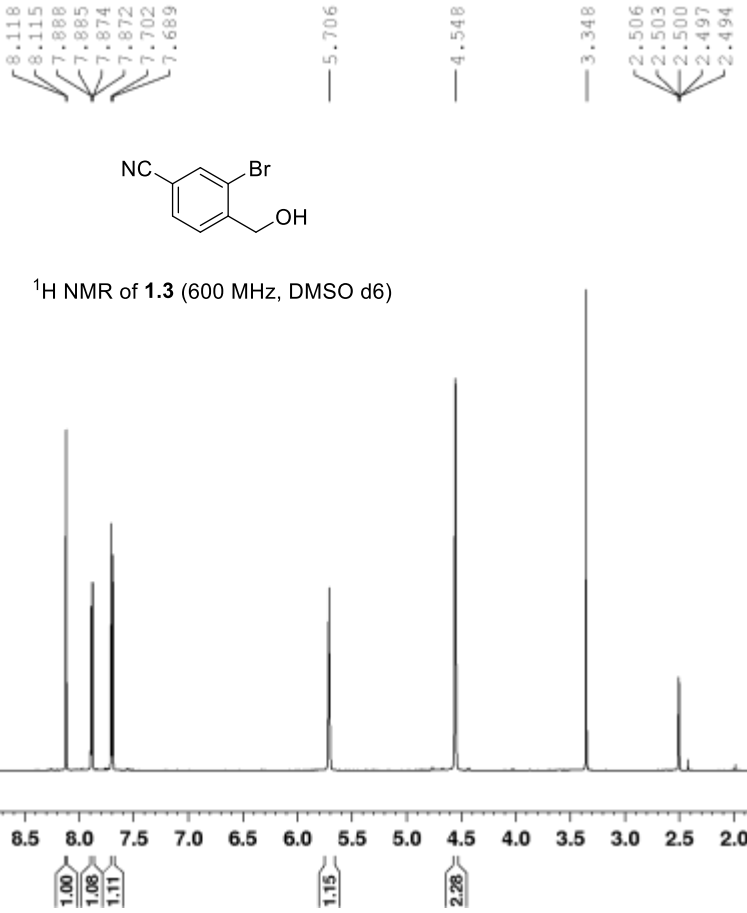

^{1}H NMR of **1.3** (600 MHz, DMSO d6)

```
Current Data Parameters
NAME        JMS56-X77 1H
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230125
Time              11.22 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG               135.67
DW               41.600 usec
DE               10.33 usec
TE               296.4 K
D1            1.00000000 sec
TD0                   1
SFO1         600.0087050 MHz
NUC1                 1H
P0                5.17 usec
P1               15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI                65536
SF           600.0050060 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
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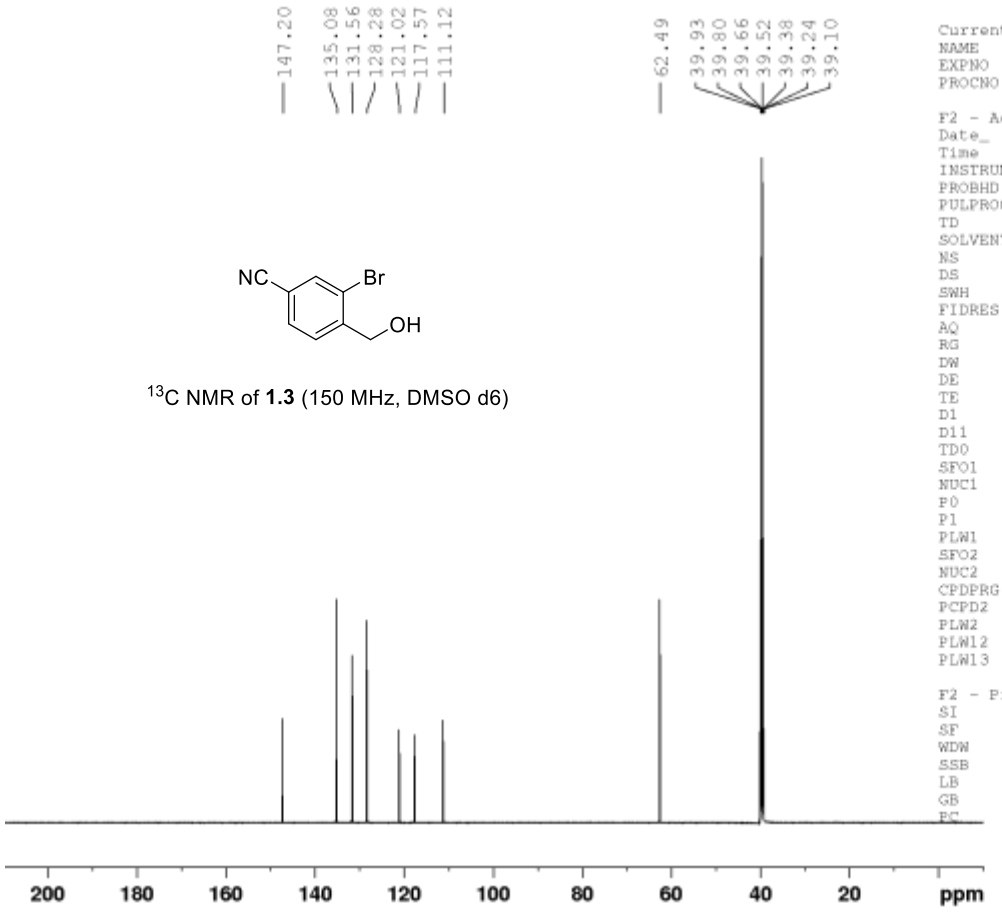

^{13}C NMR of **1.3** (150 MHz, DMSO d6)

```
Current Data Parameters
NAME       JMS56-X77 13C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230126
Time               2.55 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 5000
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 usec
DE                 6.50 usec
TE                297.6 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1         150.8864644 MHz
NUC1                 13C
P0                 4.00 usec
P1                12.00 usec
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                 1H
CPDPRG[2         waltz65
PCPD2              70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF         150.8714484 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
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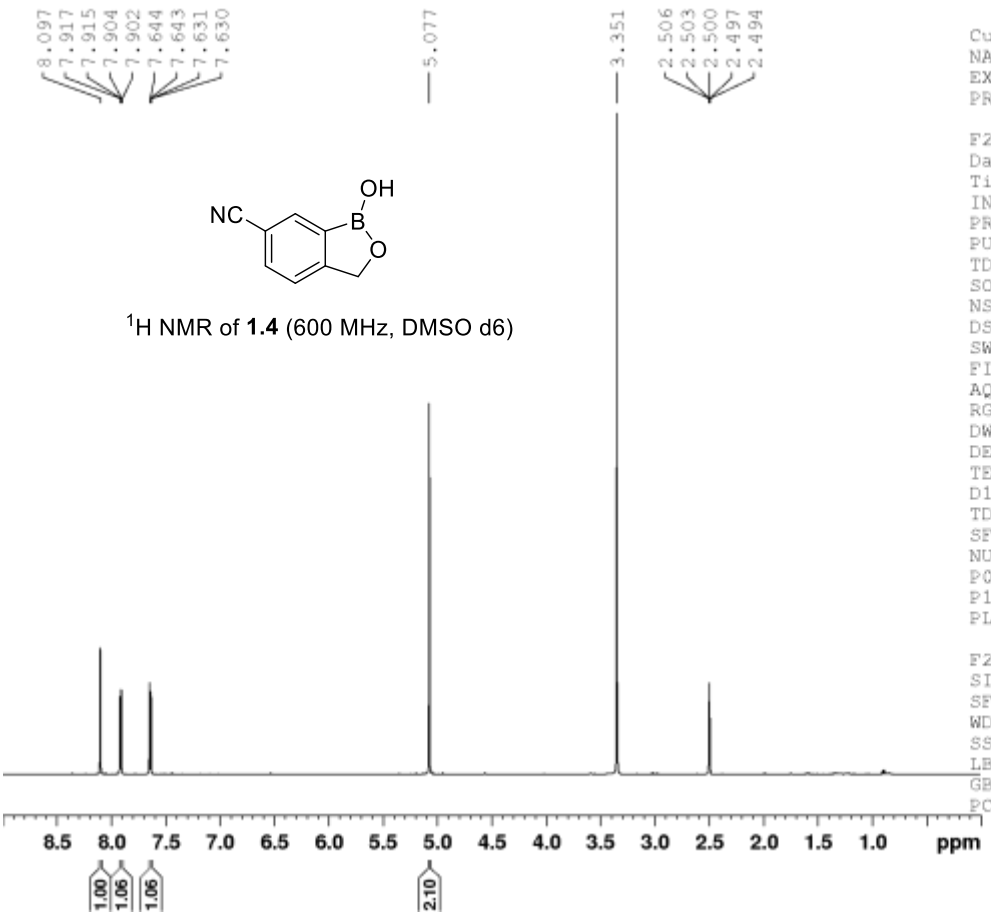
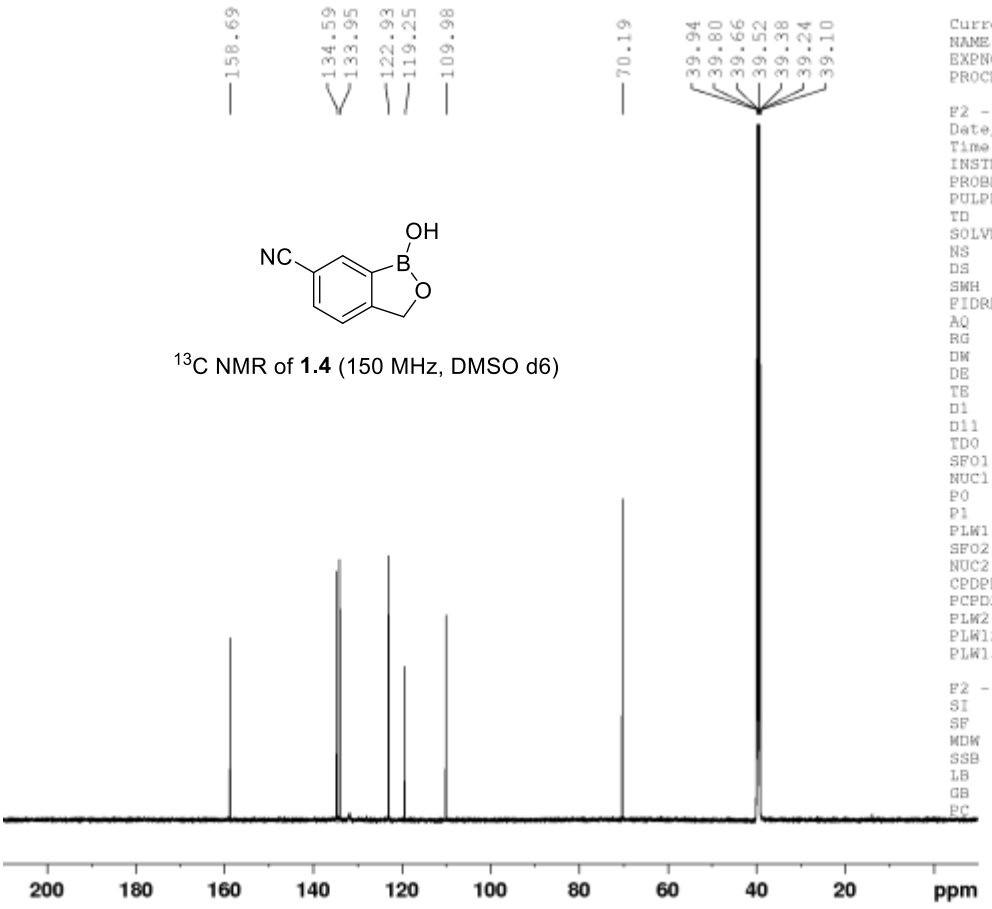


^{1}H NMR of **1.4** (600 MHz, DMSO d6)

```
Current Data Parameters
NAME        JMS56-X80 1H
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230206
Time             10.16 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT           DMSO
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               199.73
DW               41.600 usec
DE               10.33 usec
TE               296.4 K
D1           1.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                1H
P0               5.17 usec
P1               15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050061 MHz
WDW                 EM
SSB                  0
LB               0.30 Hz
GB                   0
PC                1.00
```

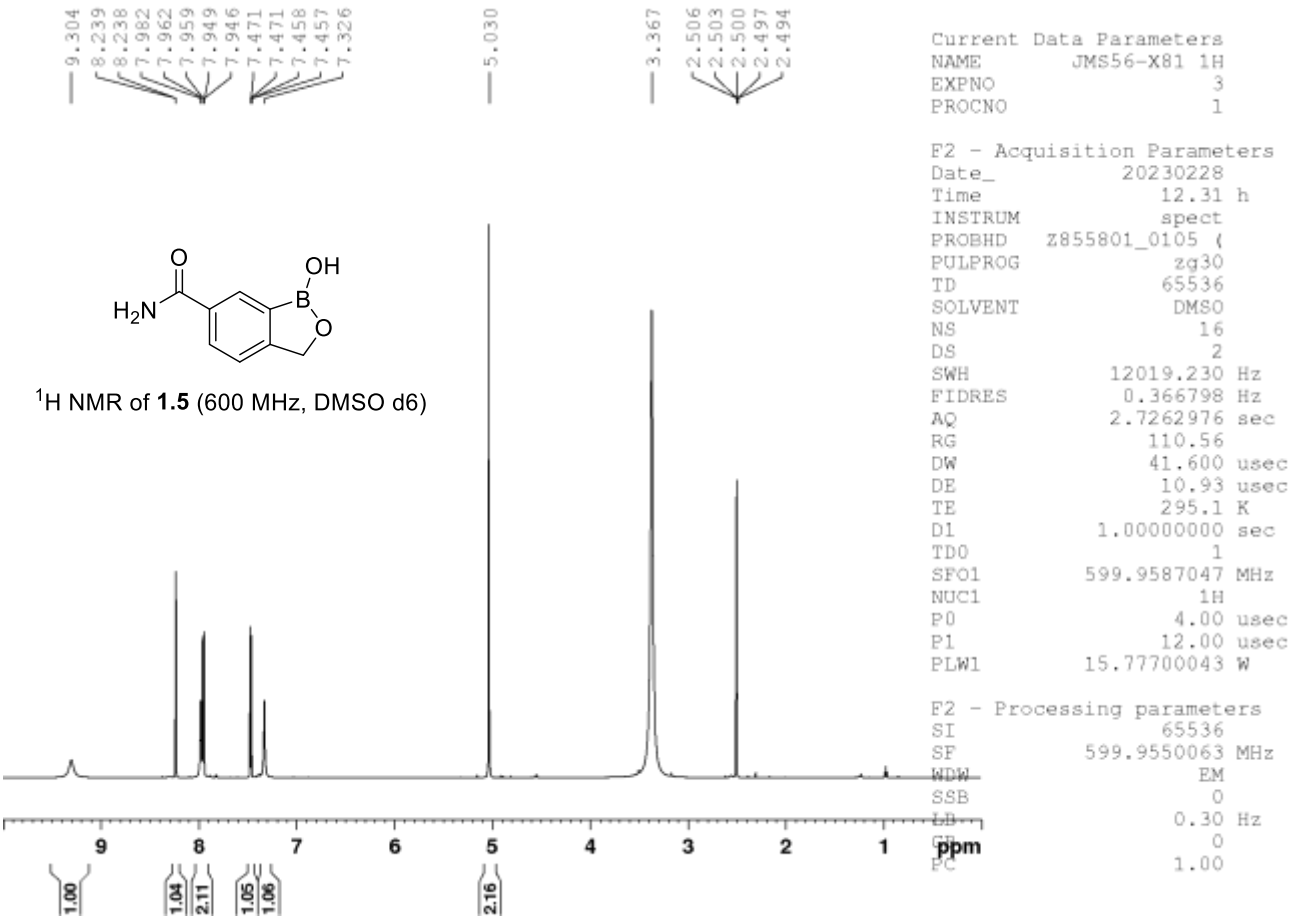


^{13}C NMR of **1.4** (150 MHz, DMSO d6)

```
Current Data Parameters
NAME       JMS56-X80 13C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230207
Time               1.44 h
INSTRUM           spect
PROBHD   2148658_0003 (
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                5000
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG               199.73
DW               13.800 usec
DE                6.50 usec
TE               297.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1       150.8864644 MHz
NUC1               13C
P0                4.00 usec
P1               12.00 usec
PLW1       77.65699768 W
SFO2       600.0074000 MHz
NUC2               1H
CPDPRG[2       waltz65
PCPD2            70.00 usec
PLW2       13.23200035 W
PLW12       0.64876997 W
PLW13       0.32633001 W

F2 - Processing parameters
SI                32768
SF         150.8714461 MHz
WDW                EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

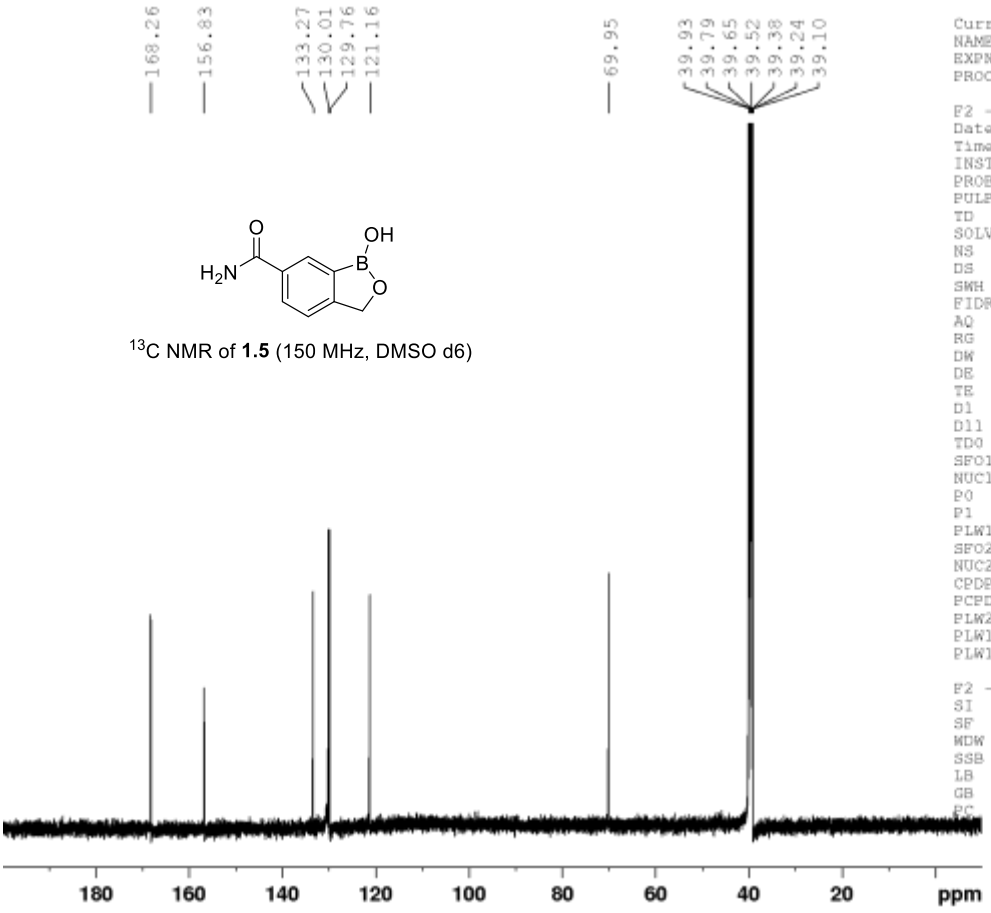


^{1}H NMR of **1.5** (600 MHz, DMSO d6)

```
Current Data Parameters
NAME        JMS56-X81 1H
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20230228
Time             12.31 h
INSTRUM            spect
PROBHD   Z855801_0105 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                110.56
DW                41.600 usec
DE                10.93 usec
TE                295.1 K
D1            1.00000000 sec
TD0                    1
SFO1         599.9587047 MHz
NUC1                  1H
P0                 4.00 usec
P1                12.00 usec
PLW1         15.77700043 W

F2 - Processing parameters
SI                 65536
SF          599.9550063 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

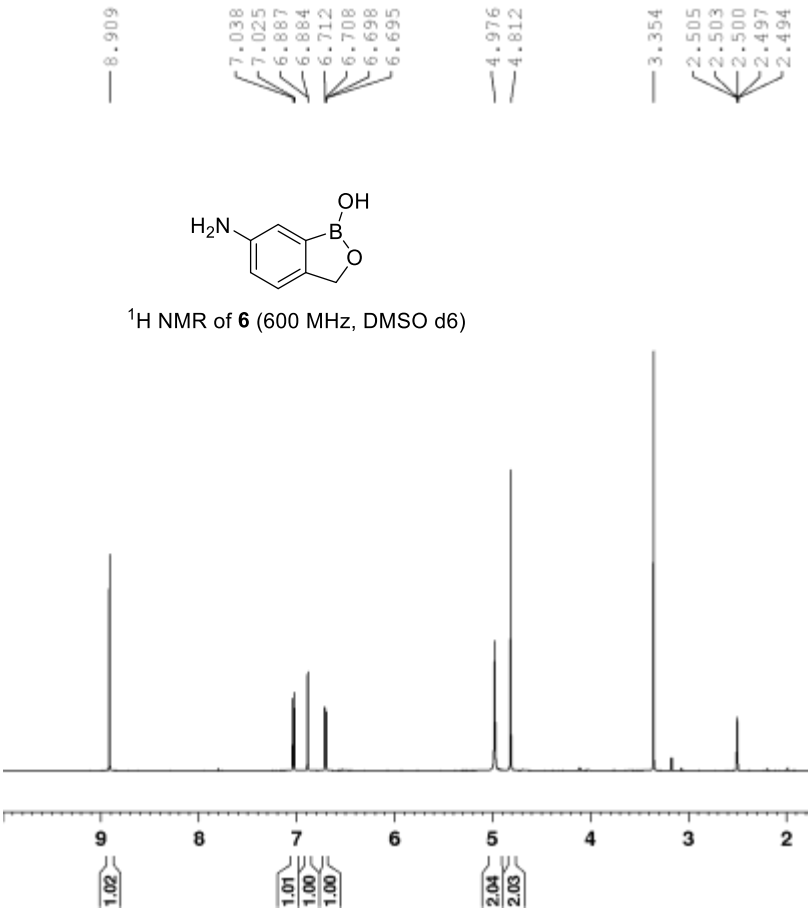


^{13}C NMR of **1.5** (150 MHz, DMSO d6)

```
Current Data Parameters
NAME       JMS56-X81 13C
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230302
Time               2.52 h
INSTRUM           spect
PROBHD   Z855801_0105 (
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                5000
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG               194.75
DW               13.800 usec
DE                6.50 usec
TE               296.6 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                  1
SFO1       150.8738906 MHz
NUC1               13C
P0                3.67 usec
P1               11.00 usec
PLW1      178.30999756 W
SFO2       599.9573998 MHz
NUC2               1H
CPDPRG[2       waltz65
PCPD2             70.00 usec
PLW2       15.77700043 W
PLW12       0.46366000 W
PLW13       0.23322000 W

F2 - Processing parameters
SI                32768
SF         150.8588751 MHz
WDW                EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.40
```

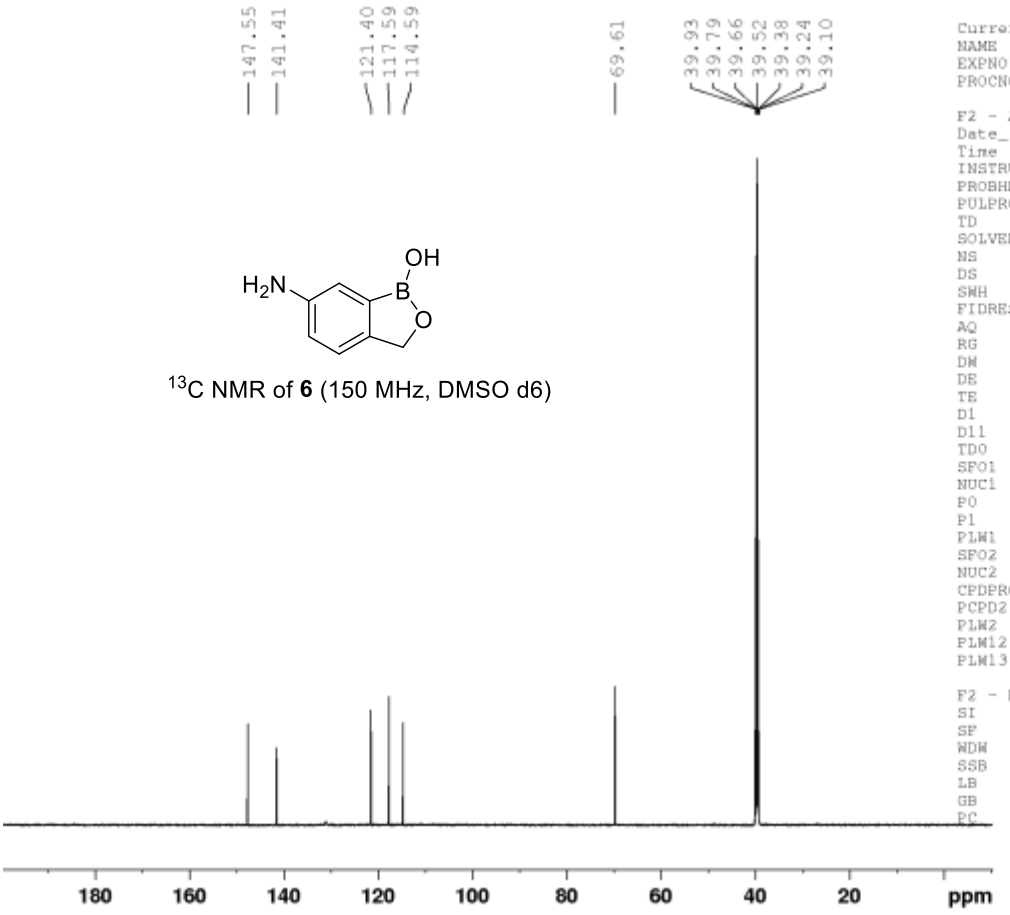


^{1}H NMR of **6** (600 MHz, DMSO d6)

```
Current Data Parameters
NAME        JMS56-X74 1H
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230221
Time              13.18 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                199.73
DW                41.600 usec
DE                10.33 usec
TE                296.2 K
D1            1.00000000 sec
TD0                    1
SFO1          600.0087050 MHz
NUC1                  1H
P0                  5.17 usec
P1                 15.50 usec
PLW1          13.23200035 W

F2 - Processing parameters
SI                 65536
SF          600.0050061 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

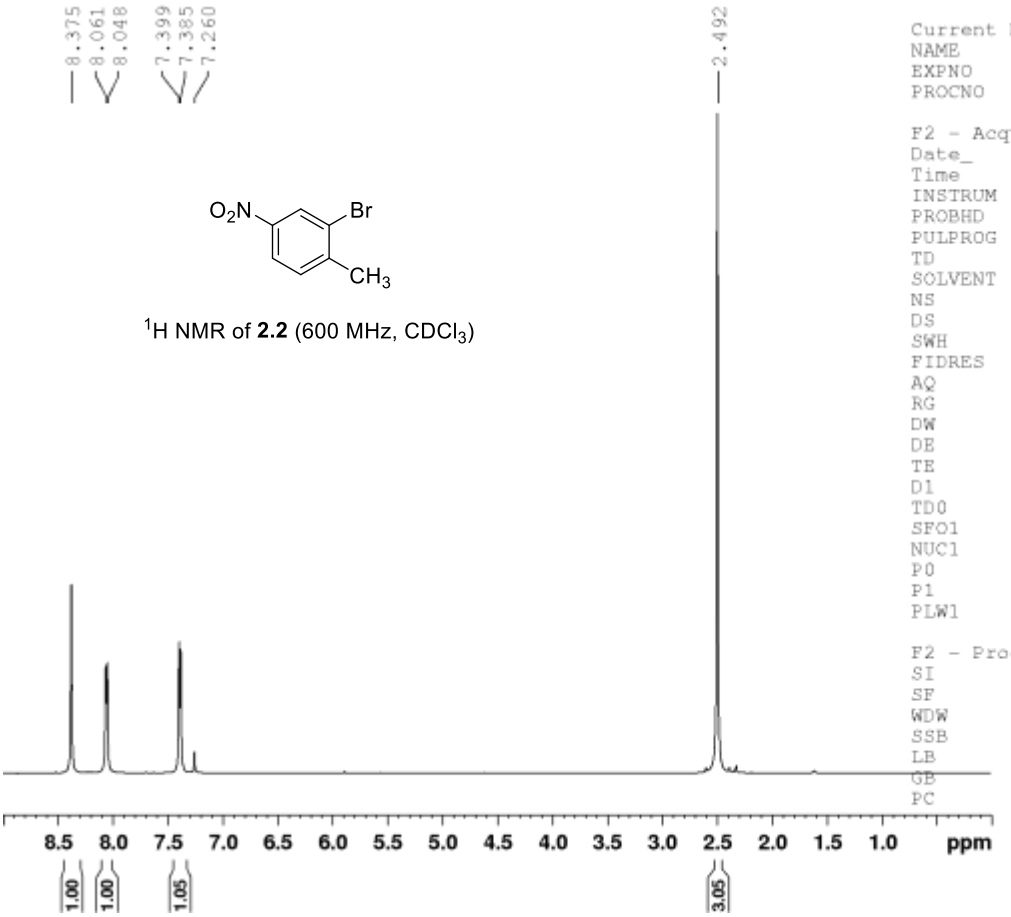


^{13}C NMR of **6** (150 MHz, DMSO d6)

```
Current Data Parameters
NAME       JMS56-X74 13C
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20230302
Time               7.05 h
INSTRUM           spect
PROBHD   Z855801_0105 (
PULPROG         zgpg30
TD              65536
SOLVENT          DMSO
NS               5000
DS                  4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG              194.75
DW              13.800 usec
DE               6.50 usec
TE              296.9 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                 1
SFO1       150.8738906 MHz
NUC1               13C
P0                3.67 usec
P1               11.00 usec
PLW1      178.30999756 W
SFO2       599.9573998 MHz
NUC2               1H
CPDPRG[2       waltz65
PCPD2            70.00 usec
PLW2       15.77700043 W
PLW12       0.46366000 W
PLW13       0.23322000 W

F2 - Processing parameters
SI                32768
SF         150.8588756 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```



^{1}H NMR of **2.2** (600 MHz, $CDCl_3$)

```
Current Data Parameters
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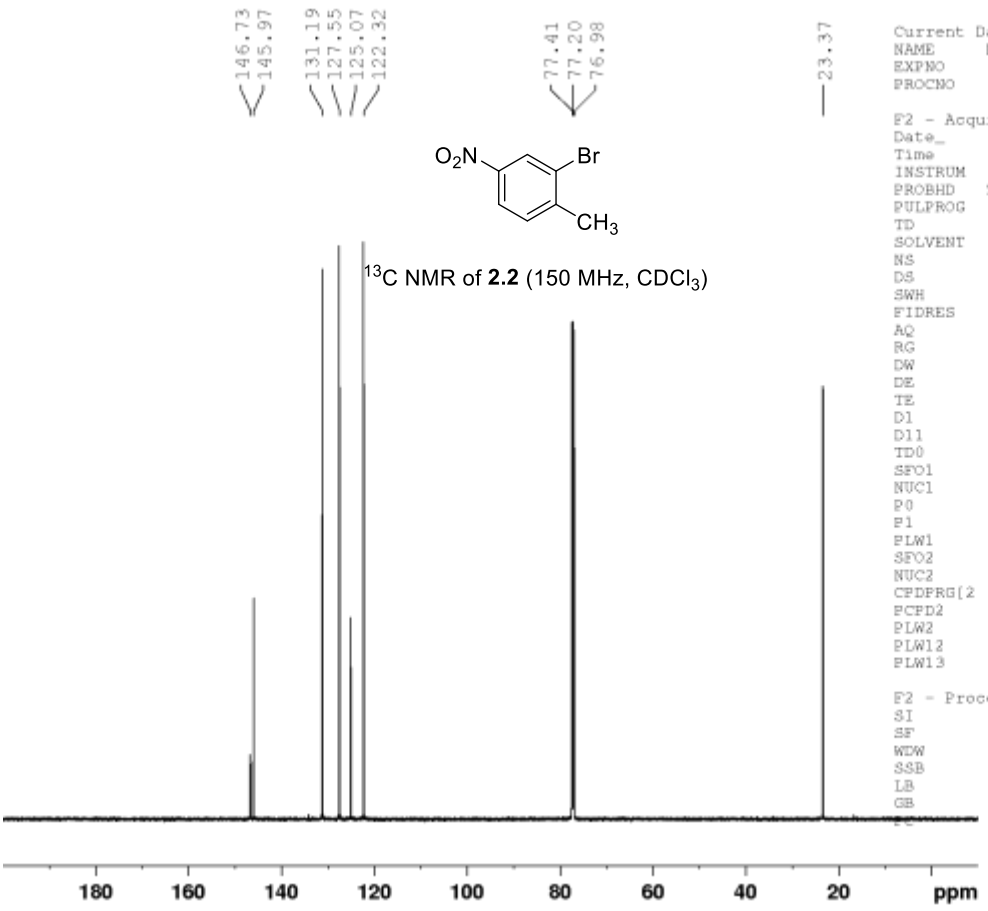
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20230106
Time             17.35 h
INSTRUM          spect
PROBHD   Z148658_0003 (
PULPROG          zg30
TD              65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               89.69
DW              41.600 usec
DE              10.33 usec
TE              296.8 K
D1           1.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                 1H
P0               5.17 usec
P1              15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI              65536
SF          600.0050160 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

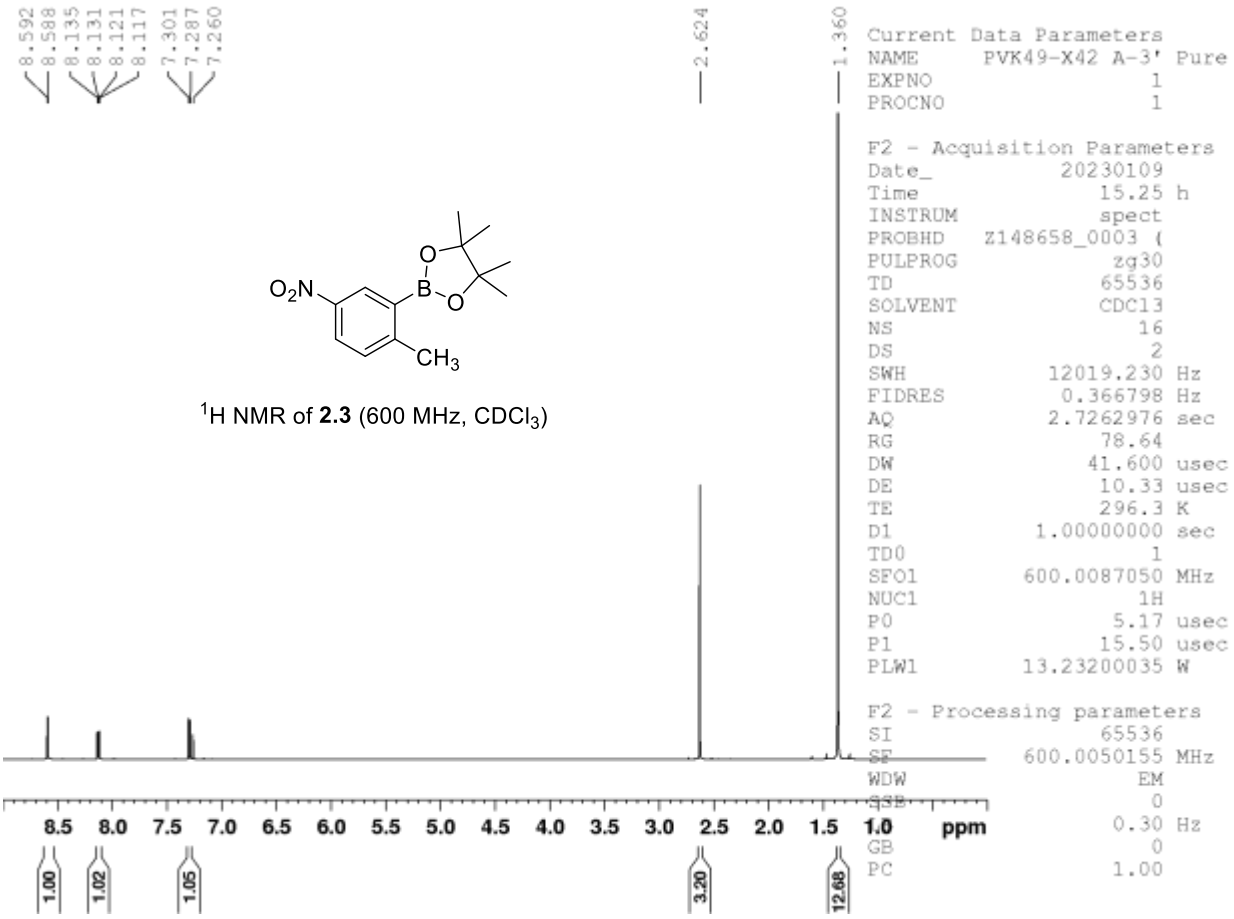


^{13}C NMR of **2.2** (150 MHz, $CDCl_3$)

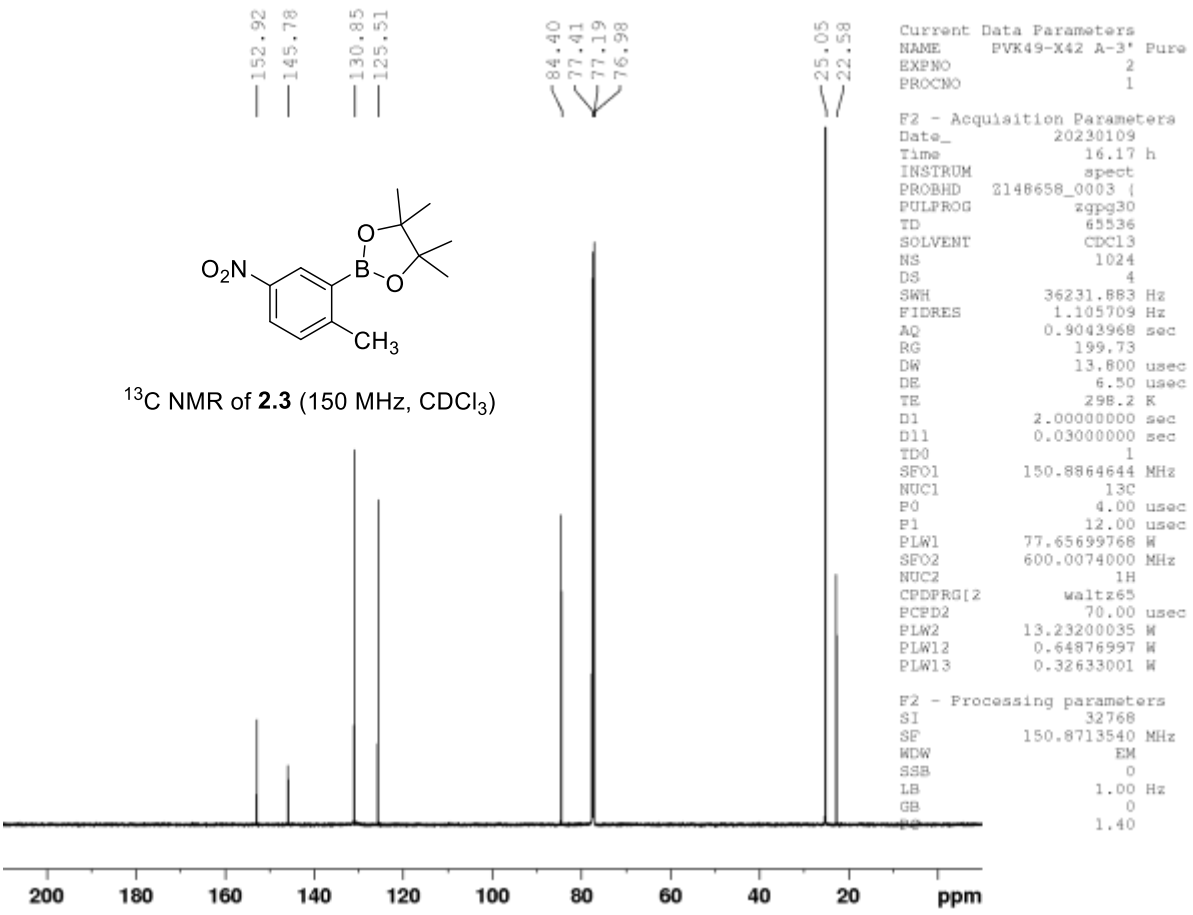
```
Current Data Parameters
NAME      PVK49-X8 Product Pure 2nd
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20230106
Time             18.27 h
INSTRUM          spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD               65536
SOLVENT          CDCl3
NS                1024
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG              199.73
DW              13.800 usec
DE               6.50 usec
TE              298.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1       150.8864644 MHz
NUC1               13C
P0                4.00 usec
P1               12.00 usec
PLW1       77.65699768 W
SFO2       600.0074000 MHz
NUC2               1H
CPDPRG[2        waltz65
PCPD2            70.00 usec
PLW2       13.23200035 W
PLW12       0.64876997 W
PLW13       0.32633001 W

F2 - Processing parameters
SI                32768
SF         150.8713585 MHz
WDW                EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```



^{1}H NMR of **2.3** (600 MHz, $CDCl_3$)

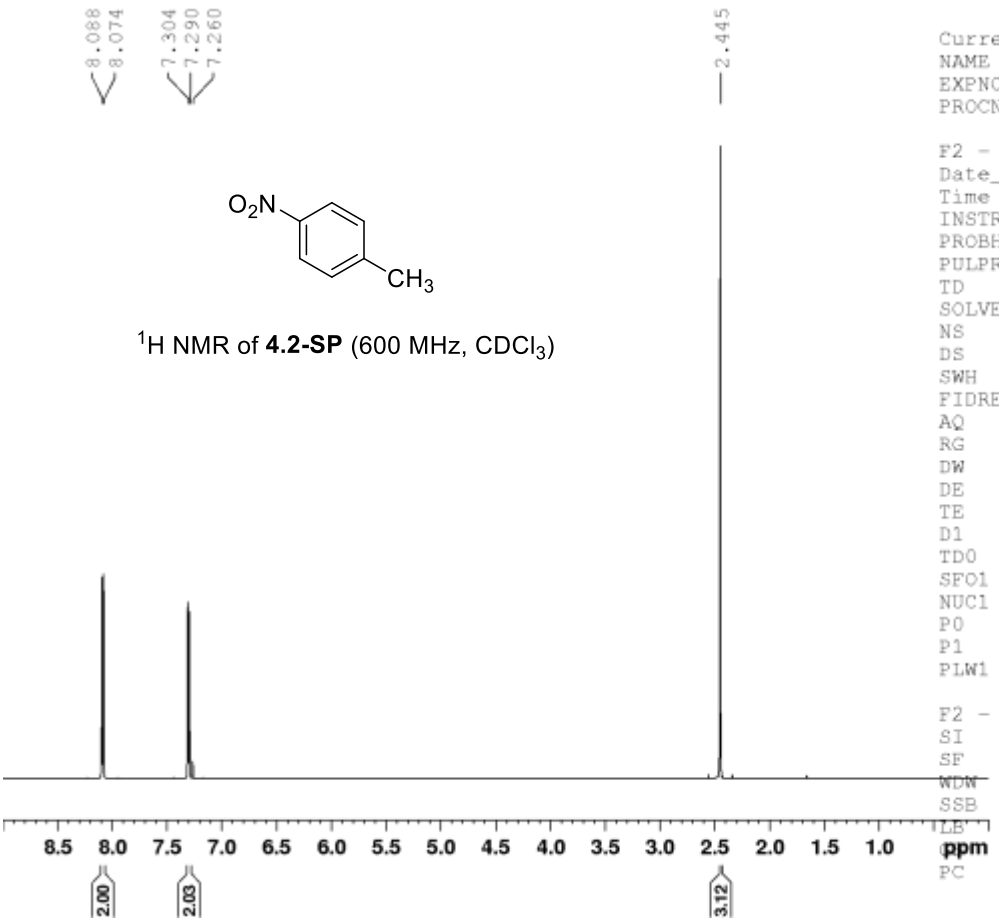


^{13}C NMR of **2.3** (150 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X42 A-3' Pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20230109
Time                 16.17 h
INSTRUM              spect
PROBHD   2148658_0003 (
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH              36231.883 Hz
FIDRES            1.105709 Hz
AQ                0.9043968 sec
RG                   199.73
DW                  13.800 usec
DE                   6.50 usec
TE                  298.2 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1
SFO1           150.8864644 MHz
NUC1                   13C
P0                   4.00 usec
P1                  12.00 usec
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                   1H
CPDPRG[2            waltz65
PCPD2                70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                   32768
SF             150.8713540 MHz
WDW                    EM
SSB                      0
LB                   1.00 Hz
GB                       0
PC                    1.40
```

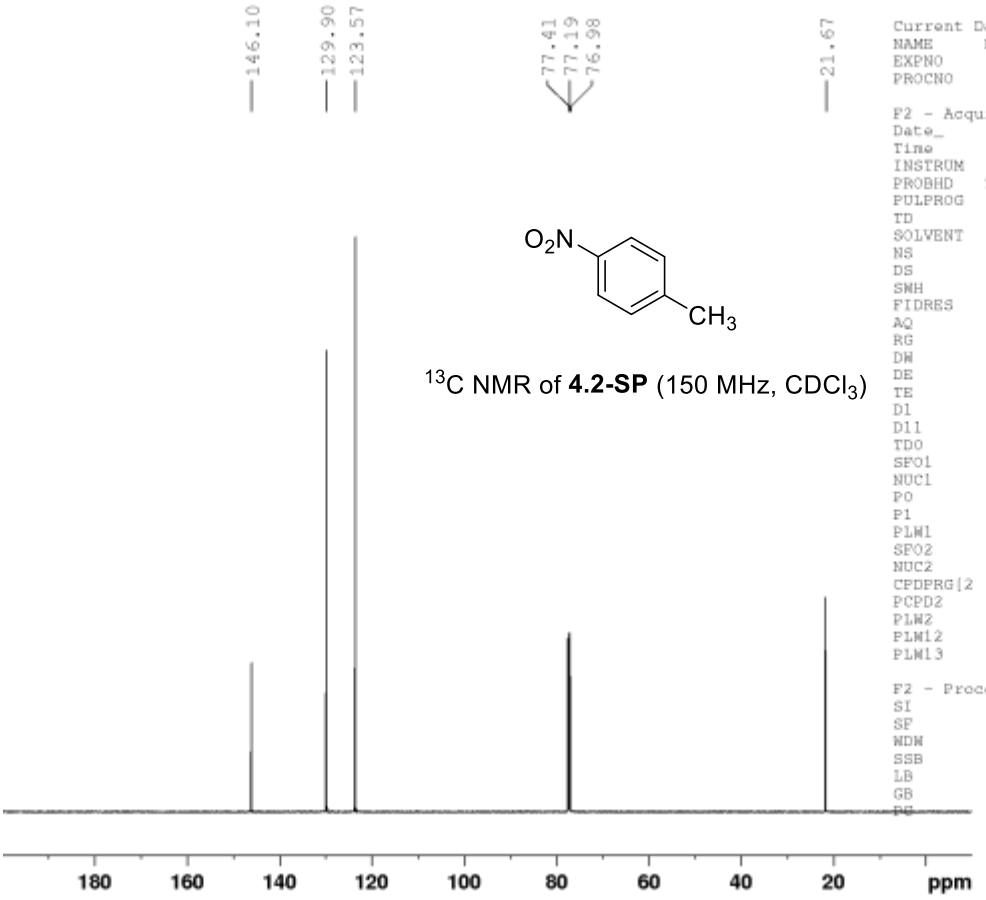


^{1}H NMR of **4.2-SP** (600 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X8 S.M Pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230106
Time              15.42 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG                 55.05
DW                41.600 usec
DE                10.33 usec
TE                296.3 K
D1           1.00000000 sec
TD0                    1
SFO1         600.0087050 MHz
NUC1                  1H
P0                 5.17 usec
P1                15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI                 65536
SF         600.0050153 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

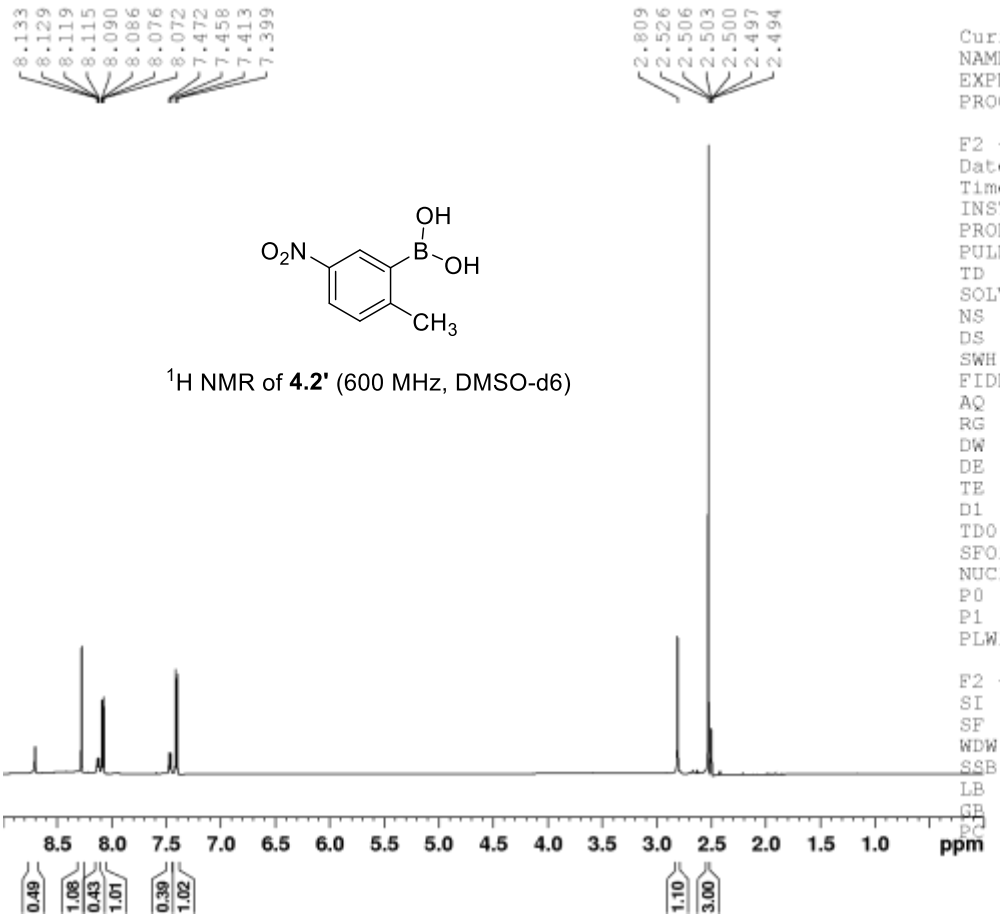


^{13}C NMR of **4.2-SP** (150 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X8 S.M Pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230106
Time              16.34 h
INSTRUM             spect
PROBHD   2148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ            0.9043968 sec
RG               199.73
DW               13.800 usec
DE                6.50 usec
TE               298.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                4.00 usec
P1               12.00 usec
PLW1         77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2              70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713629 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

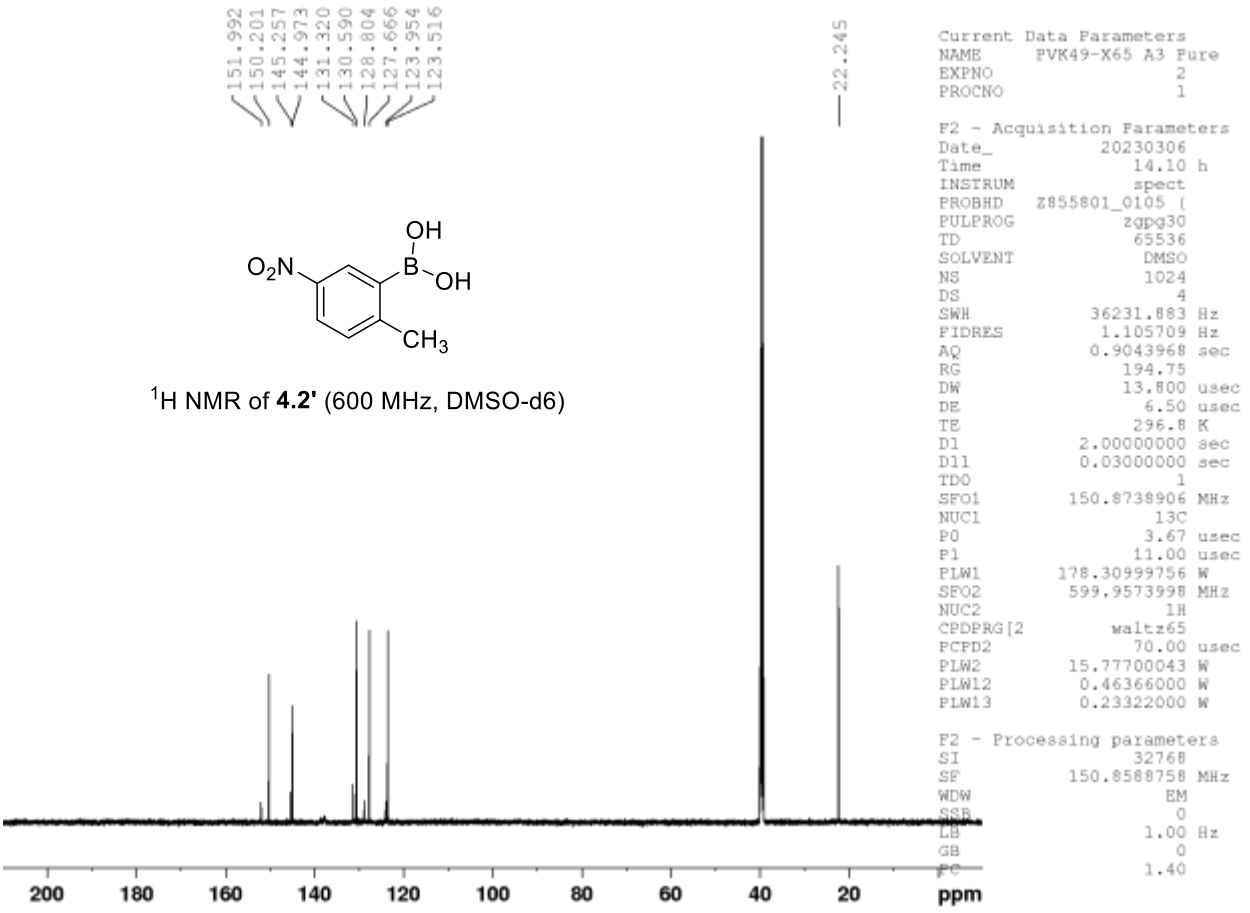


^{1}H NMR of **4.2'** (600 MHz, DMSO-d6)

```
Current Data Parameters
NAME      PVK49-X65 A3 Pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20230306
Time                 13.18 h
INSTRUM              spect
PROBHD    Z855801_0105 (
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                  63.39
DW                 41.600 usec
DE                 10.93 usec
TE                 295.0 K
D1              1.00000000 sec
TD0                     1
SFO1          599.9587047 MHz
NUC1                   1H
P0                  4.00 usec
P1                 12.00 usec
PLW1          15.77700043 W

F2 - Processing parameters
SI                  65536
SF            599.9550061 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

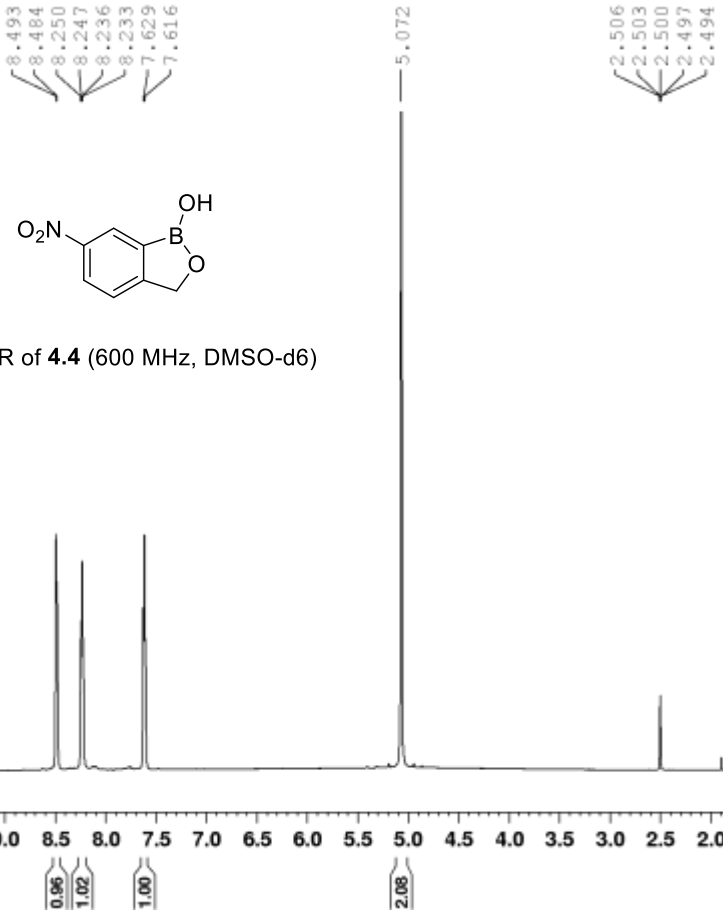


^{1}H NMR of **4.2'** (600 MHz, DMSO-d6)

```
Current Data Parameters
NAME      PVK49-X65 A3 Pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230306
Time               14.10 h
INSTRUM             spect
PROBHD   Z855801_0105 (
PULPROG           zgpg30
TD                 65536
SOLVENT              DMSO
NS                   1024
DS                      4
SWH            36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                 194.75
DW                 13.800 usec
DE                  6.50 usec
TE                 296.8 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                     1
SFO1         150.8738906 MHz
NUC1                  13C
P0                  3.67 usec
P1                 11.00 usec
PLW1        178.30999756 W
SFO2         599.9573998 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2              70.00 usec
PLW2         15.77700043 W
PLW12         0.46366000 W
PLW13         0.23322000 W

F2 - Processing parameters
SI                  32768
SF           150.8588758 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

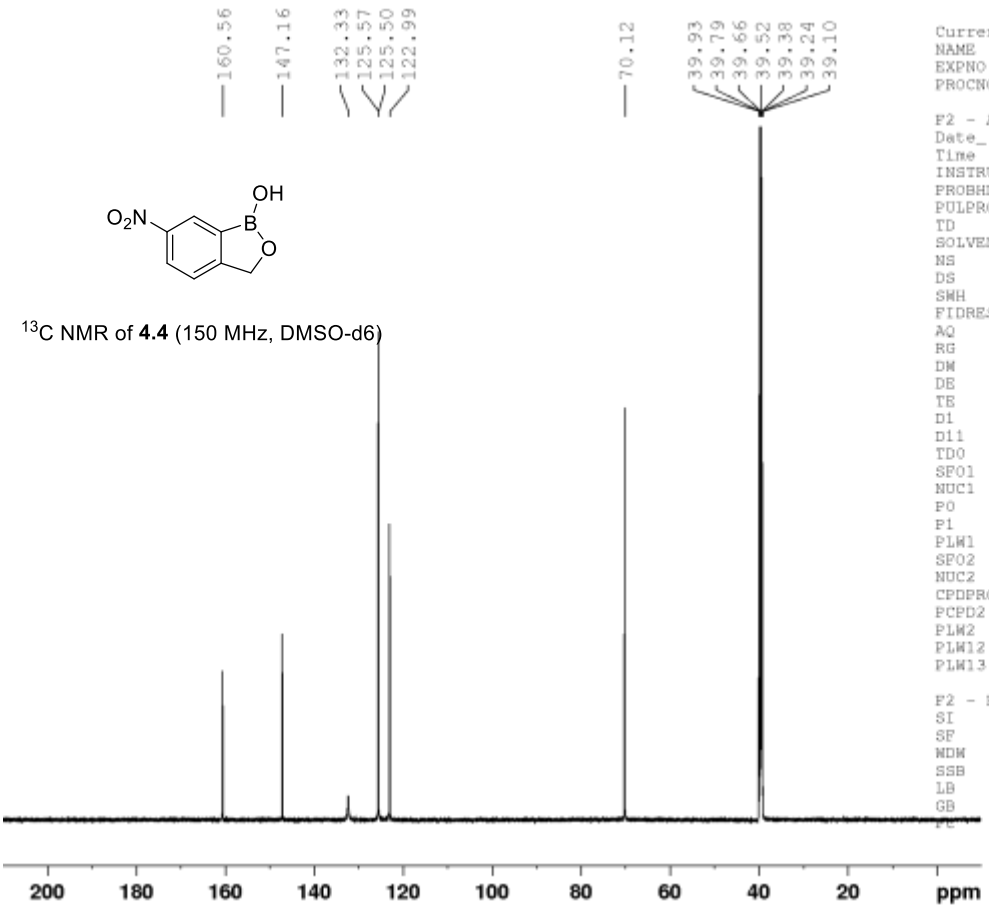


^{1}H NMR of **4.4** (600 MHz, DMSO-d6)

```
Current Data Parameters
NAME      PVK49-X68 Pure A-4
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230110
Time              15.19 h
INSTRUM             spect
PROBHD   Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG                    61
DW               41.600 usec
DE               10.33 usec
TE               296.2 K
D1            1.00000000 sec
TD0                    1
SFO1         600.0087050 MHz
NUC1                  1H
P0                5.17 usec
P1               15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI                 65536
SF         600.0050064 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.00
```

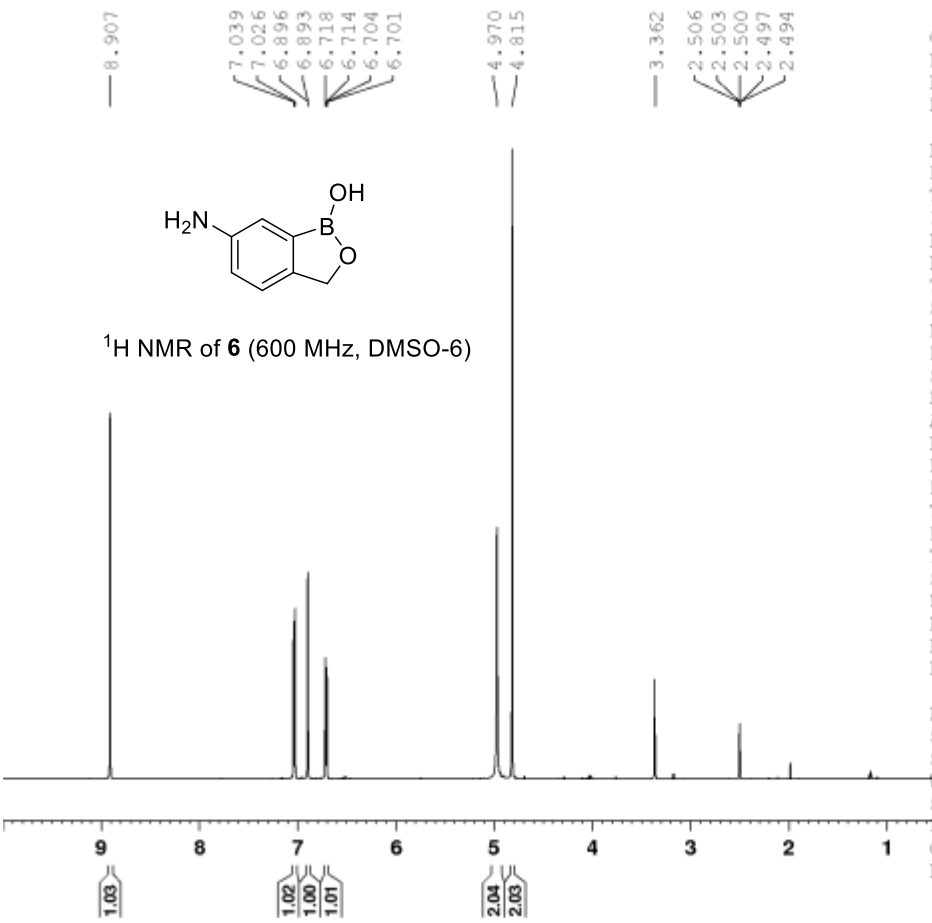


^{13}C NMR of **4.4** (150 MHz, DMSO-d6)

```
Current Data Parameters
NAME      PVK49-X68 Pure A-4
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20230110
Time                 16.11 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   1024
DS                      4
SWH             36231.883 Hz
FIDRES           1.105709 Hz
AQ               0.9043968 sec
RG                  199.73
DW                  13.800 usec
DE                    6.50 usec
TE                  298.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          150.8864644 MHz
NUC1                  13C
P0                    4.00 usec
P1                   12.00 usec
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                  1H
CPDPRG[2           waltz65
PCPD2                70.00 usec
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                   32768
SF            150.8714319 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

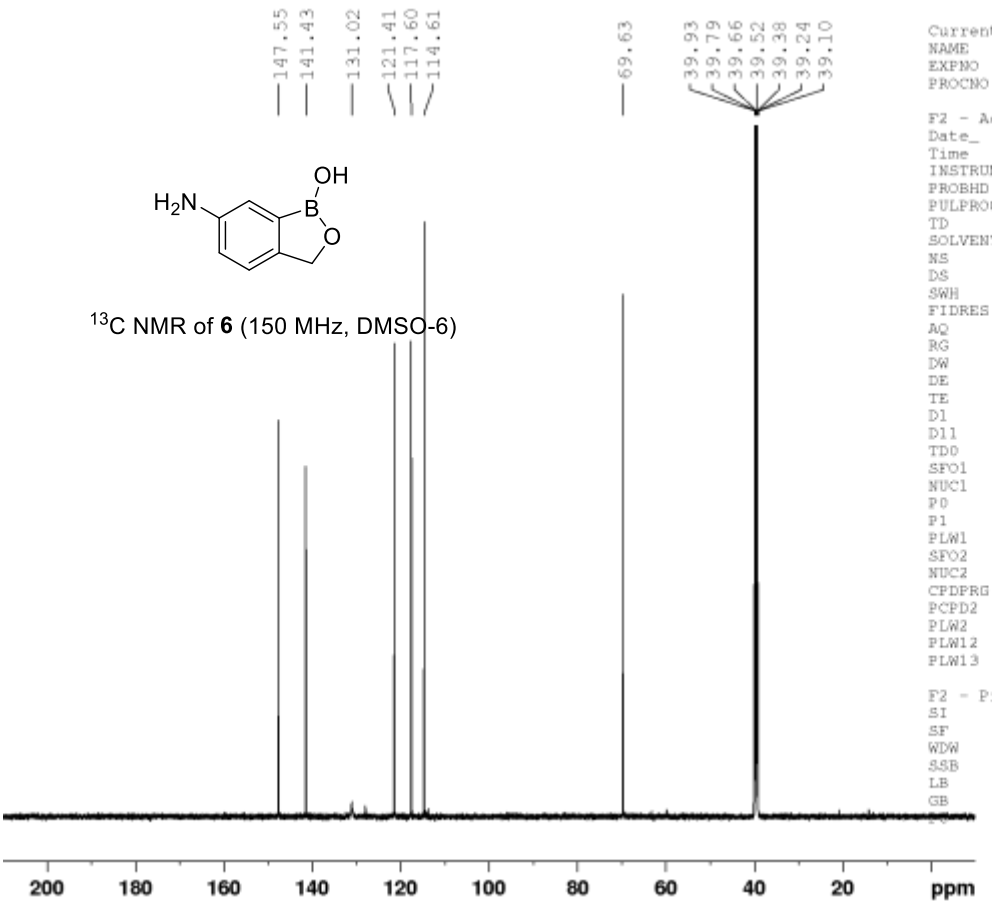


^{1}H NMR of **6** (600 MHz, DMSO-6)

```
Current Data Parameters
NAME      PVK49-X78 A-5 Pure_2
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230111
Time              16.33 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG                106.9
DW               41.600 usec
DE               10.33 usec
TE               298.0 K
D1           1.00000000 sec
TD0                    1
SFO1        600.0087050 MHz
NUC1                  1H
P0                5.17 usec
P1               15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI                 65536
SF          600.0050063 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

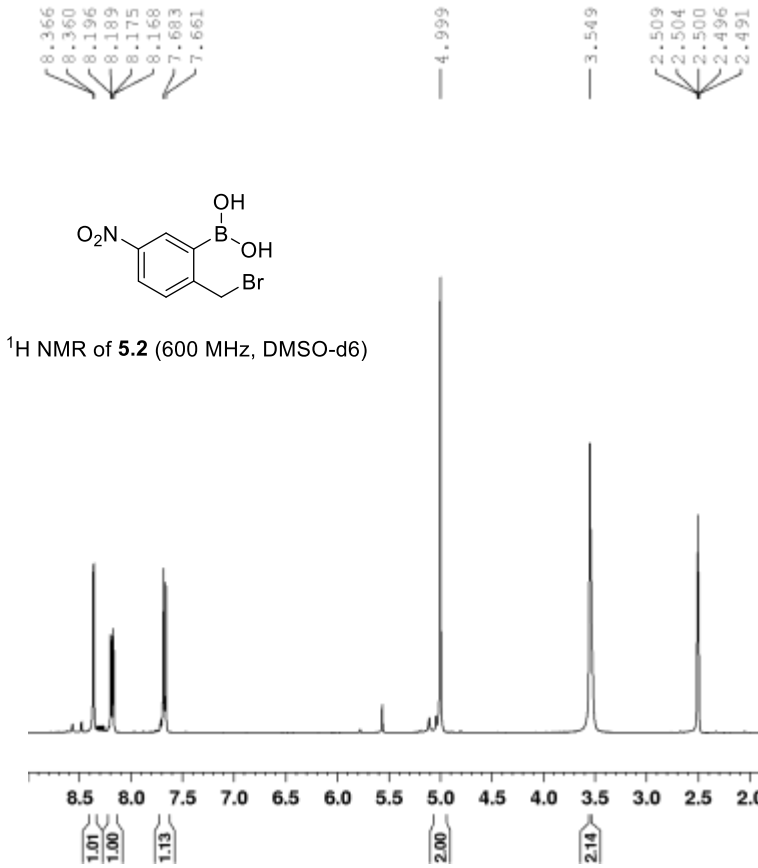


^{13}C NMR of **6** (150 MHz, DMSO-6)

```
Current Data Parameters
NAME      PVK49-X78 A-5 Pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20230111
Time                17.25 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                    1024
DS                       4
SWH              36231.883 Hz
FIDRES            1.105709 Hz
AQ                0.9043968 sec
RG                   199.73
DW                  13.800 usec
DE                   6.50 usec
TE                  298.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1
SFO1           150.8864644 MHz
NUC1                   13C
P0                   4.00 usec
P1                  12.00 usec
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                   1H
CPDPRG[2            waltz65
PCPD2                70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                   32768
SF             150.8714473 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
                      1.40
```

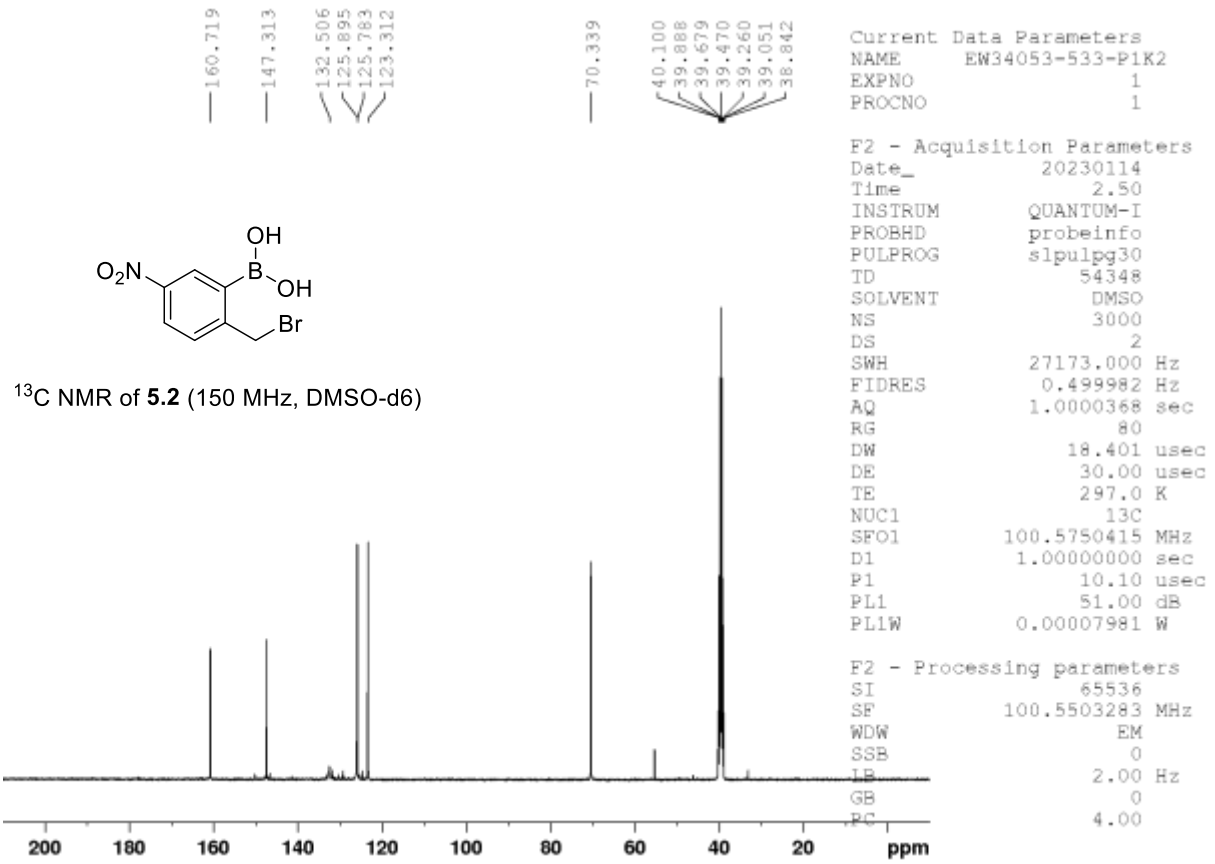


^{1}H NMR of **5.2** (600 MHz, DMSO-d6)

```
Current Data Parameters
NAME      EW34053-533-P1H1
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20230111
Time                22.44 h
INSTRUM            Avance
PROBHD   Z163739_0607 (
PULPROG                 zg
TD                   32786
SOLVENT               DMSO
NS                       1
DS                       0
SWH               8196.722 Hz
FIDRES            0.500013 Hz
AQ               1.9999460 sec
RG                    11.3
DW                  61.000 usec
DE                  10.16 usec
TE                  297.8 K
D1                      0 sec
TD0                     1
SFO1          400.1324708 MHz
NUC1                   1H
P1                   8.00 usec
PLW1         21.89800072 W

F2 - Processing parameters
SI                   65536
SF            400.1300035 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
                     1.00
```

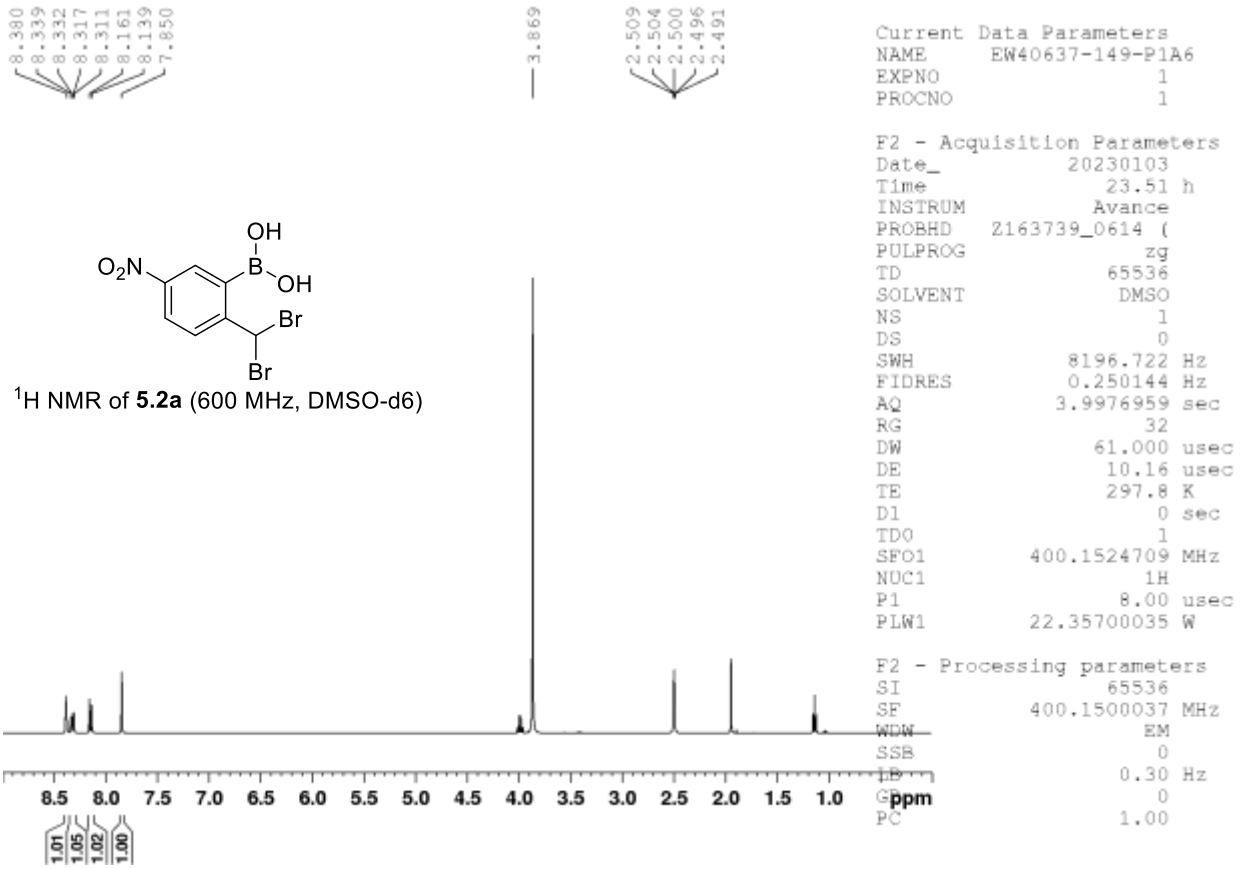


^{13}C NMR of **5.2** (150 MHz, DMSO-d6)

```
Current Data Parameters
NAME      EW34053-533-P1K2
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20230114
Time                 2.50
INSTRUM         QUANTUM-I
PROBHD          probeinfo
PULPROG         slpulpg30
TD                  54348
SOLVENT              DMSO
NS                   3000
DS                      2
SWH              27173.000 Hz
FIDRES           0.499982 Hz
AQ               1.0000368 sec
RG                     80
DW                 18.401 usec
DE                 30.00 usec
TE                 297.0 K
NUC1                 13C
SFO1           100.5750415 MHz
D1              1.00000000 sec
P1                 10.10 usec
PL1                51.00 dB
PL1W           0.00007981 W

F2 - Processing parameters
SI                   65536
SF             100.5503283 MHz
WDW                     EM
SSB                      0
LB                    2.00 Hz
GB                       0
PC                    4.00
```

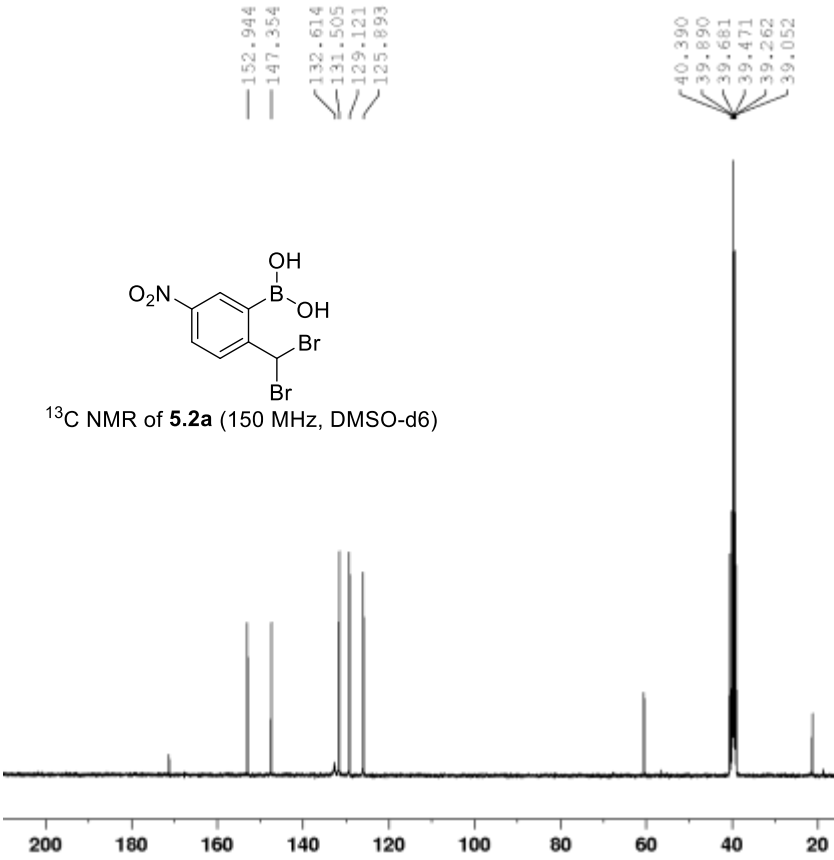


^{1}H NMR of **5.2a** (600 MHz, DMSO-d6)

```
Current Data Parameters
NAME      EW40637-149-P1A6
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230103
Time              23.51 h
INSTRUM           Avance
PROBHD   Z163739_0614 (
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    1
DS                    0
SWH            8196.722 Hz
FIDRES         0.250144 Hz
AQ            3.9976959 sec
RG                   32
DW                61.000 usec
DE                10.16 usec
TE                297.8 K
D1                    0 sec
TD0                   1
SFO1         400.1524709 MHz
NUC1                 1H
P1                 8.00 usec
PLW1        22.35700035 W

F2 - Processing parameters
SI                65536
SF         400.1500037 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

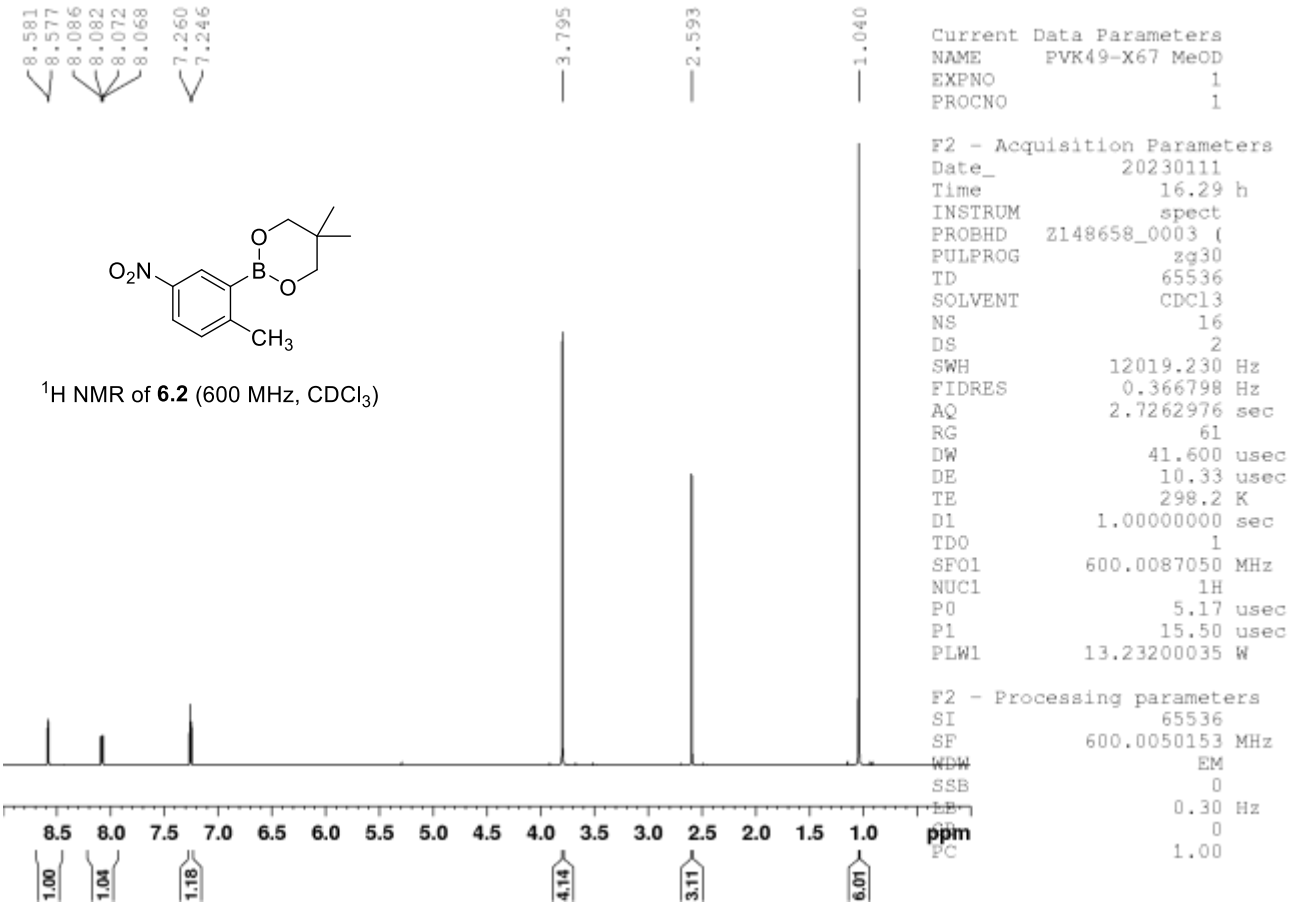


^{13}C NMR of **5.2a** (150 MHz, DMSO-d6)

```
Current Data Parameters
NAME      EW40637-149-P1H5
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20230104
Time               11.45
INSTRUM        QUANTUM-I
PROBHD         probeinfo
PULPROG        s1pulpg30
TD                 54348
SOLVENT             DMSO
NS                  1024
DS                     2
SWH            27173.000 Hz
FIDRES          0.499982 Hz
AQ             1.0000368 sec
RG                    80
DW                18.401 usec
DE                30.00 usec
TE                297.6 K
NUC1                13C
SFO1         100.5750415 MHz
D1           1.00000000 sec
P1                10.10 usec
PL1               51.00 dB
PL1W         0.00007981 W

F2 - Processing parameters
SI                 65536
SF           100.5503152 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  4.00
```

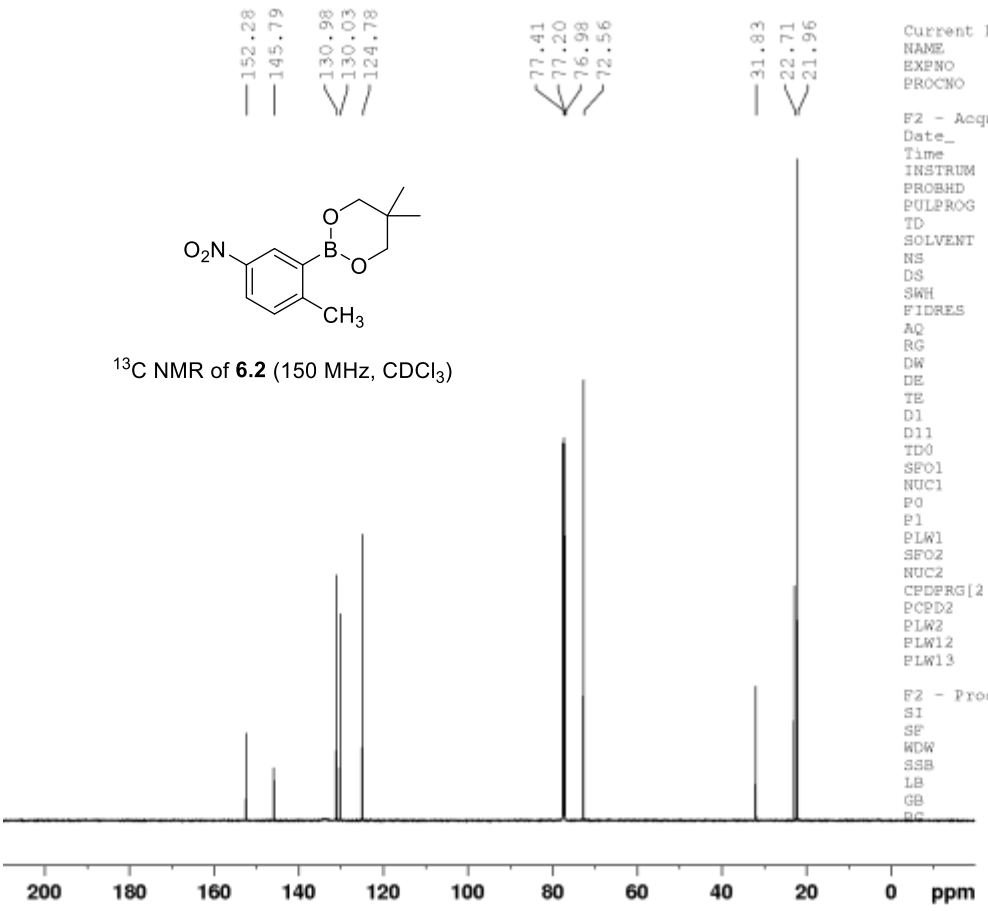


^{1}H NMR of **6.2** (600 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X67 MeOD
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20230111
Time               16.29 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             2.7262976 sec
RG                    61
DW                41.600 usec
DE                10.33 usec
TE                298.2 K
D1           1.00000000 sec
TD0                    1
SFO1         600.0087050 MHz
NUC1                  1H
P0                 5.17 usec
P1                15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI                 65536
SF           600.0050153 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

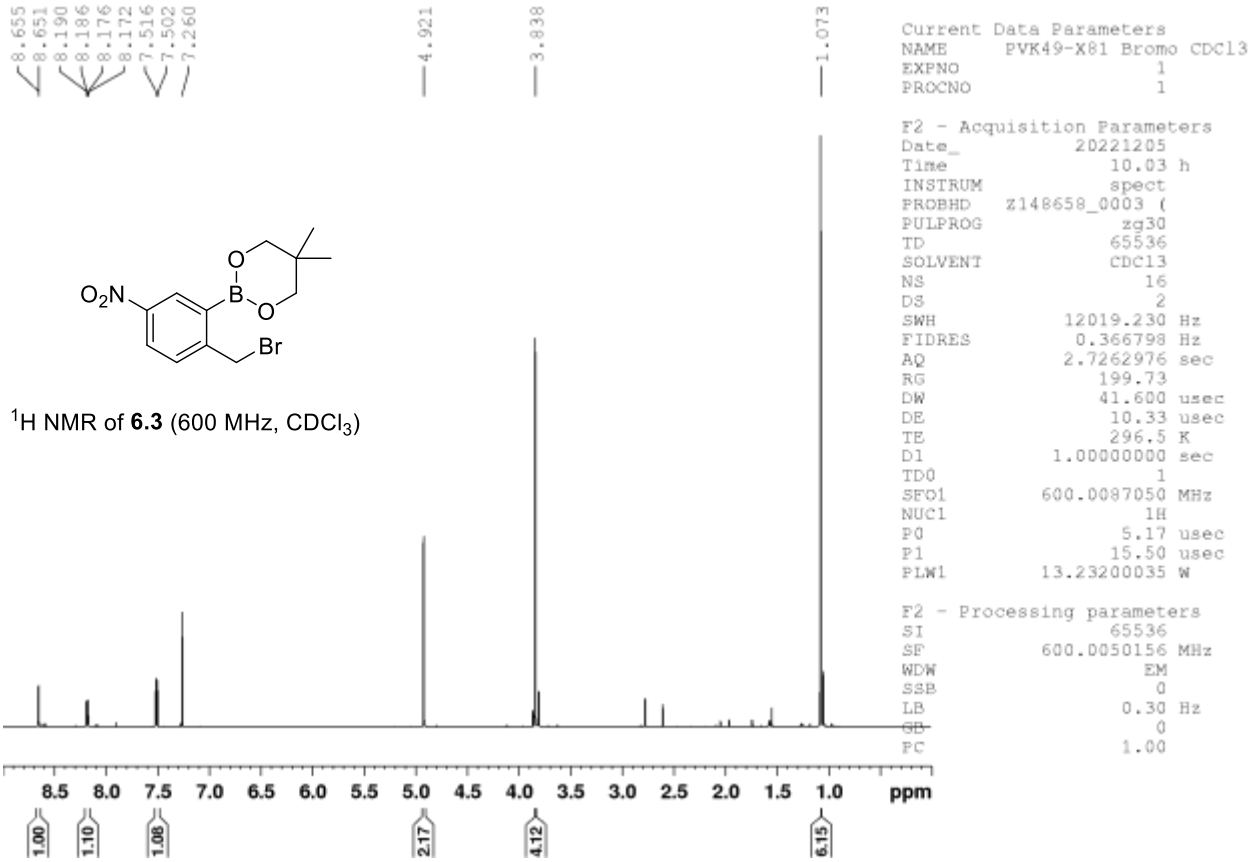


^{13}C NMR of **6.2** (150 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X67 Neopentyl Pure
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20230112
Time             16.14 h
INSTRUM          spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD               65536
SOLVENT          CDCl3
NS                1024
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG              199.73
DW               13.800 usec
DE                6.50 usec
TE              298.3 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1         150.8864644 MHz
NUC1                 13C
P0                4.00 usec
P1               12.00 usec
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                 1H
CPDPRG[2          waltz65
PCPD2            70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF           150.8713562 MHz
WDW                  EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40
```

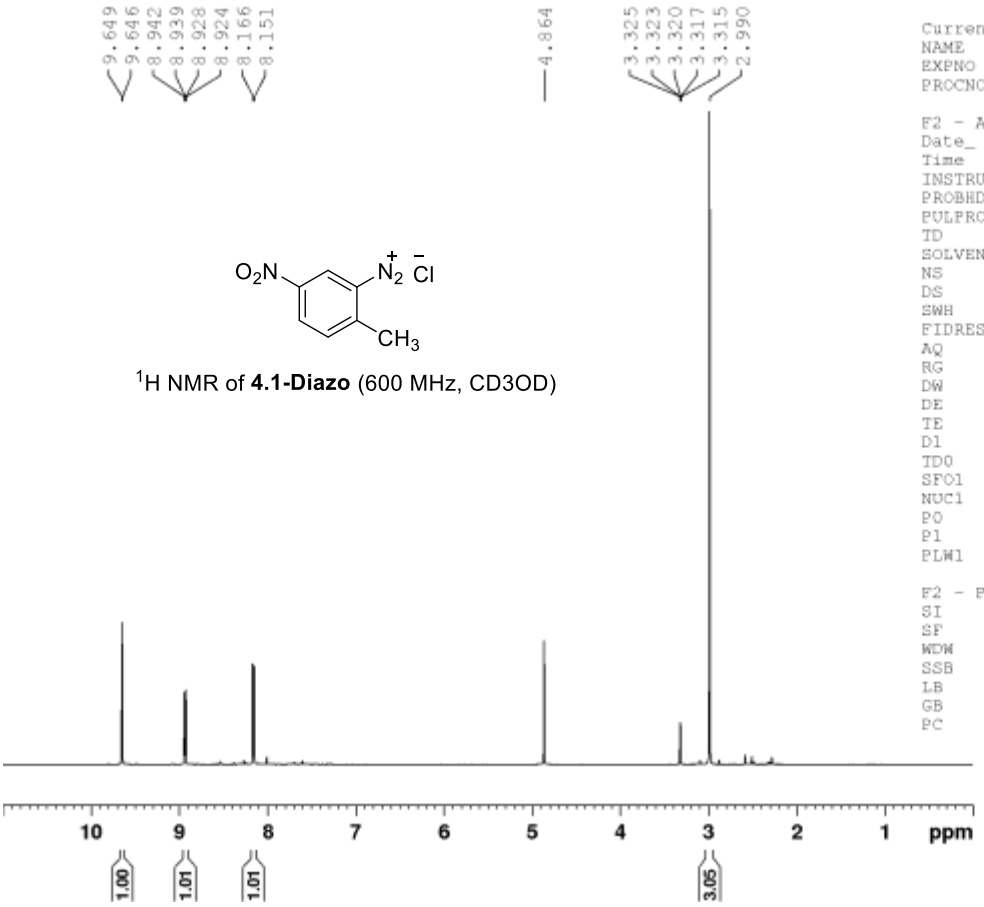


^{1}H NMR of **6.3** (600 MHz, $CDCl_3$)

```
Current Data Parameters
NAME      PVK49-X81 Bromo CDCl3
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_           20221205
Time              10.03 h
INSTRUM           spect
PROBHD   z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               199.73
DW               41.600 usec
DE               10.33 usec
TE               296.5 K
D1           1.00000000 sec
TD0                  1
SFO1         600.0087050 MHz
NUC1                 1H
P0                5.17 usec
P1               15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050156 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

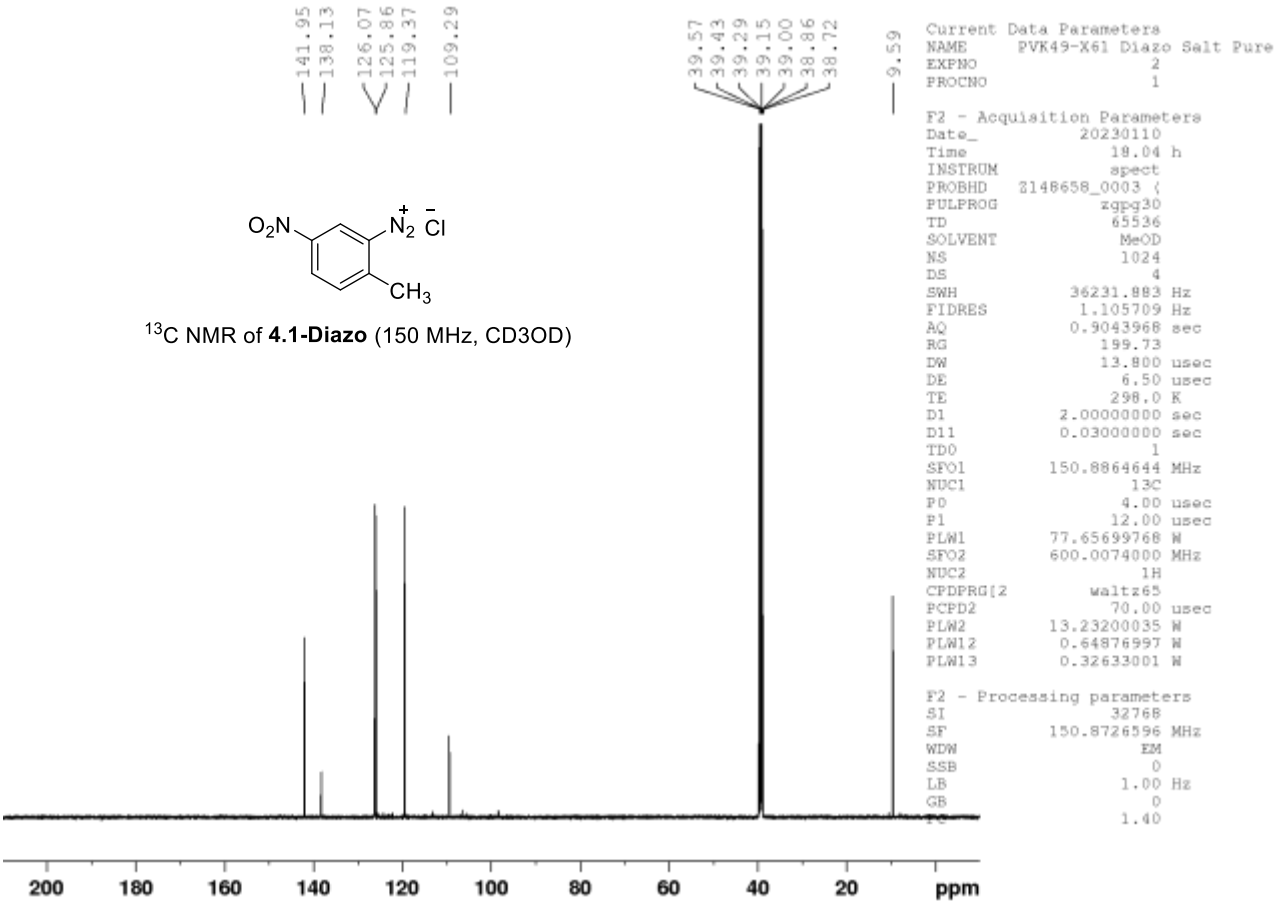


^{1}H NMR of **4.1-Diazo** (600 MHz, CD3OD)

```
Current Data Parameters
NAME      PVK49-X61 Diazo Salt Pure
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20230110
Time              17.12 h
INSTRUM           spect
PROBHD   2148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT           MeOD
NS                  16
DS                   2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG               157.38
DW               41.600 usec
DE               10.33 usec
TE               296.6 K
D1           1.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 usec
P1               15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050056 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```



^{13}C NMR of **4.1-Diazo** (150 MHz, CD3OD)

```
Current Data Parameters
NAME      PVK49-X61 Diazo Salt Pure
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20230110
Time              18.04 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG         zgpg30
TD               65536
SOLVENT           MeOD
NS                1024
DS                   4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG               199.73
DW               13.800 usec
DE                6.50 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                  1
SFO1         150.8864644 MHz
NUC1                13C
P0                4.00 usec
P1               12.00 usec
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

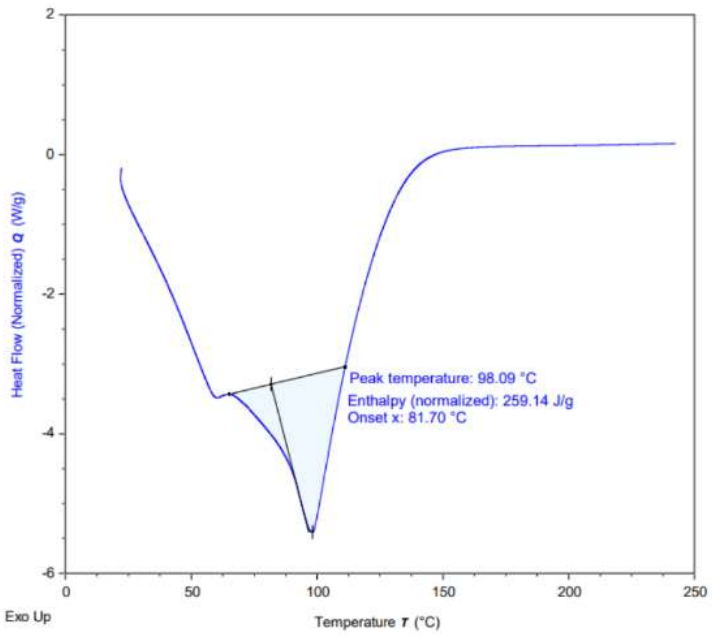
F2 - Processing parameters
SI                32768
SF           150.8726596 MHz
WDW                  EM
SSB                  0
LB                1.00 Hz
GB                   0
                  1.40
```

Appendix

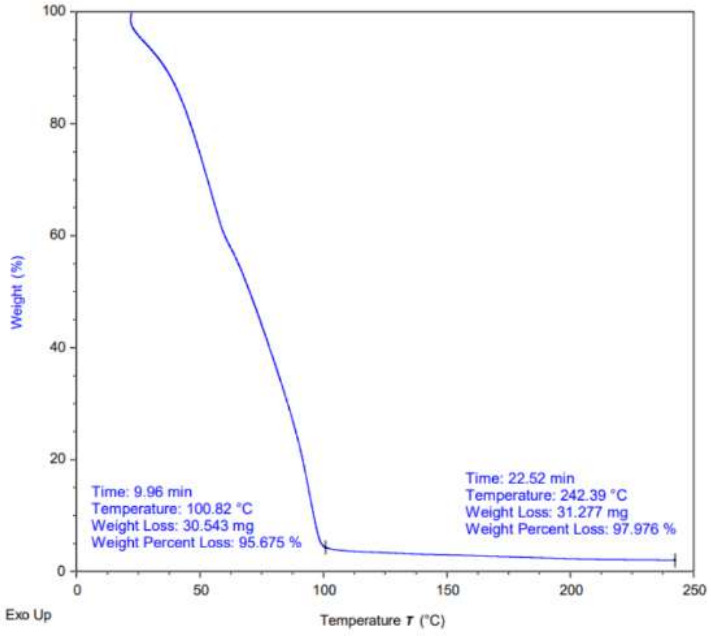
1. DSC and TGA studies of Diazonium salt

1) Sample collected directly from a reaction mixture

PVK49-X61 (DSC)

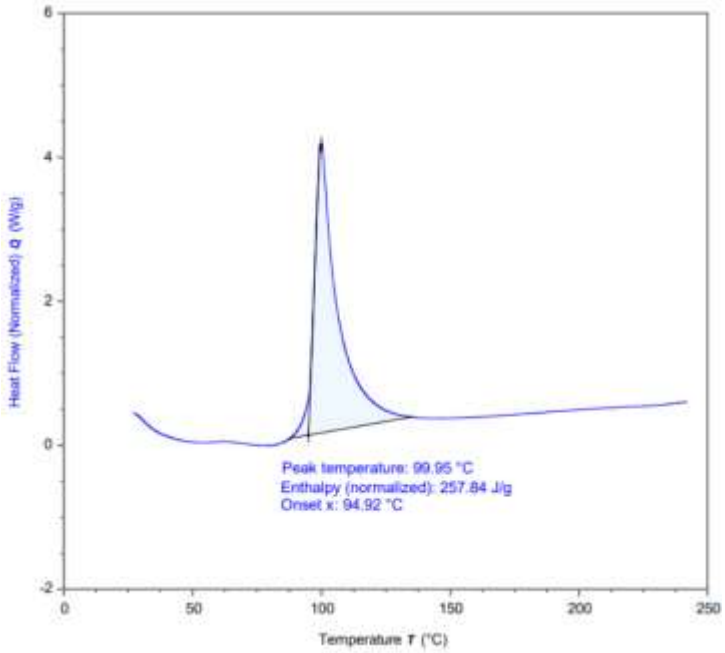


PVK49-X61 (TGA)

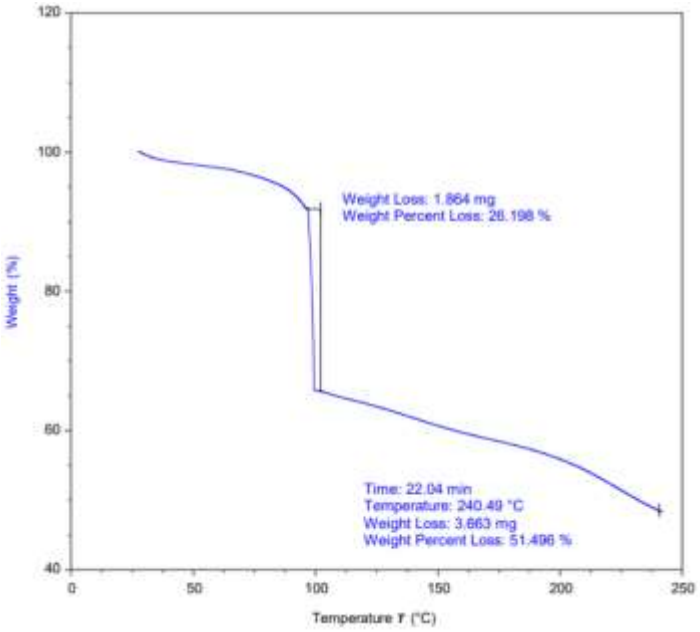


2) Pure Isolated solid diazonium salt (4.1-Diazo)

DSC



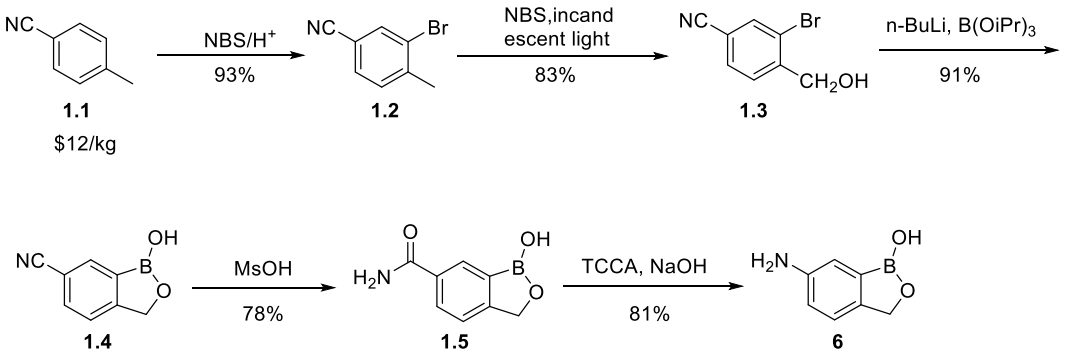
TGA



2. Development Summary

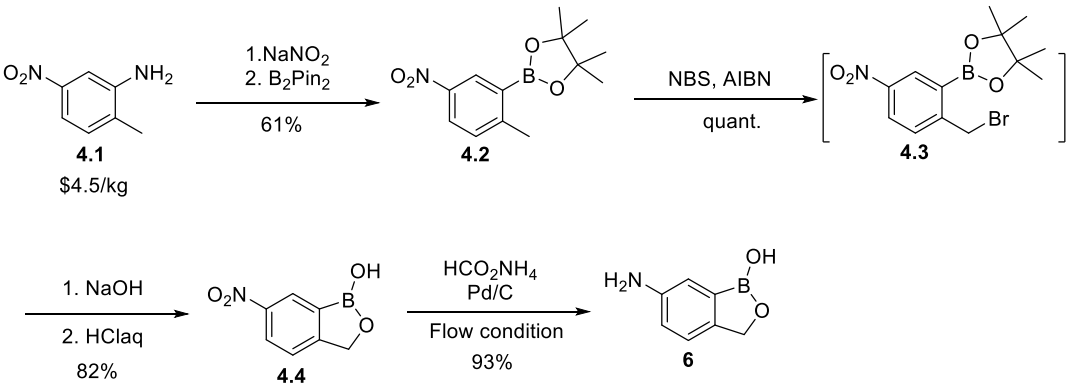
Key Idea 1 Summary:

- Synthesis of 6-ABB (**6**) from the commodity starting material *p*-tolunitrile (**1.1**) has been demonstrated;
- While the key bond-forming steps have been proven, the process was not fully optimized, reproduced by a 3rd party, nor was it scaled up during the course of this work;
- Full optimization of this process could **reduce API RM costs by up to 80% vs published baseline**.



Key Idea 2 Summary:

- Synthesis of 6-ABB (**6**) from the commodity starting material 2-methyl-5-nitroaniline (**4.1**) has been demonstrated;
- While the key bond-forming steps have been proven, the process was not fully optimized, reproduced by a 3rd party, nor was it scaled up during the course of this work;
- Full optimization of this process could **reduce API RM costs by up to 90% vs published baseline**.



3. Acronyms

6-ABB	6-amino-1-hydroxy-2,1-benzoxaborolane
API	Active pharmaceutical ingredients
-Ac	acetyl
BPO	benzoyl peroxide
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DNDI	Drugs for Neglected Diseases Initiative
DSC/TGA	Differential Scanning Calorimetry and Thermogravimetric Analysis
-MOM	Methoxymethyl ether
NBS	azobisisobutyronitrile
NCS	N-Chlorosuccinimide
NHPI	N-Hydroxyphthalimide
PMA	Phosphomolybdic acid
-Piv	pivaloyl
RMC	raw material cost
RSM	regulatory starting material
TCCA	trichloroisocyanuric acid
TE	Techno-economic
TLC	Thin layer chromatography
VL	Visceral Leishmaniasis