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NEW STUDY OF THE REACTIVITY AND SELECTIVITY OF BORON REAGENT'S IN THE RHODIUM CATALYZED 1,4-ADDITION

BACHELOR'S DEGREE FINAL PROJECT

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Degree of Chemistry

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Table of Contents

List of Abbreviations

TLC	Analytical thin layer chromatography
NMR	Proton nuclear magnetic resonance spectra
Aq.	Aqueous
^{o}C	Degree Celsius
cod	1,5-cyclooctadiene
equiv	Equivalents
h	Hour
Me	Methyl
ml	Millilitres
mmol	Millimols
M	Molar
Ph	Phenyl
r.t	Room temperature
Dppb	1,4-Bis(diphenylphosphino)butane
BINAP	(2,2'-bis(diphenilphosphino)-1,1'-binaphthyl)
Dppp	1,3-Bis(diphenylphphino)propane
Dppe	1,2-Bis(diphenylphosphino)ethane
PPh3	Triphenylphosphine
Ar	Aryl
Bu	Buthyl
tBu	tert-butyl
H	Proton
Rh	Rhodium
Acac	2,4-pentanedione
OH	Hydroxyl
CO	Carbon Monoxide
MIDA	Methyliminodiacetic Acid
Pin	Pinacol
DME	Dimethoxyethane
PhOHBX	*ortho*-hydroxyphenyl boron especies
PhBX	phenyl boron species

List of Tables

List of Figures

List of Schemes

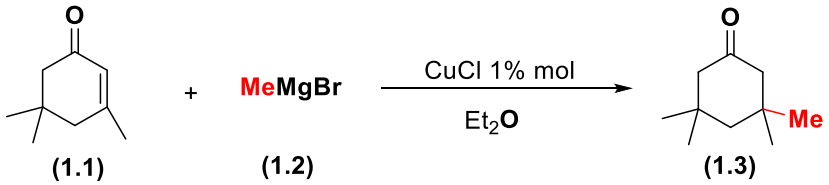
Chapter 1 – Introduction

1.1 1,4-Addition to Activated Alkenes via Rhodium Catalysis

Alkenes are one of the most useful and fundamental functional groups in organic chemistry as they undergo a multitude of reactions such as oxidation, reduction, and addition to name some of them. The metal catalyzed conjugate addition of organometallic reagents to activated alkenes is a long standing and well stablished process most often utilizing copper as the metal catalyst and organolithium, diorganozinc, or Grignard reagents as the organometallic component[1], while copper is most common other metals have been known to catalyze the reaction[2]. While these reactions are, in most cases, very versatile and high yielding, competitive 1,2-addition of the organometallic reagent is commonly a problem. Moreover, while progress has been made towards enantioselective variants[3], a mild, robust, stereoselective, and efficient method for metal catalyzed conjugate addition was not available until the late 1990s[4]. The discovery of a rhodium catalyzed conjugate addition protocol of organoboron reagents to enones by Miyaura and co-workers in 1997 provided an attractive alternative to the standard methods. The reaction was tolerant to more functional groups, took place under milder conditions, was insensitive to water, and employed mild organoboron reagents which do not undergo 1,2-addition as a secondary reaction. This methodology was rapidly adopted and since its commencement notable progress has been made including the discovery of enantioselective variants and the expansion of the substrate class which have greatly increased the synthetic utility in organic synthesis.

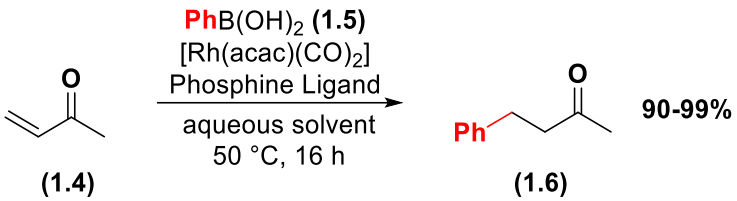
1.1.1 Conjugate Addition to Enones

The conjugated addition to enones has been known since 1900 when Kharasch and co-workers successfully reacted isophorone (**1.1**) with methyl magnesium bromide (**1.2**) in the presence of catalytic quantity of copper chloride, to give 3,3,5,5-tratramethylcyclohexanone (**1.3**) (Scheme 1.1-1)[5]



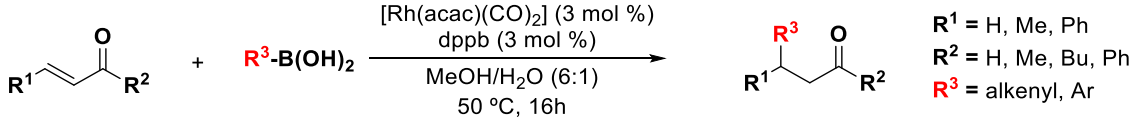
Scheme 1.1-1: Kharasch and co-workers initial observation of teh conjugated addition to enones

However, the first report of a rhodium catalyzed conjugate addition of boronic acids to enones came from Miyaura and co-workers in 1997, as previously mentioned this provided an attractive alternative to traditional coper catalyzed processes. Initially focusing on the addition of phenylboronic acid (**1.5**) to methyl vinyl ketone (**1.4**), the authors determined that the use of $[Rh(acac)(CO)_2]$ with a phosphine ligand in a mixed organic/aqueous solvent system provided the conjugate addition product (**1.6**) in excellent yield (Scheme 1.1-2)[4].



Scheme 1.1-2: Miyaura and co-workers initial observation of the Rh catalyzed addition of boronic acids to enones

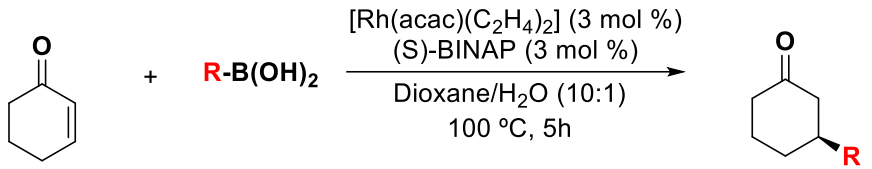
The reaction with methyl vinyl ketone (**1.4**) worked well under a number of solvent systems and phosphine ligands, extending the methodology to some less reactive enones clarify some details of the effect of these two factors. Utilizing 2-octen-4-one as a substrate, the authors found that the most effective system for a wide variety of substrates was a combination of methanol/water. They also realized that the phosphine ligand had a large impact on the yield of the reaction and were able to determine that order of reactivity in terms of phosphine ligand was: dppb > dppp > TFP > dppe, PPh_3, and $AsPh_3$; from this the conclusion was that the reaction is accelerated increasing the bite angle of the ligand. This all lead to an optimized set of general conditions that was able to affect the required transformation in high yields on a wide variety of enone substrates (Scheme 1.1-3)[4].



Scheme 1.1-3: Optimized conditions for Miyaura and co-workers addition to enones

One important observation made by the authors was the fact that the presence of water in the reaction system was necessary for high yields thought they were not able to elucidate the specific reason as to why. Furthermore, a wide variety of boronic acids were tolerated (Aryl, alkenyl) and the electronic nature seemed to have no significant impact, steric effects were noticeable however as *ortho*-substituted boronic acids were found to retard the reaction. Finally, the only secondary reaction observed was the protodeborylation of the boronic acids, which incited the use of a large excess in their optimized conditions, while no 1,2-addition was observed in any case which highlight the excellent selectivity of this protocol in comparison to the traditional copper catalyzed methods[4].

Soon after the initial publication, the first report of an enantioselective version of the reaction was reported by Hayashi and Miyaura in 1998 utilizing a chiral phosphine ligand[6] (Scheme 1.1-4). This protocol allowed the addition of several aryl and alkenyl boronic acids to both cyclic and acyclic enones with good to excellent yields and excellent enantiomeric excess.

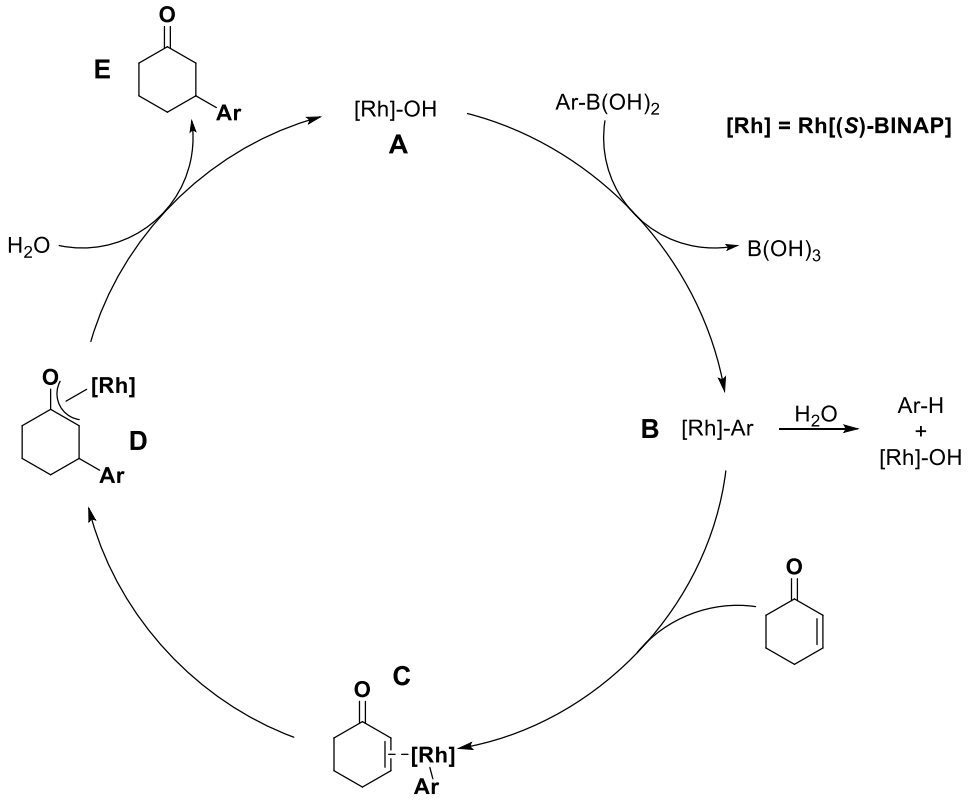


64-99% yield, 91-99% ee

R = Ph, 4-MePh, 3-MePh, 4-CF_3Ph, 3-ClPh, (E)-tBuCH=CH, (E)-1-heptenyl

Scheme 1.1-4: Enantioselective addition of boronic acids to enones

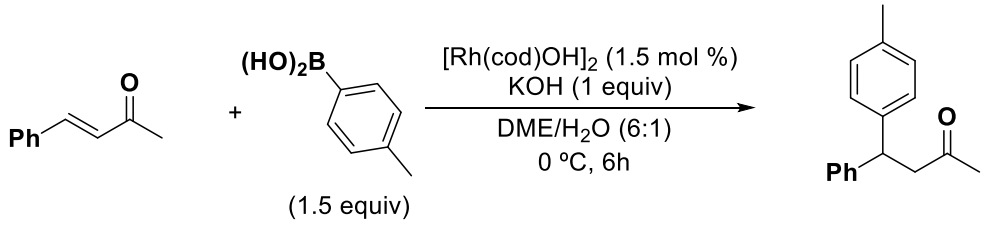
Although some mechanistic pathways for the reaction had been proposed in initial reports, it wasn't until 2002 when Hayashi and co-workers that elucidated the mechanism[7]. The catalytic cycle for the reaction begins with the formation of the catalytically active rhodium-hydroxide complex (**A**, Scheme 1.1-5) from Rh(acac)[(S)-BINAP]. The next step involves the transmetalation of the arylboronic acid from boron to rhodium which produces boric acid and the aryl-rhodium species (**B**, Scheme 1.1-5). The enone substrate can then co-ordinate to aryl-rhodium species (**C**, Scheme 1.1-5); a competing side reaction is the hydrolysis of the aryl-rhodium species which reforms the rhodium-hydroxide complex and the product of formal protodeborylation. In the productive pathway, a carborhodation occurs where the alkene of the enone substrate inserts into rhodium-carbon bond which forms a rhodium-oxa-π-allyl species (**D**, Scheme 1.1-5) and constructs the new carbon-carbon bond. Protonolysis of species (**D**, Scheme 1.1-5) releases the product of the reaction (**E**, Scheme 1.1-5) and regenerates the active catalytic species (**A**, Scheme 1.1-5)[7].



Scheme 1.1-5: Catalytic cycle for the Rh catalyzed addition of boronic acids to enones

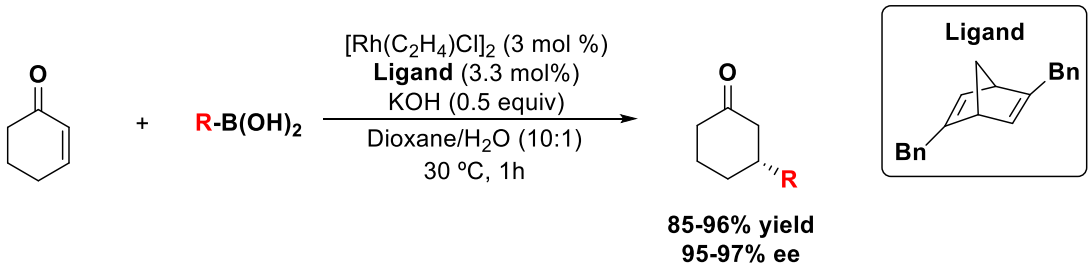
In the process of clarifying the mechanism the author found that the rate determining step of the reaction was the transmetalation of the boronic acid to rhodium, and moreover the rhodium species used for the reaction had a large impact on the speed of the reaction. By switching to a rhodium-hydroxide complex as the catalyst, such as $[Rh(BINAP)OH]_2$, the reaction was able to be conducted at 35°C to give 96% of desire product with 99% ee. Thus, by clarifying the full mechanism of the transformation, the authors were able to discover a new more active catalyst for the reaction which allowed much milder conditions while retaining excellent yield and ee.

While reinvestigating the effect of different ligands on the reaction, Miyaura and co-workers discovered that diene ligands, specifically 1,5-cyclooctadiene, showed much high catalytic activity than the standard phosphine ligands[8]. The authors then noticed a large accelerating effect on the reaction when an inorganic base was added, with KOH showing the largest increase in rate. There were two reasons for this effect: first, the base plays a role in the regeneration of the rhodium-hydroxide complex and serves to form the boronoic acid which greatly facilitates the transmetalation. The optimized system, while not enantioselective, allowed for the addition to several cyclic and acyclic enones at 0 °C in 6 h with near quantitative yields (Scheme 1.1-6)[8].



Scheme 1.1-6: Addition to enones utilizing achiral diene ligands with an inorganic base.

The same year, Hayashi and co-workers set out to extend the concept of using diene ligands for the reaction by creating chiral dienes to affect a stereoselective variant as had previously been done with the phosphine ligands. The authors synthesized a chiral diene based on the norbornadiene scaffold and found that it was able to affect the addition with some of the best enantioselectivity ever seen for this reaction (Scheme 1.1-7)[9]. The success of this study spurred a large interest in chiral dienes as ligands for asymmetric catalysis and, since the initial report several groups have reported new and improved chiral dienes which reached improved yields and selectivity and also a large expansion of the substrate scope[10].



85-96% yield
95-97% ee

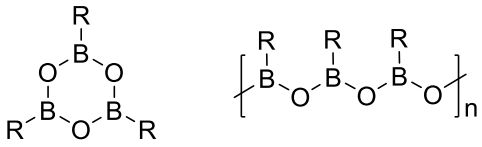
R = Ph, 3-OMePh, 4-OMePh, 4-MePh, 3-ClPh, 2-napthyl

Scheme 1.1-7: Asymmetric Rh catalyzed 1,4-addition utilitzin a chiral diene ligand

1.1.2 Organoboron Compounds

The outer shell bonding electrons ($2s^2$, $3p^1$) in neutral boron can engage in three sp^2 hybridised bonds, resulting in a trigonal planar geometry, with the resulting non-bonding vacant p-orbital orthogonal to the plane. This empty p-orbital dominates the reactivity pattern and physical characteristics of all neutral sp^2 boron compounds and renders them susceptible towards electron donation from Lewis base.

The boron reagents initially employed for Miyaura coupling were alkenylboranes and catechol boronic esters, both conveniently obtained through the hydroboration of terminal alkynes. However, by the 1990s boronic acids had become the reagents of choice, especially for aryl couplings, primarily due their enhanced reactivity and high atom-economy. Pinacol boronic esters also became popular. In general, boronic acids or esters bearing sp^2-hybridized substituents react very well under coupling condition. However, the boronic acids are often subject to dimerization and cyclic trimerization with loss of water to form boronic acid anhydrides (**1.7**) and boroxines (**1.8**) (Figure 1.1-1), respectively, and the determination of precise stoichiometry can be extraordinarily difficult, requiring an excess of these compounds in the coupling reactions.



(1.8) **(1.7)**

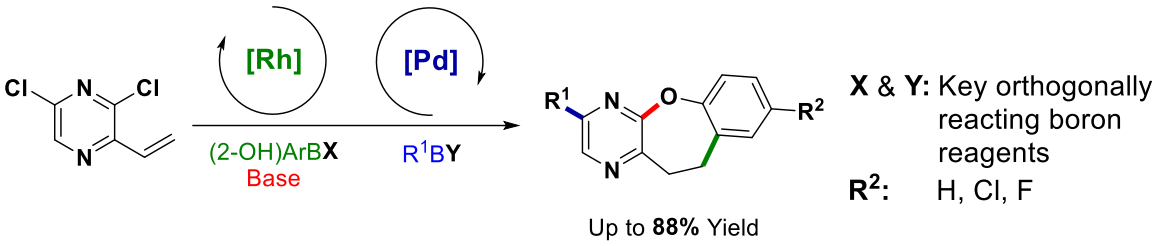
Figure 1.1-1: Bornic Acid anhydrides and boroxines structures

Pinacolyl boronate esters have the advantage of being stable compunds. Although they are useful substrates for cross-coupling chemistry in their own right, many procedures are more efficient with or have an absolute requirement for free boronic acids in order to proceed and higher yields achievement. Hence, the conversion of pinacolyl organoboronate esters to the corresponding organoboronic acids is of much interest.

However, the use of organoboranes has different disadvantages as aerobic oxidation, dehydroboration and proto-deboronation, which not only limit their application, but also decreases yields during coupling reactions. One the other hand, potassium organotrifluorobarates salts and MIDA borate species offer solutions for these problemes. These species are easily prepared and purified, but they are also air and moisture stable. Offering an alternative to commonly used organoboron compounds. However, It was shown for the Suzuky-Miyaura reaction that both MIDA and trifluoroborates species are not active coupling reagents but rather slowly hydrolyze to the respectively boronic acids[11] by a base in the reaction mixture. Elucidation the important role of the base for the transmetalation step when using these borane species.

1.2 Previous Work by our Group

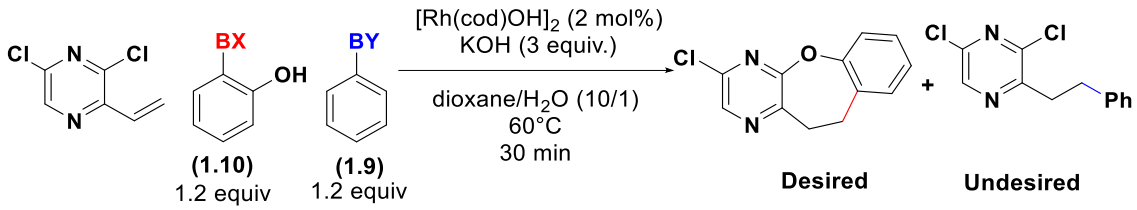
Our group recently reported a novel Multicomponent-Multicatalytic Reaction of a vinyl pyrazine substrate combining a Rh catalyzed hydroarylation, base mediated SNAr cyclization and a Pd catalyzed Suzuki coupling (Scheme 1.2-1)[12].



Scheme 1.2-1: Multicomponent-Multicatalytic Rection of Vinyl pyrazine reported by Lauten's group.

Furthermore, some competition experiments with the boron coupling reagents in the Rh catalyzed hydroarylation were carried out because the Suzuki coupling and the Rh catalyzed hydroarylation both typically employ boronic acid coupling partners. Consequently, showing some selectivity issues arising from the combination of these two reactions in the Multicomponent-Multicatalytic reaction. It was reasoned that the selectivity only needed to be achieved in the rhodium step, allowing a quick consumption of one of the boron species and leaving only the second one (**R'BY**, Scheme 1.2-1) available for the Suzuki coupling. Two different boronic substrates were employed, phenylboronic acid (**PhB(OH)$_2$**) and the *ortho*-hydroxyphenylboronic acid (**PhOHB(OH)$_2$**), which were later used to synthesise all boronic reagents for the competition experiment. The *ortho*-hydroxiphenylboronic partner was used instead of another kind of boronic reagent because it is the one leading to the desire product for the following cyclization.

Table 1.2-1: Competiton experiments of boron coupling reagents in the Rh catalyzed hydroarylation.



B(OHPh)X \ B(Ph)Y	BF_3K	BMIDA	$B(OH)_2$	BPin
BF_3K	0.27:1	0.05:1	0.02:1	2.57:1
BMIDA	1:1	0.35:1	0.02:1	1.53:1
$B(OH)_2$	2.3:1	2.04:1	0.59:1	2.62:1
BPin	**>25:1**	20:1	1.31:1	1.79:1

The combinations within the diagonal of the table were investigated first (Table 1.2-1), to elucidate the effect of this hydroxyl group of the borane partner on the reactivity. This experiment showed a slight inhibiting effect for the ortho-hydroxy substituted boronic acid, MIDA boronate, and trifluoroborate coupling partners. However, an acceleration was observed in the *ortho* substituted pinacol ester (**PhOHBPin**). As a general conclusion of the table (Table 1.2-1), a trend was observed when the boronic acids have a higher reactivity than MIDA boronates, which are more reactive than trifluoroborates. Besides it was also found that the BPin esters do not fall nearly into this scale, showing the non-substituted BPin to be the least reactive species of any boron species whereas the substituted BPins ester was the most reactive one, demonstrating a significant role of the *ortho*-hydroxy group in the activation of the BPin ester. However, to better understand these trends an analogy was draw to Suzuki couplings, in which MIDA boranes and trifluoroborates are not active coupling reagents but rather slowly hydrolyze to active boronic acids[11,13]. Due to this, they were considered as boronic acids and attribute the lower reactivity of these reagents to the slowly hydrolysis step. The boronic esters were thought to react directly in ester form rather than requiring hydrolysis to the acid.[14]

Chapter 2 – Objective

Really interesting results were shown within a brief selectivity study of boron reagents for the rhodium catalysed 1,4-addition (Table 1.2- 1). As no previous studies were found about this topic a hypothesis was raised.

Hypothesis: *"The boron reagents selectivity is general for substrates of different reactivityunder the Hayashi-Miyaura conditions"*

Keeping that in mind, it was outlined the idea of continuing this selectivity study between phenylborates and *ortho*-hydroxyphenylborates, to see if this hypothesis can be approved. It was decided to carry out different competition experiments with substrates that are known to be less reactive than pyrazines but that have different reactivity between them (Figure 2.-1), such as benzyl acrylate (**2.1**), oct-1-3-one (**2.2**), cyclohexenone (**2.3**) and acrylamide (**2.4**).

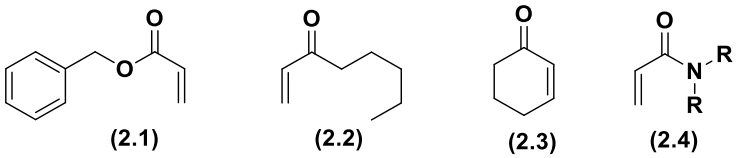
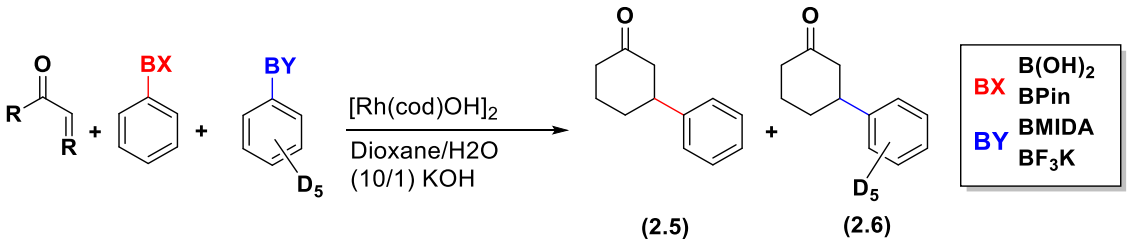


Figure 2.-1: All substrates suggested for the further competition experiments.

Checking out the literature was also noticed that studies of the relative boron species reactivity for the rhodium 1,4-addition have not been done. Taking that into account, it was decided to carry out different competition experiments between deuterated and non deuterated phenylboronic species to see the relative reactivity of the different boronic species (Scheme 2.-1).



Scheme 2.-1: Phenylboronic species relative reactive experiments.

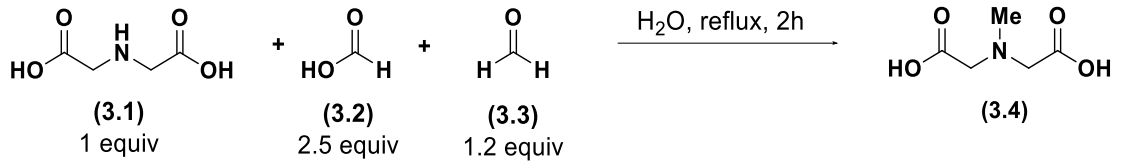
Chapter 3 – Results and Discussion

3.1 *Ortho*-hydroxyphenylboronic and phenylboronic species selectivity study

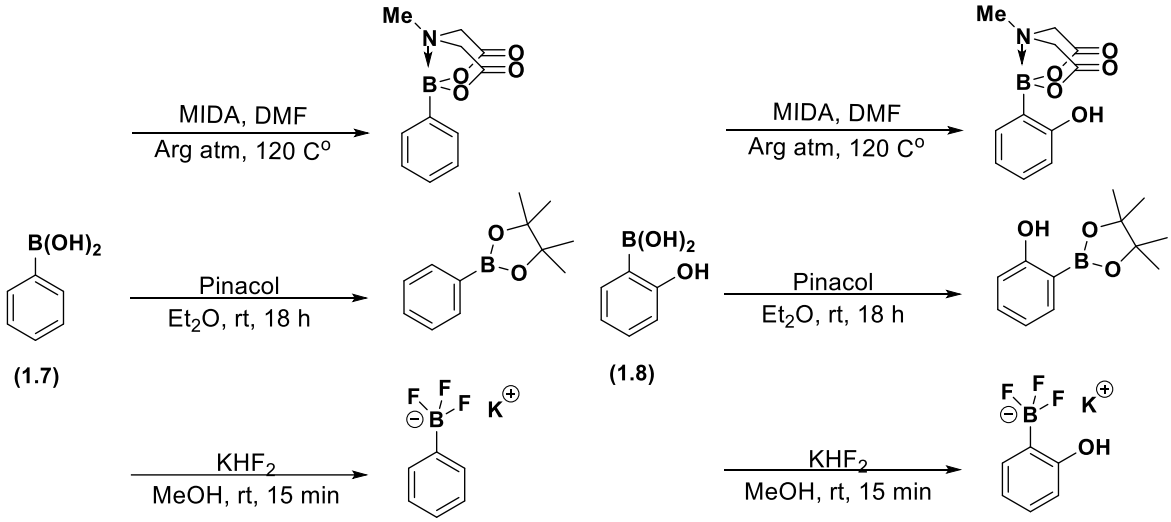
3.1.1 MIDA ligand and oct-1-en-3-one synthesis

To be able to carry out the competition experiments, it was essential to synthesise all the reagents that were need for it, boronic species (Scheme 3.1-2) and substrate (**2.2**). All the boronic species were easily synthesised following the previous work (Scheme 3.1-2). However, the MIDA ligand (**3.4**) was need to be synthesised[15]as it is shown in (Scheme 3.1-1), employing iminodiacetic (**3.1**), formic acid (**3.2**) and formaldehyde (**3.3**), for the later borane MIDA species synthesis.

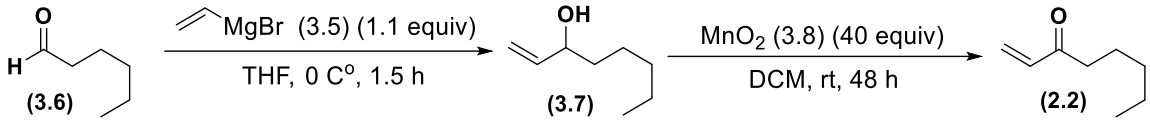
Thereafter, it was decided to go towards the substrate (**2.2**), which was synthetized by 1.2-addition of vinylmagnesium Bromide (**3.5**), to hexanal (**3.6**), and followed by allylic oxidation of (**3.7**) with Manganese Dioxide[16] (**3.8**), forming oct-1-en-3-one (**2.2**) (Scheme 3.1-3).



Scheme 3.1-1: Conditions for MIDA ligand synthesis



Scheme 3.1-2: Synthesis pathways for all boronic reagents

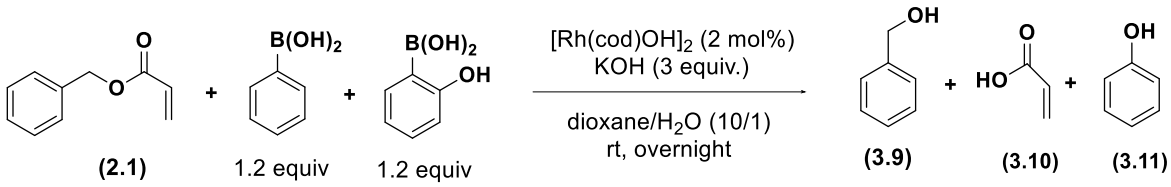


Scheme 3.1 -3: Substrate 3.2 synthesis by 1.2-addition and an allylic oxidation.

3.1.2 Benzyl acrylate competition experiments

Following the previous work on dichlorovinylpyrazines (section 1.2) it was decided to carry out competition experiments on a comparably reactive substrate. As an electron-poor mono-substituted Benzyl acrylate appeared to be a suitable starting point for the following investigations.

The first competition experiment was considered with substrate (**2.1**) purchased from Aldrich. Two reactions were set up, one with **$PhB(OH)_2$** and the other one with **$PhOHB(OH)_2$**, trying to obtain the pure products for each one. Although the conditions were the same as previously described (Table 1.2-1), only changing from the initial temperature to room temperature and allowing to stir overnight, surprisingly no product was observed in either of them (Scheme 3.1-4). However, the formation of phenylmethanol (**3.9**) and acrylic acid (**3.10**) was noticeable. Afterwards, the reactions were carried out with a bigger amount of borane reagents (1.3, 1.4, and 1.5 equivalents), the results kept the same pathway. It was clear that the substrate (**2.1**) could not survive to the Hayashi-Miyaura conditions and phenylmethanol (**3.9**), and acrylic acid (**3.10**) were formed as major products by a saponification reaction. Finally, phenol (**3.11**) was reasoned to be caused by the proto-deboronation of the aryl-rhodium species and the **$PhOHB(OH)_2$** hydrolysis.



Scheme 3.1-4: Competition experiment of substrate 3.1 showing no formation of the desire product.

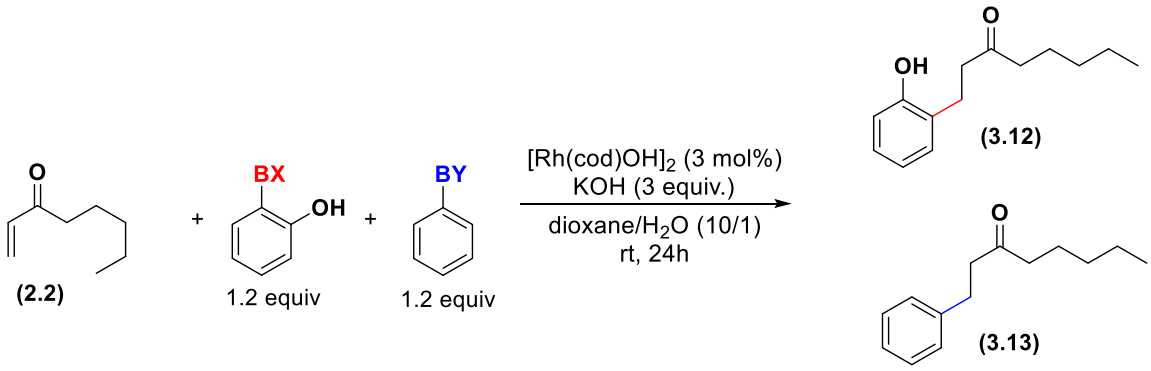
3.1.3 Oct-1-en-3-one competition experiments

Circumventing the observed saponification of the benzyl acrylates in the previous chapter, ongoing investigations focussed on oct-1-en-3-one as a stable and even more reactive substrate.

Taking the results in section 3.1.2 into account, the competition experiments with substrate (**2.2**) employing 1.2 equivalents of the respective borane based coupling partners were subsequently set up and allowed to stir overnight, providing products (**3.12**) and (**3.13**).Highly interesting

results were obtained with these competition experiments (Table 3.1-1): Direct investigation of the OH-effect (diagonal in the table) showed some dramatic difference. While the **Ph(OH)BF_3K** showed an exceptional product ratio in favour for the ortho-substituted product, the remaining combinations proved to be surprisingly unselective. Taking a look on the trends within the columns, no outstanding selectivity in favour for one of the two possible products was found. The combination of **$PhB(OH)_2$** and **Ph(OH)BMIDA** represents an exception as good selectivity was found for the non-ortho-subtituted product (11:1). It is worth mentioning that the combination of **PhOHBPin** with the non-substituted reagents gave a consistent trend in favour for the ortho-substituted product, underlining a potential activation of the hydroxyl group, as it was shown in Table 1.2-1 in the previous work.

Table 3.1-1: Competition experiments with oct-1-en-3-one (4.12).

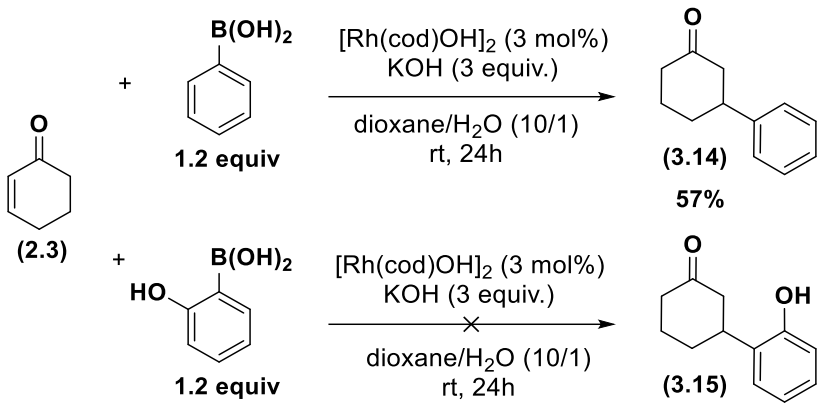


B(OHPh)X \ B(Ph)Y	BF_3K	BMIDA	$B(OH)_2$	BPin
BF_3K	25:1 64%-[a]n%	1:4 13%-53%	1:4.4 9%-40%	1:2.4 19%-46%
BMIDA	25:1 50%-[a]n%	1:1.3 63%-[a]n%	1:11 6%-51%	1:1.58 20%-32%
$B(OH)_2$	25:1 52%-[a]n%	1.78:1 41%-23%	1:1.4 32%-45%	1.53:1 33%-22%
BPin	**>25:1** 56%-[a]n%	1.57:1 34%-22%	2.34:1 37%-16%	1.5:1 48%-24%

Note: NMR yields using 1,3,5-trimethoxybenzene as internal standard, can be observed (OHPh - Ph). [a] No product observed.

3.1.4 Cyclohexenone competition experiments

To evaluate the influence of the reactivity of the targeted substrate, cyclohexenone was selected due to its significant lower reactivity. Therefore, analogue competition experiments were carried out to show, if the observed selectivities of the different boron species is influenced by this factor (Table 3.1-1.).



Scheme 3.1-5: 1,4-addition Hayashi-Miyaura reaction employing non-substituted boron species.

Though interesting results were achieved with substrate (**2.2**), the reactions with the two boron based coupling reagent were carried out separately under the same conditions applied before. The first one with the non-substituted boron showed full conversion of the starting material, forming the desired product (67%, 3.14) (Scheme 3.1-5). The second one with the *ortho*-substituted (1.2 equiv), however, revealed that no product was observed through TLC and NMR. Solely, starting material and phenol was identified in the reaction mixture. Taking this into account, it was decided to rise the equivalent of the substituted boron species to enforce product formation. Nevertheless, the same results were achieved showing that the 1,4-addition is too slow to outcompete the proto-deborelation process. As it has been shown that the reaction works with highly reactive enones we turned our attention to a deeper understanding of this finding with aim of understanding the origin of the fast formation of phenol.

3.1.5 Mechanistic experiments and Base free competition experiments

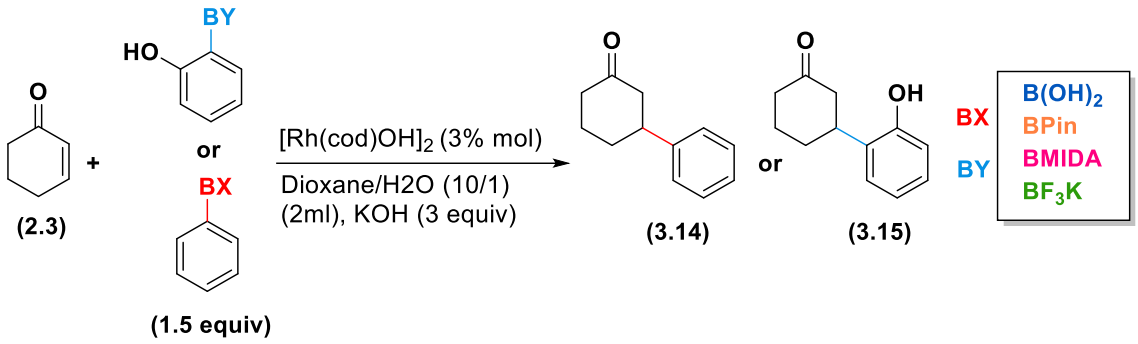
Seeing the results that were shown in section 3.1.4, different experiments were carried out to elucidate the reason for the predominant proto-deborelation when using the *ortho*-substituted boronic reagent (Table 3.1-2).

In this regard, entry **1a** (Table 3.1-2) shows that in the absence of substrate and rhodium catalyst the boron reagent is not undergoing the observed hydrolysis under the reaction conditions applied before. On entry **2** (Table 3.1-2), where the rhodium catalyst is additionally present, phenol formation was observed, elucidating that the proto-demetalation occurs from the Rh-Ar species as full stability was observed in the absence of the Rh-catalyst. A control experiment

(entry **3b**) was set up to investigate the influence of phenol as a potential catalyst poison. (WORD) Under the same conditions a decrease in yield from 62 to 36% was shown suggesting an inhibiting effect to the 1,4-addition by the phenol, but still, product formation was observed. This may be a result of a competitive coordination to the rhodium catalyst, disturbing the desired catalyst performance. Knowing that the proto-demetalation is only happening in the presence of the rhodium catalyst (entry **2**), a last control experiment in the absence of base should show, if the reaction could be realized under neutral conditions. As depicted in entry **4** and entry **5** both reagents provided the targeted products (62%, 3.14 and 51%, 3.15). Moreover, phenol was still in the mixture but in much lower concentration. Afterwards, a water free control experiment (entry **6**, Table 3.1-2) was set up showing no product (**3.15**) formation, which was expected due to the essential need of water for the protonation of the rhodium enolate within the catalytic cycle. Having fixed the proto-demetalation problem we were now able to perform the desire competition experiments. These modified conditions also worked for the other reagents in isolated cases, showing product formation **PhBF$_3$K** (91%, entry **10**) and **PhBPin** (66%, entry **8**). For the MIDA system (P**hBMIDA** entry **9**), exceptionally, no conversion was detected. This fact is not surprising, as in analogy to the Pd-couplings MIDA has to be hydrolysed to the respective boronic acids prior to a reaction. Much more interesting, **PhBF$_3$K** undergoes the 1,4-addition,suggesting that these reagents may be able to transmetalate directly from the trifluoroborate species rather than slowly hydrolyse to the specific boron acid. As under neutral conditions HF is produced during hydrolysis, the equilibrium should be shifted towards the condensation back to the trifluroborate reagent.

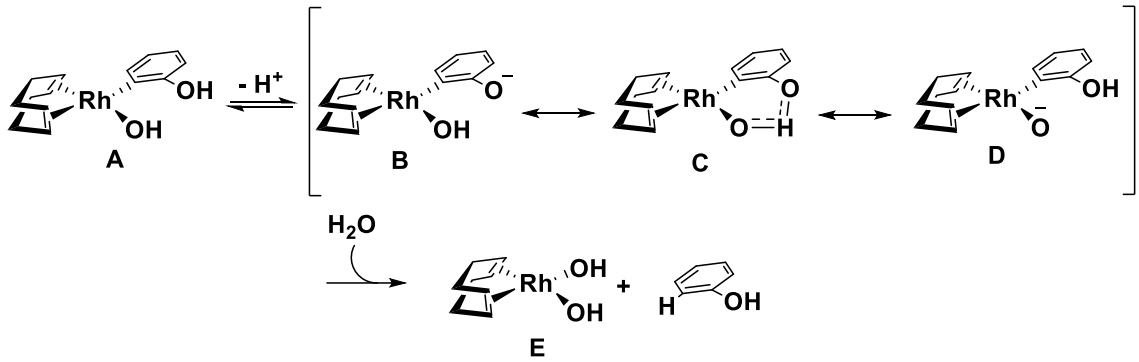
Taking the formation of product (**3.14**) under base-free conditions into account, a possible mechanism was reasoned to explain the role of base in the proto-derhodation. It is suggested that the transmetalation occurs, which is supported by the fact that proto-derhodation is observed within the control experiments in table 3.1-2 (entry **1a**). When the transmetalation has been completed (**A**) it is likely that due to its acidity the phenol exists in its deprotonated form. The resulting negative charge can be delocalized via hydrogen bonding with the hydroxy ligand coordinated to the rhodium, being able to form a six member ring intermediate **B-D**. As a result of this delocalisation the Lewis acidity at the rhodium decrease weakening the Rh-C bond, which allows for a more facile proto-derhodation of the aryl-rhodium species forming phenol and **E**.

Table 3.1-2: Mechanistic experiments to elucidate the reason of no product being formed. Showing what was and what was not added to the reaction mixture in each time.



Entry	Subs (2.3)	[Rh]	BX	BY	Temp °C	KOH	Dioxane	H_2O	Product Yield (%)
1a	-	-	-	●	25	✓	✓	✓	-
2	-	✓	-	●	25	✓	✓	✓	-
3b	✓	✓	●	-	25	✓	✓	✓	36
4	✓	✓	●	-	25	-	✓	✓	62
5	✓	✓	-	●	25	-	✓	✓	51
6	✓	✓	-	●	25	-	✓	-	-
7	✓	✓	-	●	60	✓	✓	✓	<10
8	✓	✓	●	-	25	-	✓	✓	66
9	✓	✓	●	-	25	-	✓	✓	-
10	✓	✓	●	-	25	-	✓	✓	91

Note: Dioxane: 1.8 ml were used. H_2O: 0.2 ml were used. 1a) No phenol was formed. 3b) 1 equiv of phenol was added**.** Product yield were calculated by NMR using 1,3,5-trimethoxybenzene as internal standard.



Scheme 3.1-6: Proposed proto-derhodation mechanism when base is added.

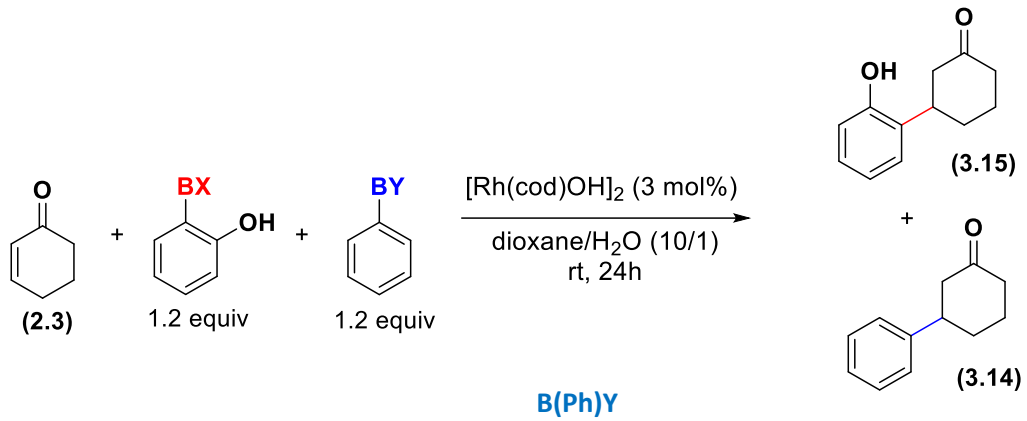
Finally, showing that the 1,4-addition with *ortho*-hydroxy boron reagents can be realized under base-free conditions, we were interested in carrying out analog competition experiments (Table 3.1-3). The MIDA species were not employed for these competition experiments because of its lack of reactivity (entry **9**, Table 3.1-2).

Taking a look to the results, the **PhOHBPin** showed by far to be *once again* the most selective one when it is combined with **PhBF$_3$K** (25:1), being the only highly selective among the *ortho*-

hydroxyphenyl boron reagents. Gratifyingly, the combination of **PhBF$_3$K-PhB(OH)2** showed good *inverted* selectivity (1:9) which is fully corresponding to the work on pyrazines and Table 3.1-1. Besides that, **BPin** also showed good selectivities against **PhOHB(OH)$_2$** (8:1), while the other combination showed no predominant selectivities.

Ongoing work will focus on an understanding of the observed selectivities. With regard to this, the kinetics of the 1,4-addition reaction for each reagent has to be investigated, as the speed of the 1,4-addition could have an significant impact on the observed product ratios. Outstanding is the phenomenon approved for the **PhOHBPin** reagent, which consistently shows superior selectivities, clearly pointing on a hydroxyl substituent effect. Deeper investigations have to be conducted to understand this exceptional activation.

Table 3.1-3: Base free cyclohexenone competition experiments.

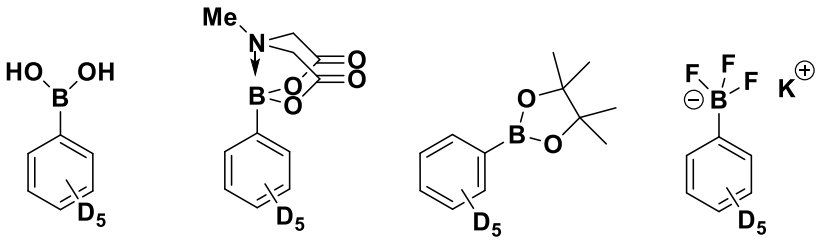


B(OHPh)X \ B(Ph)Y	BF_3K	$B(OH)_2$	BPin
BF_3K	1:1.5 57%-14%	1:9 10%-81%	1:3.5 19%-66%
$B(OH)_2$	1:1.6 38%-61%	1:1.2 34%-47%	1:8 12%-80%
BPin	25:1 72%-5%	1:1.6 36%-58%	2:1 26%-13%

Note: Dioxane: 1.8 ml were used. H_2O: 0.2 ml were used. NMR yields using 1,3,5-trimethoxybenzene as internal standard, can be observed (OHPh - Ph).

3.2 Boron's reagents relative reactivity

Discovered in the nineties the Hayashi-Miyaura is a young reaction in the organic chemistry world. For this reason, there is still a long way to its totally understanding. As mentioned in Section 2, relative reactivity experiments of the boron species used for this reaction have not been done. Taking this into account, it was decided to carry out different competition experiments between deuterated (Figure 3.2-1), and not deuterated borane species. These experiments would allow to see the different reactivity between each borane species without being affected by the aryl electronic properties.

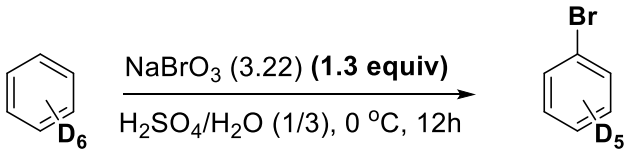


(3.16) (3.17) (3.18) (3.19)

Figure 3.2-1: All deuterated borane species being synthesised.

3.2.1 Deuterated species synthesis

For this study, deuterated benzene (**3.20**) was used as the substrate for the deuterated bromobenzene (**3.21**) synthesis[17] (Scheme 3.2-1). A mixture of sulfuric acid and water (1:3), and sodium bromate (**3.22**) were mixed at 0 ^{o}C to avoid di/tri-bromination. Afterwards, a destilation under low-pressure was carried out for its purification.



(3.20) (3.22)

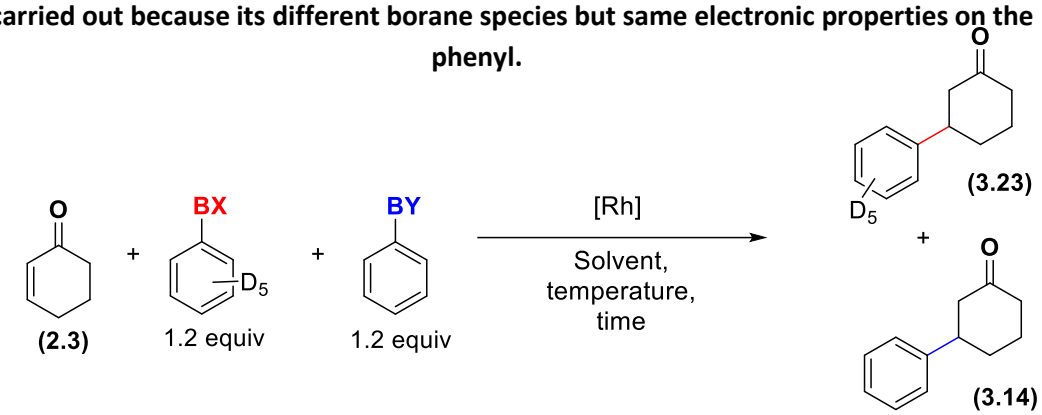
Scheme 3.2-1: Deuterated bromobenzene synthesis.

3.2.2 Our aim in the future

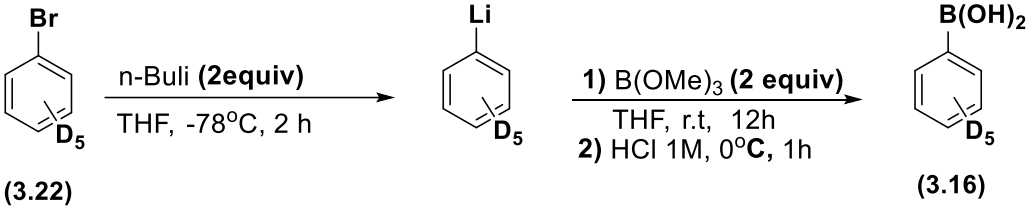
The synthesis of deuterated phenylboronic acid [18](scheme 3.2-2) has shown some issues making necessary the reaction condition to be optimized. As soon as, the deuterated boronic acid is successfully synthesised, all the deuterated boron reagents (Figure 3.2-1) have to be synthesised following the condition showed in (Scheme 3.1-2). Afterwards, the main goal is to carry out different competition experiments (Table 3.2-1), where reactivity variations between all different borane reagents are expected to be shown in the proton and carbon NMR. However, different reaction conditions and catalysts as $[Rh(cod)OH]_2$ and $[Rh(cod)Cl]_2$, are also being tried

looking forward higher yields when a base is in the mixture. Allowing the MIDA boron reagent to be used as well.

Table 3.2-1: Shown with green circles the different competition experiments that will have to be carried out because its different borane species but same electronic properties on the phenyl.



B(Ph)Y / B(Ph$_{D5}$)X	BF_3K	BMIDA	$B(OH)_2$	BPin
BF_3K		-	-	-
BMIDA	●	-	-	-
$B(OH)_2$	●	●	-	-
BPin	●	●	●	-



Scheme 3.2-2: Deuterated boronic acid synthesis conditions.

Chapter 4 – Conclusions

To summarize, the main goal of the project was to investigate if the excellent selectivity found for the pyrazines substrates is general for a different set of substrates regarding the Hayashi-Miyaura reaction.

With oct-1-en-3-one representing a highly reactive substrate all the *ortho*-hydroxy substituted boron reagents showed an exceptional high selectivity (25:1) against **$PhBF_3K$**. Besides that the combination of **$PhB(OH)_2$** with **PhOHBMIDA** and **$PhOHBF_3K$** showed a good inverse selectivity (1:11) (1:4.4) respectively, favoring the non-substituted phenyl product.

For cyclohexenone being a low reactive substrate the reaction with the substituted boron reagents could not be realized due to the complete proto-demetalation of the boron reagent. The control experiments showed that the proto-demetalation occurs from the Aryl-Rhodium species. It was found that the reaction can be performed without base allowing the realization of the analog competition experiments. MIDA species were unreactive under these reaction conditions. The reactivity in the absence of base indicates a very facile transmetalation process, as usually base is added to catalyze this step in the catalytic cycle of the Hayashi-Miyaura reaction[19]. However, exceptional high reactivity was again shown for the **PhOHBPin** against **$PhBF_3K$** (25:1). Moreover, the combination of **$PhB(OH)_2$** with **$PhBF_3K$** and **PhBPin** with **$PhB(OH)_2$** showed high selectivity (1:9) (1:8) respectively, favouring the non-substituted phenyl product.

Comparing the obtained results with the former study on pyrazines, the same trends were observed. Outstanding selectivity was realized when reacting **PhOHBPin** and **$PhBF_3K$** in competition. Moreover, the same reagent combinations **$PhB(OH)_2$** with **$PhOHBF_3K$** consistently gave the inverse selectivity favouring the phenyl substituted product. Therefore, the generality regarding the selectivity of boron based reagents employing high and low reactive substrates has been approved. Interestingly, the fact that fast proto-derhodation was found for the cyclohexenone as slower reacting substrate indicates a high reactivity of the Rh-Ar-species. This species undergoes fast 1,4-additions in the presence of a highly reactive substrate, whereas with a slower one proto-deborelation outcompetes the desired pathway. This effect can be attributed to the presence of an ortho-hydroxy group, which supports the theory of an activating effect of this substituent. Further studies are underway to understand this potential accelerating effect.

Besides these interesting results, it was found that trifluoroborates are good coupling partners even in the absence of base, which suggests that a transmetallations occurs without prior hydrolysis to the respective boronic acids.

Further studies are underway to investigate the general selectivity of boronic based reagents apart from substituent effects. Here, cross-experiments are planned to compare the different combinations of phenyl-reagents and their deuterated counterparts to focus on the effect of the reagent's nature.

Chapter 5 – Supporting Information

4.1 General Considerations

General Experimental Procedures: Unless otherwise noted, catalytic reactions were carried out under argon atmosphere in sealed 2-dram glass vials with magnetic stirring while non-catalytic reactions were carried out under argon atmosphere in single-necked round bottom flasks fitted with a rubber septum, with magnetic stirring. TLC was performed with EMD Millipore™ normal phase silica plates (60 Å pore diameter, F254 indicator). Visualization of developed plates was performed under UV light (254 nm) or by immersion in potassium permanganate ($KMnO_4$) stain, followed by heating with a heat gun. Purification of products was accomplished by silica flash column chromatography with Silicycle Ultra-Pure™ 230-400 mesh silica gel.

Materials: Unless otherwise noted, starting materials, ligands, and catalysts were purchased from Aldrich, Strem, Combi-Blocks, or VWR and used without further purification. Dichloromethane and 1,4-dioxane were freshly distilled over calcium hydride before use and tetrahydrofuran was freshly distilled over sodium/benzophenone before use.

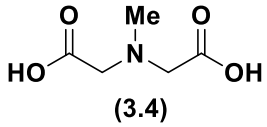
Instrumentation: 1H NMR and13C NMR were recorded at 23 °C with a Bruker Advance III 400 MHz, an Agilent DD2 500 MHz, or a Varian VnmrS 400 NMR spectrometer. Shifts for 1H NMR spectra are reported in parts per million (δ scale) and are referenced to the residual solvent signal ($CDCl_3$, δ = 7.26 ppm) or tetramethylsilane (δ = 0 ppm). Chemical shifts for carbon resonances are reported in parts per million (δ scale) and are referenced to the carbon resonance of the solvent ($CDCl_3$, δ= 77.16 ppm). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constant (J, Hz).

Chemical nomenclature generated using CambridgeSoft ChemBioDraw Ultra 13.0 software.

4.2 Synthesis of Compounds

Synthesis of MIDA:

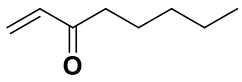
2,2'-(methylazanadiyl)diacetic Acid[15]



(3.4)

To a 3-neck 1 L round bottom flask equipped with a large stir bar was added iminodiacetic Acid (100 g, 1 equiv, 0.75 mol), water (84 ml) and formic Acid (2.26 mol, 86 ml of 98% solution). The flask was fitted with a thermometer, a 500 ml pressure-equalizing addition funnel charged with formalin (1.14 mol, 230 ml 37% solution) and a water-cooled Friedrich condenser vented to ambient atmosphere. The mixture was heated to a gentle reflux. To the stirred mixture was added dropwise the formalin at a rate necessary to control the effervescence. Following the addition, the mixture was maintained at reflux for an additional 2 h. The solution was cooled to room temperature and transferred, washing with water, to a 5 L Erlenmeyer flask. Onto the aqueous solution was layered acetone (3 L) such that the aqueous phase remained undisturbed and the phase did not mix. The mixture was allowed to stand undisturbed for 1 week during which time the product crystallized as large colorless crystals. The crystals were collected via filtration, washed with acetone and dried *in vacuo* to afford white crystals (97g, 88% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 3.37 (s, 4H), 2.41 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 176.67, 61.93, 46.76.

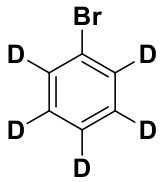
Synthesis of oct-1-en-3-one (2.2)[16]



(2.2)

To a 3 neck round bottom flask equipped with a stir bars was added hexanal (3 g, 7.75 ml) and tetrahydrofuran anhydrous (30 ml). The mixture was cooled to 0 ^{o}C and vinyl magnesium bromide (41.9 ml, 1M solution) was added dropwise. It was allowed to stir during 1 h at 0 ^{o}C. The mixture was washed with saturated ammonium chloride and purified by flash column. The product (oct-1-en-3-ol) was diluted with dichloromethane into a round bottom flask followed by the addition of manganese dioxide (40 equiv), and allowed to stir for 48 h. The mixture was filtrated, washed down with dichloromethane and purified by flash column with pentanes/ethyl ether as eluent. The solution was dried *in vacuo* and rapidly diluted with dichloromethane to avoid the polymerization. (66% overall steps yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 6.35 (dd, J = 17.79 Hz, 1H), 6.20 (dd, J = 17.72 Hz, 1H), 5.80 (dd, J = 10.55 Hz, 1H), 2.57 (m, 2H), 1.64 (m, 2H), 1.30 (m, 4H), 0.89 (m, 3H).

Synthesis of 1-bromobenzene-2,3,4,5,6-d_5 (2.2)[17]



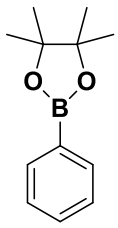
(3.22)

To a vigorous stirred solution of sulfuric acid (16.65g, 9.05 ml) in water (33.3 ml), deuteriobenzene (4.212 g, 1equiv, 50 mmol, 4.43 ml) was added in one portion at 0 °C. Thereafter, nodium bromate (8.30 g, 55 mmol) was added in two portions with an interval of 1 h at the same temperature. The reaction mixture was stirred for an additional 10 h at ambient temperature, pured into ice-cold water (100 ml) and extracted with *n*-pentane (3 x 40 ml). The combines extracts were washed with ice-cold water (2 x 50 ml), sat aqueous sodium hydrogen carbonate solution (2 x 50 ml), brine (40 ml), and dried. *n*-Pentane was carefully evaporated through a 40 x 2-cm column packet with glass helices, and the residue was ""bulb-to-bulb"distilled at 45 °C (0.1 Torr) into a cold (-78 °C) trap to give the product (66%). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 131.43, 131.18, 130.92, 129.82, 129.58, 129.33, 126.67, 126.42, 126.18, 122.34.

General Procedure for the Synthesis of Arylboronic acid pinacol esters:

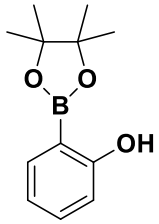
A non-flame dried round bottom flask was charged with boronic acid, pinacol (2 equiv), and Ethyl Ether (0.1M) and allowed to stir at room temperature for 18 hours. The solvent was removed in vacuo and the crude was filtered through a plug of silica eluting with Ethyl Ether.

4,4,5,5-tetramethyl-2-phenyl-1,2,3-dioxaborolane



Phenylboronic acid (3 g, 24.6 mmol) and pinacol (8.9 g, 50 mmol) were used giving the product (5.4g, 99% yield) as a white solid crystals. Spectroscopic data is consistent with that reported in the literature. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.81 (m, 2H), 7.46 (m, 1H), 7.38 (m, 2H), 1.35 (s, 12H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 134.72, 131.22, 127.68, 83.74, 24.86.

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol:

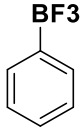


2-hydroxyphenylboronic acid (3.7 g, 26.8 mmol) and pinacol (6.2 g, 52.5 mmol) were used giving the product (5.7 g, 99% yield) as an amber oil. Spectroscopic data. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.81 (m, 1H), 7.62 (m, 1H), 7.38 (m, 1H), 6.89 (m, 2H), 1.38 (s, 12H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 163.68, 135.75, 133.84, 119.53, 115.48, 84.45, 24.82.

General Procedure for the Synthesis of aryl trifluoroborates:

To a solution of boronic acid in a minimal amount of methanol, a saturated aqueous solution of KHF_2 (3.3 equiv) was added dropwise. The solution was allowed to stir for 10 min over which time significant precipitation of the product is observed. The solvent was removed *in vacuo* and the crude product was kept under vacuum until completely dry. The crude was taken up in acetone, decanted, and dried again *in vacuo*. The resulting white powder was dissolved in a minimal amount of hot acetone followed by precipitation with ethyl ether which produce the pure trifluoroborate after collection.

Potassium trifluoro(phenyl)borate



Phenylboronic acid (6.8 g, 55.8 mmol) and KHF_2 (3.3 equiv, 14.6 g, 186.9 mmol) were used giving the product (10.1 g, 97% yield) as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 6.50 (m, 2H), 6.24 (m, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 131.73, 131.71, 126.61, 126.30.

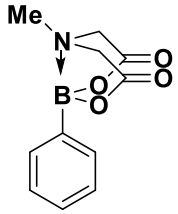
Potassium trifluoro(2-hydroxyphenyl)borate

2-hydroxyphenylboronic acid (4.2 g, 30.5 mmol) and KHF_2 (3.3 equiv, 7.9 g, 101.1 mmol) were used giving the product (5.3 g, 90% yield) as a white powder.**^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.74 (q, J = 11 Hz, 1H), 7.53 (d, J = 6.92 Hz, 1H), 7.34 (td, J = 7.52, 1.85 Hz, 1H), 7.02 (m, 1 H), 6.91 (d, J = 7.88 Hz, 1H), 3.73 (s, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 133.33, 133.31, 127.33, 118.70, 113.65.

General Procedure for the Synthesis of aryl MIDA borates

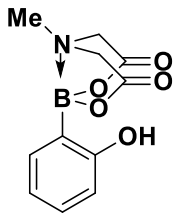
A non-flame dried round bottom flask was charged with boronic acid and MIDA, after been purged with argon DMF was transferred into it and allowed to stir at 120 °C overnight. The reaction mixture was cooled until room temperature and concentrated under reduced pressure. The crude was re-dissolved in acetone and de unreacted MIDA was removed by filtration. The filtrate was purified by flash column chromatography on silica with acetone as an eluent to afford a white powder. The solid obtained was dissolved in a minim amount of acetone and ethyl ether was slowly added to promote the crystallization. The MIDA borate was finally collected by filtration.[20]

6-methyl-2-phenyl-1,3,6,2-dioxazaborocane-4,8-dione



Phenylboronic acid (0.5g, 4.1 mmol) and MIDA (3 equiv, 1.8g, 12.3 mmol) were used giving the product (0.7g, 70% yield) as a white fluffy powder.). . **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.39 (m, 5H), 4.33 (m, 2H), 4.11 (m, 2H) 2.5 (s, 3H).**^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 169.34, 132.30, 128, 82, 127.62, 61.75, 47.55.

2-(2-hydroxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

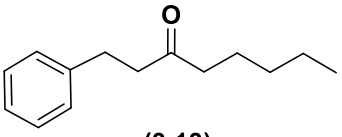


2-hydroxyphenylboronic acid (1.1g, 8 mmol) and MIDA (3 equiv, 3.3g, 22.4 mmol) were used giving the product (1.2g, 68% yield), as a white powder. **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 9.54 (s, 1H), 7.37 (dd, J = 7.35, 1.64 Hz, 1H), 7.15 (ddd, J = 9.45, 7.46, 1.94 Hz, 1H), 6.75 (m, 2H), 4.31 (d, J = 16.9 Hz, 2H), 4.02 (d, J = 16.8 Hz, 2H), 2.61 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 169.86, 160.49, 134.48, 130.73, 119.17, 115.04, 63.58, 47.60.

General Procedure for Rhodium Hayashi-Miyaura Reaction.

A 2-draw-vial was charged with organoborane reagent (1.2 eq), potassium hydroxide (3 eq,), hydroxy(cyclooctadiene)rhodium(I) dimer (3 % mol), then purged with argon. The oct-1-en-3-one (1 eq) and the solvent, Dioxane/H_2O (3/1) were added consecutively and allowed to stir overnight. The crude was concentrated under reduced pressure. The crude was re-dissolved in Ethyl Acetate and filtered with silica, as Ethyl Acetate as solvent. The solution was dried under reduced pressure to afford a yellow-brown oil. The crude was later purified by flash column chromatography on silica with Hexanes/Ethyl Ether as eluent.

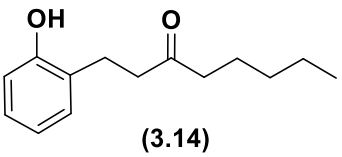
1-Phenyloctane-3-one



(3.13)

Phenylboronic reagent (1.2 eq, 0.4 mmol), oct-1-en-3-one (1 eq, 0.3 mmol, 54.6 mg), hydroxy(cyclooctadiene)rhodium(I) dimer (3 % mol, 0.009 mmol, 4.79 mg), potassium hydroxide (3 eq, 0.9 mmol, 50 mg) and Dioxane/H_2O as solvent (3 ml) were used giving the product as a yellow-brown oil. **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.28 (m, 2H), 7.19 (tt, J = 3.38 Hz, 3H), 2.90 (dd, J = 7.35 Hz, 2H), 2.72 (m, 2H), 2.37 (t, J = 8.02, 2H), 1.56 (m, 2H), 1.27 (m, 4H), 0.88 (t, J = 6.90 Hz, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 210.33, 141.17, 128.44, 128.29, 126.03, 44.23, 43.02, 31.37, 30.86, 29.79, 23.48, 22.42, 13.89.

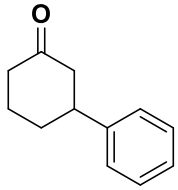
1-(2-hydroxyphenyl)octan-3-one



(3.14)

Orto-hydroxyphenylboronic reagent (1.2 eq, 0.4 mmol), oct-1-en-3-one (I eq, 0.3 mmol, 54.6 mg), hydroxy(cyclooctadiene)rhodium(I) dimer (3 % mol, 0.009 mmol, 4.79 mg), potassium hydroxide (3 eq, 0.9 mmol, 50 mg) and Dioxane/H_2O as solvent (3 ml) were used giving the product as a yellow-brown oil. **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.74 (s, 1H), 7.08 (m, 2H), 6.85 (m, 2H), 2.85 (m, 4H), 2.40 (t, J = 7.31 Hz, 2H), 1.54 (m, 2H), 1.27 (m, 4H), 0.86 (t, J = 7.42 Hz, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 214.33, 154.39, 130.44, 127.93, 120.61, 117.51, 44.37, 42.58, 31.22, 23.48, 23.11, 22.35, 13.83.

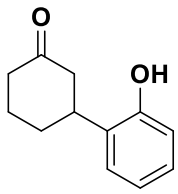
3-phenylcyclohexan-1-one



(3.15)

Phenylboronic reagent (1.2 eq, 0.4 mmol), 2-cyclohexen-1-one (1 eq, 0.3 mmol, 28.83 mg), hydroxy(cyclooctadiene)rhodium(I) dimer (3 % mol, 0.009 mmol, 4.79 mg), potassium hydroxide (3 eq, 0.9 mmol, 50 mg) and Dioxane/H_2O as solvent (3 ml), were used giving the product as a yellow-brown powder. **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.33 (m, 2H), 7.24 (m, 3H), 3.01 (m, 1H), 2.50 (m, 4H), 2.12 (m, 2H), 1.82 (m, 2H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 210.93, 144.34, 126.67, 126.56, 48.93, 44.74, 41.18, 32.77, 25.53.

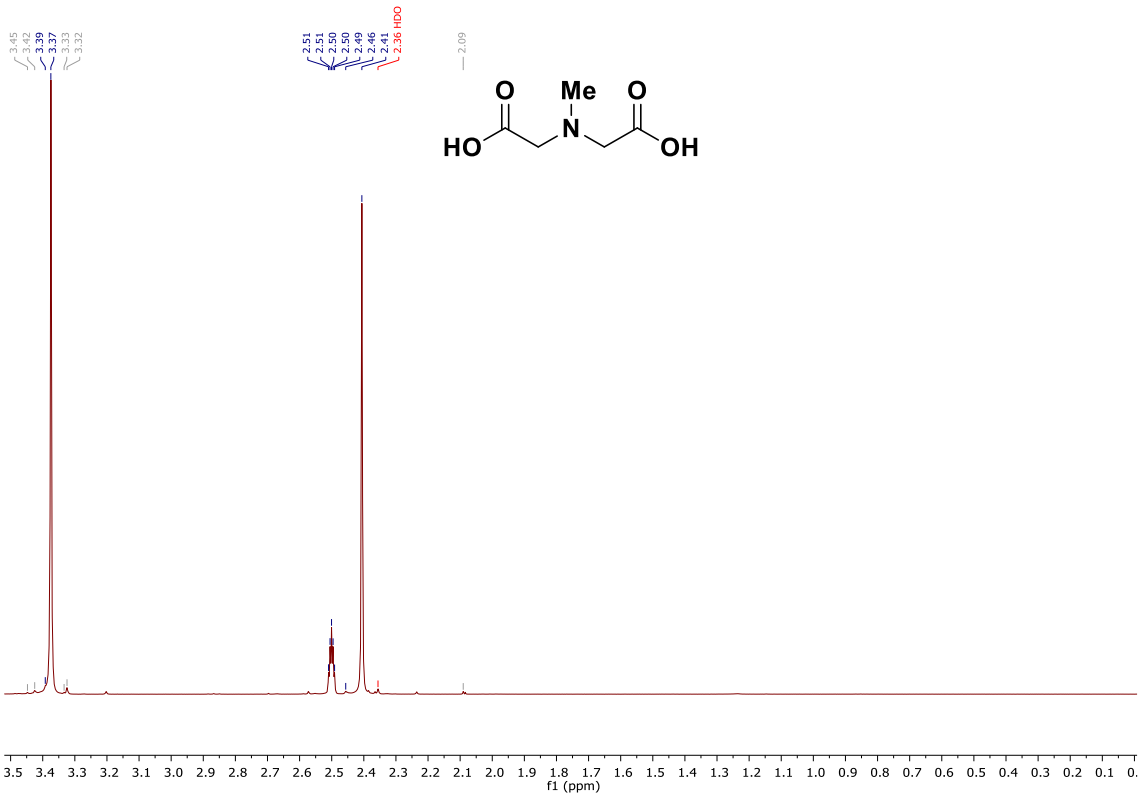
3-(2-hydroxyphenyl)cyclohexan-1-one

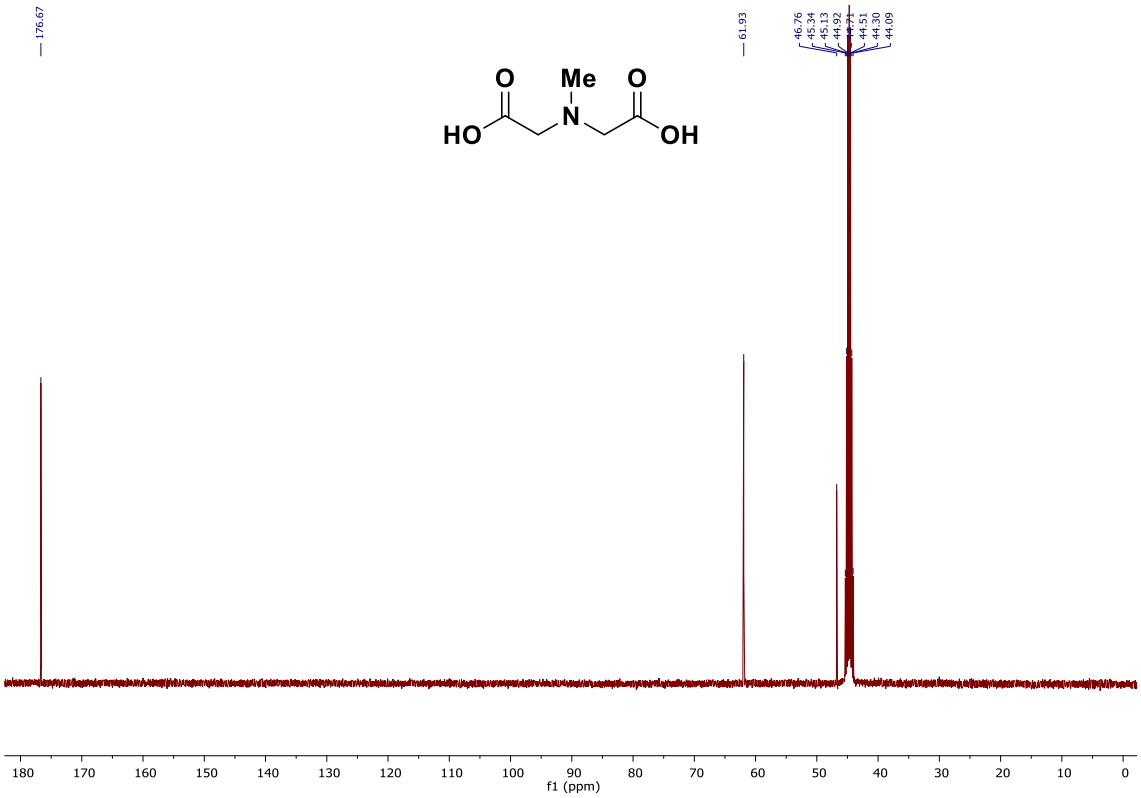


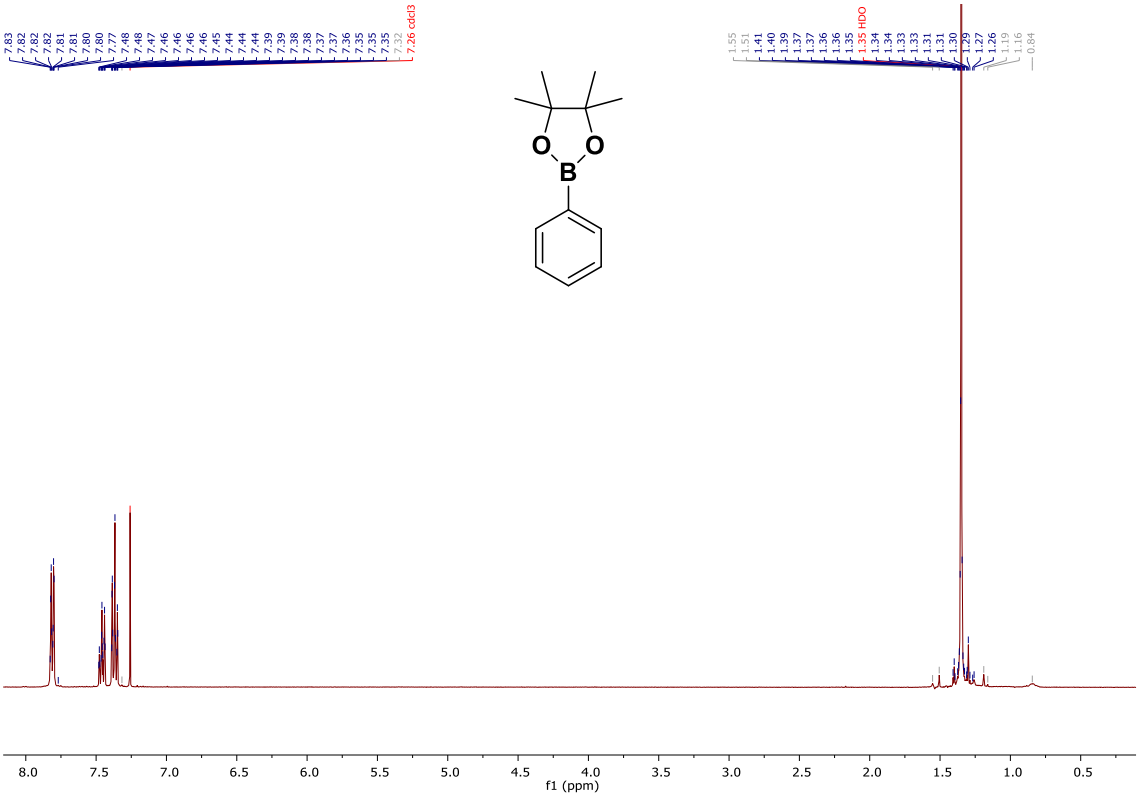
(3.14)

Orto-hydroxyphenylboronic reagent (1.2 eq, 0.4 mmol),), 2-cyclohexen-1-one (1 eq, 0.3 mmol, 28.83 mg), hydroxy(cyclooctadiene)rhodium(I) dimer (3 % mol, 0.009 mmol, 4.79 mg) and Dioxane/H_2O as solvent (3 ml), were used giving a white powder (20 mg, 51% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$), δ: 7.12 (ddd, J = 8.45 Hz, 1H), 7.00 (dd, J = 7.45 Hz, 1H), 6.83 (m, 2H), 3.18 (q, 1H), 2.80 (s, 1H), 2.07 (m, 2H), 1.96 (dtd, J = 12.36 Hz, 1H), 1.69 (m, 4H), 1.42 (m, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 155.48, 127.79, 127.64, 125.34, 119.96, 115.06, 98.40, 77.19, 38.96, 36.31, 35.05, 32.02, 18.73.

Chapter 6 - Compounds Spectra



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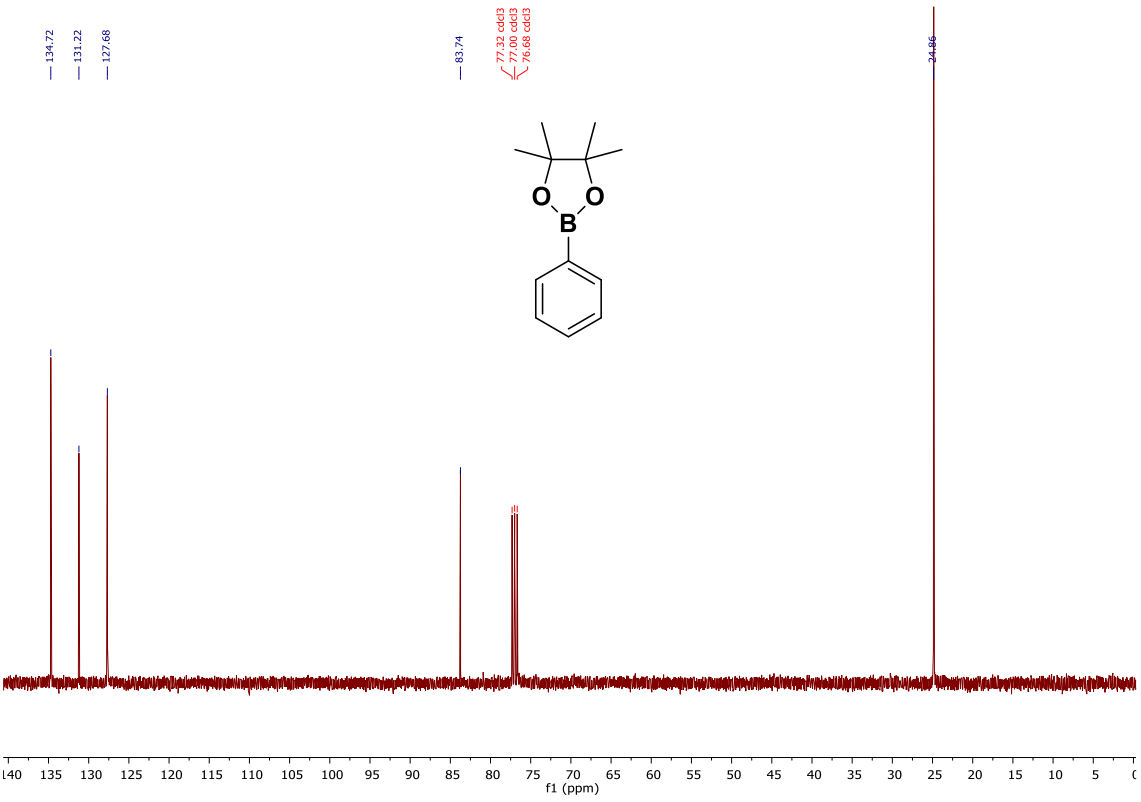
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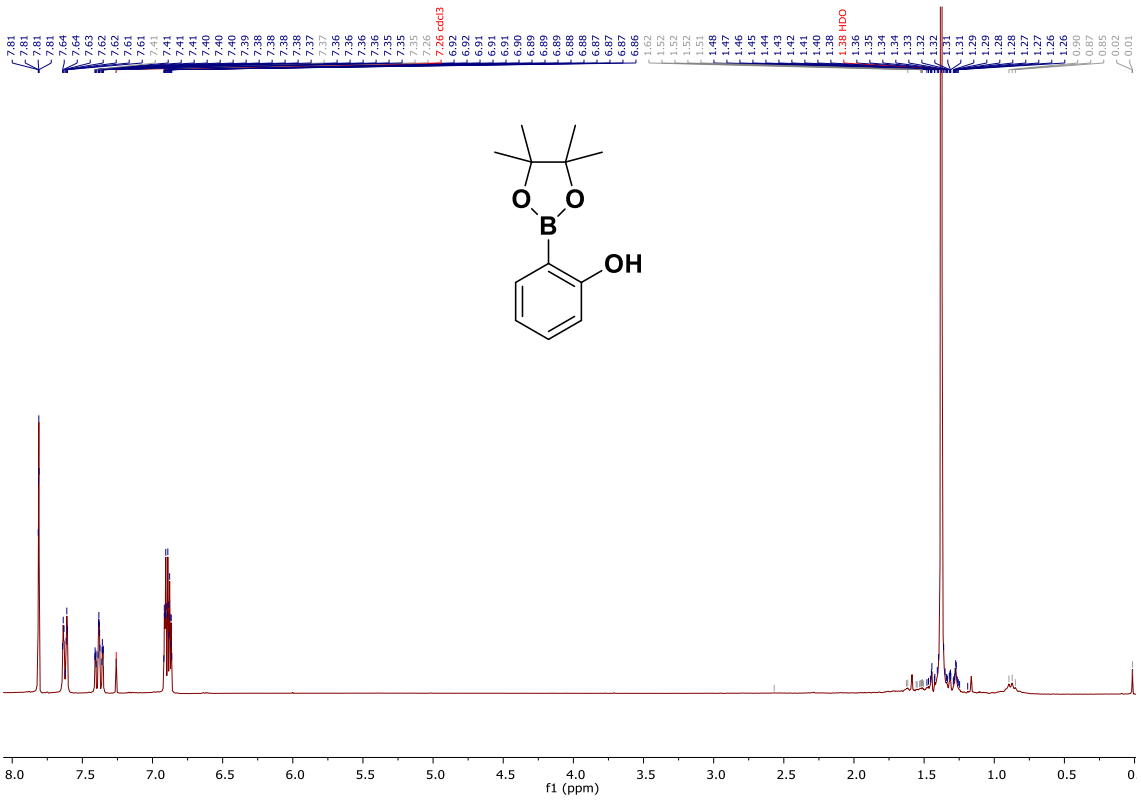
f1 (ppm)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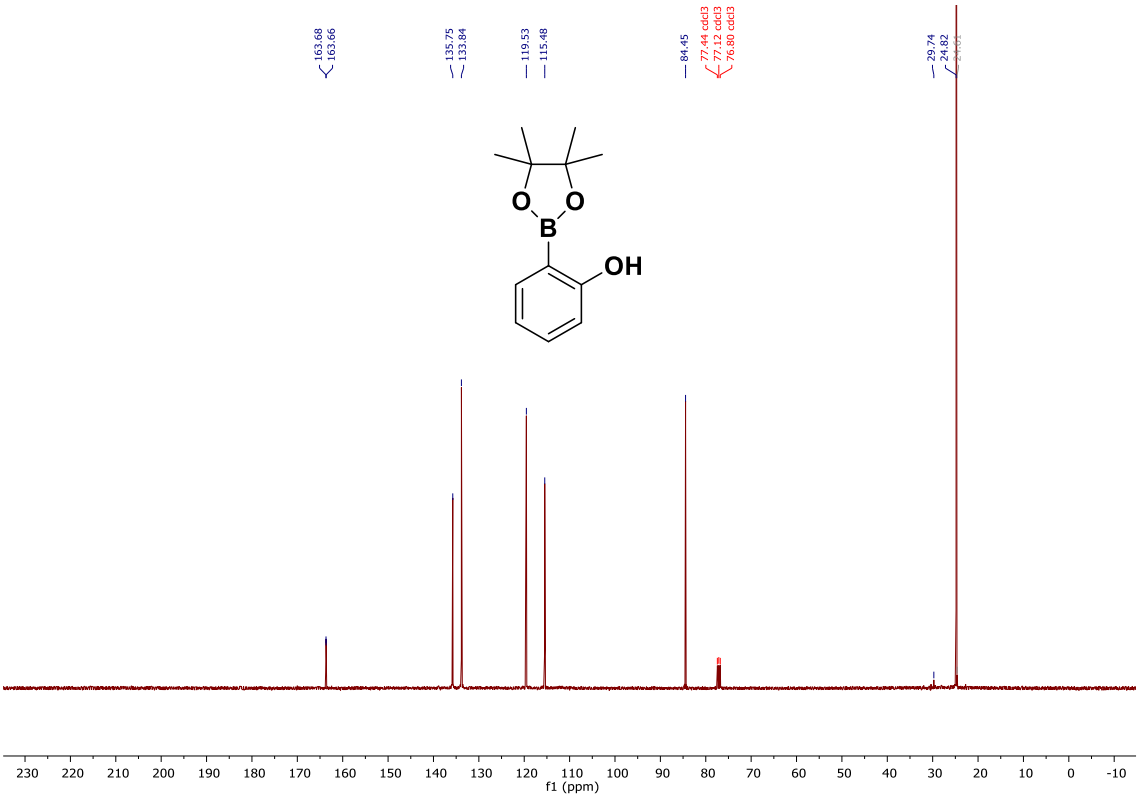
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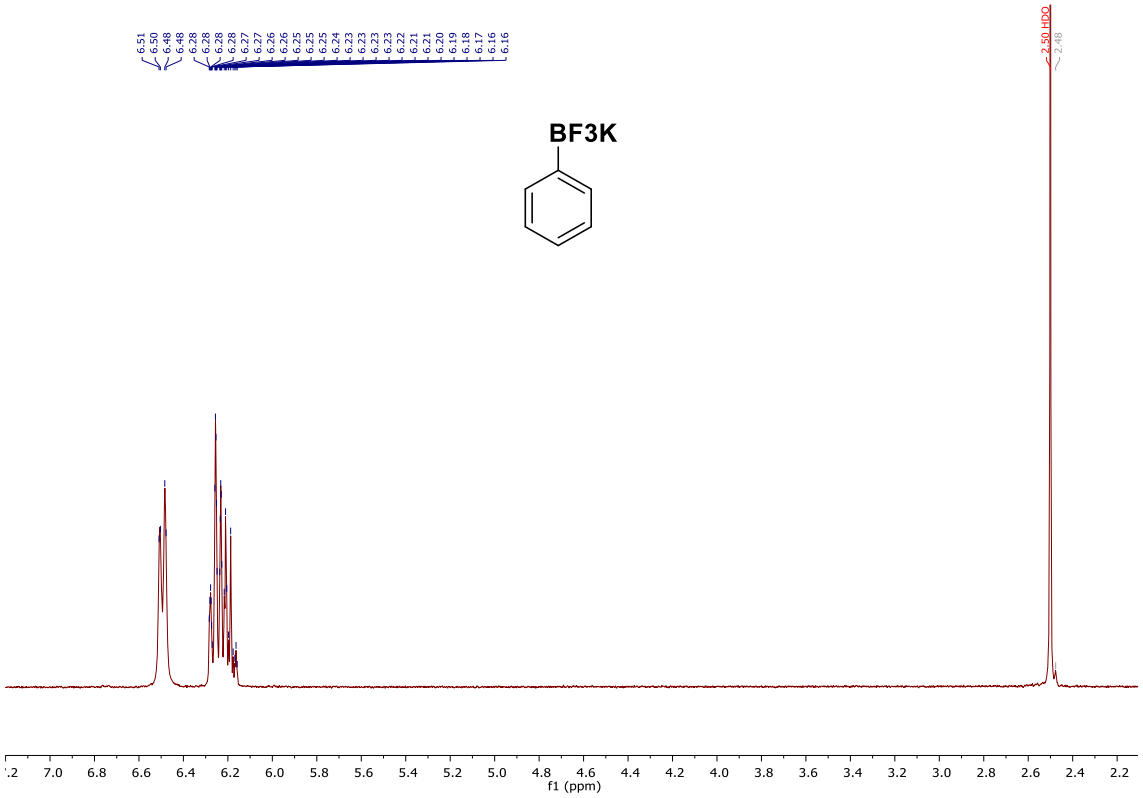
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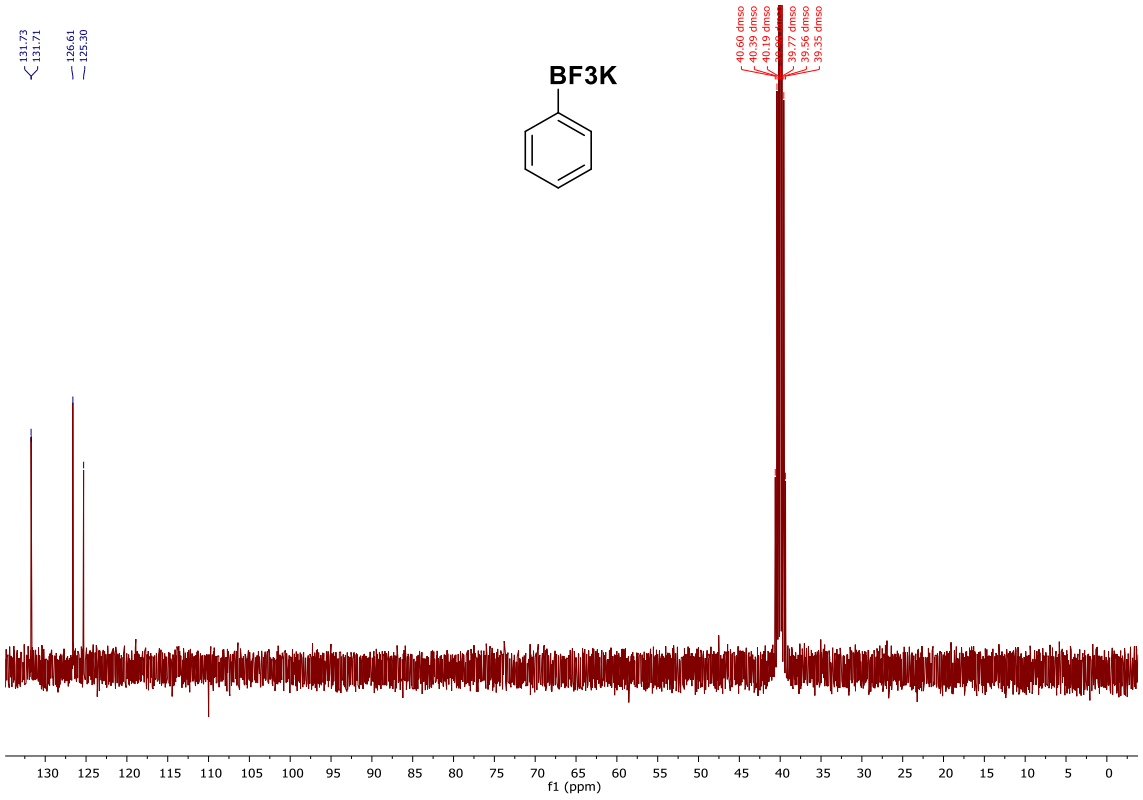
BF3K
f1 (ppm)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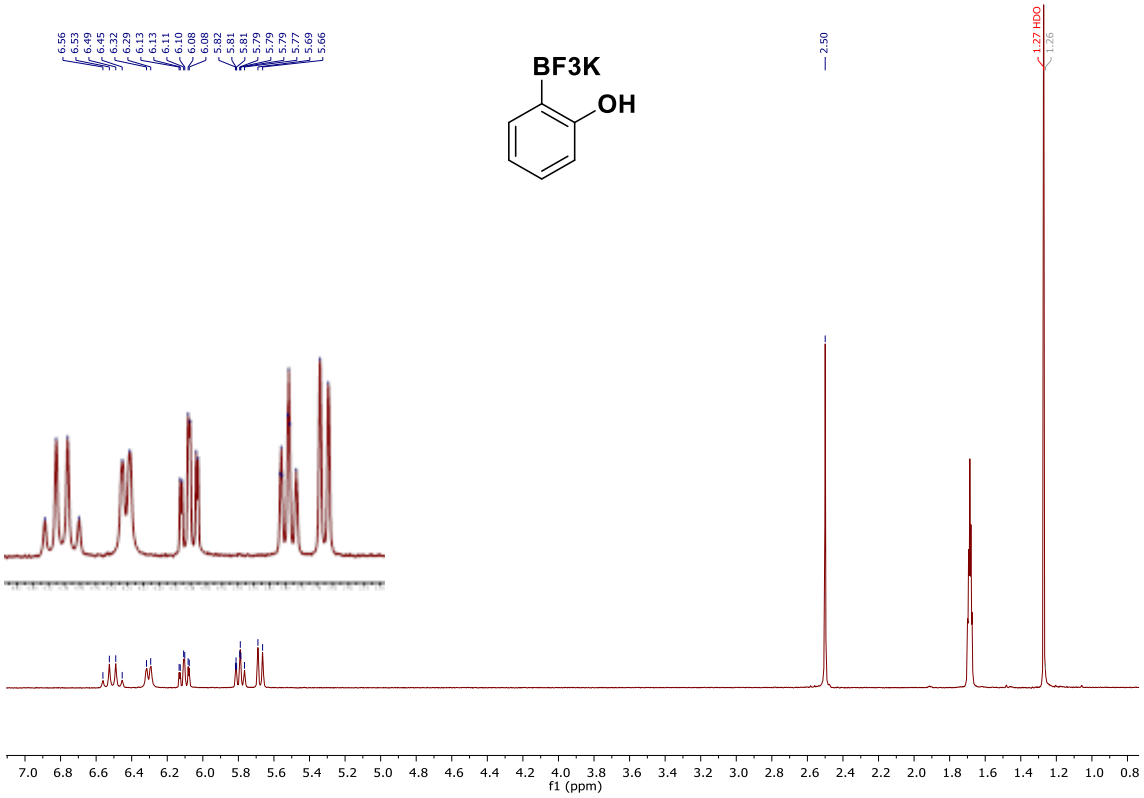
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5.66
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1.26
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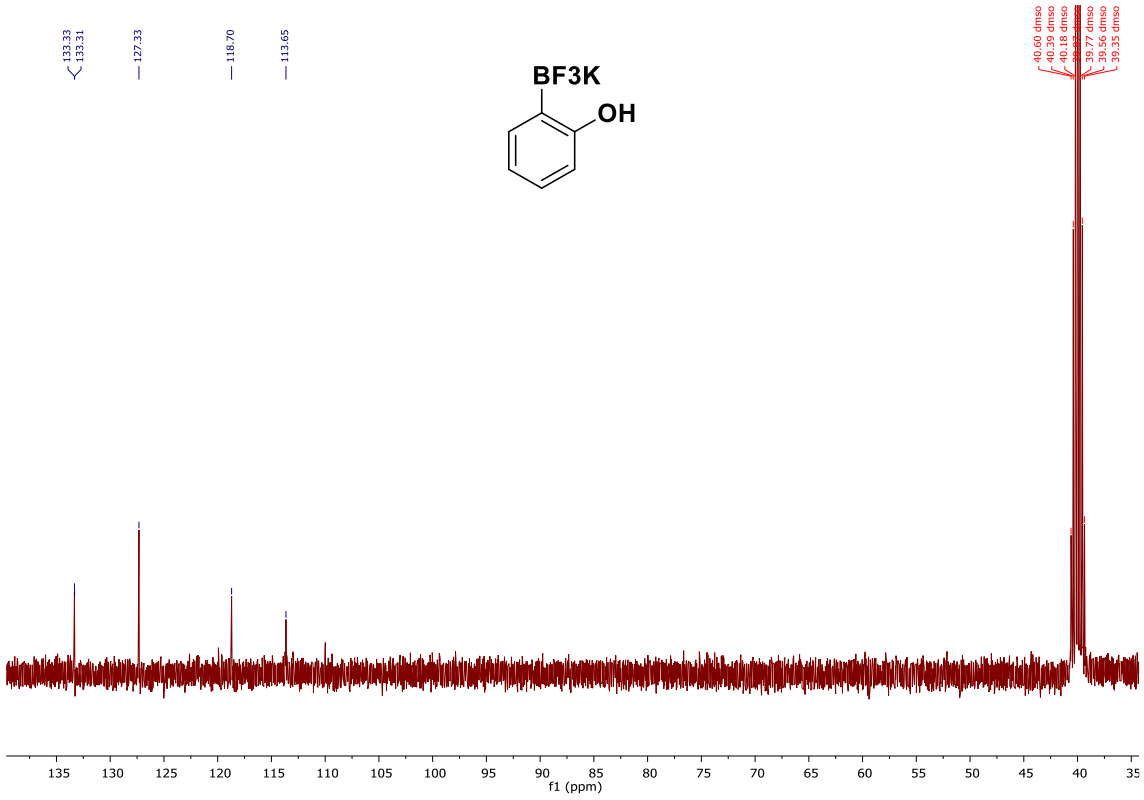
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39.56 dmso
39.35 dmso
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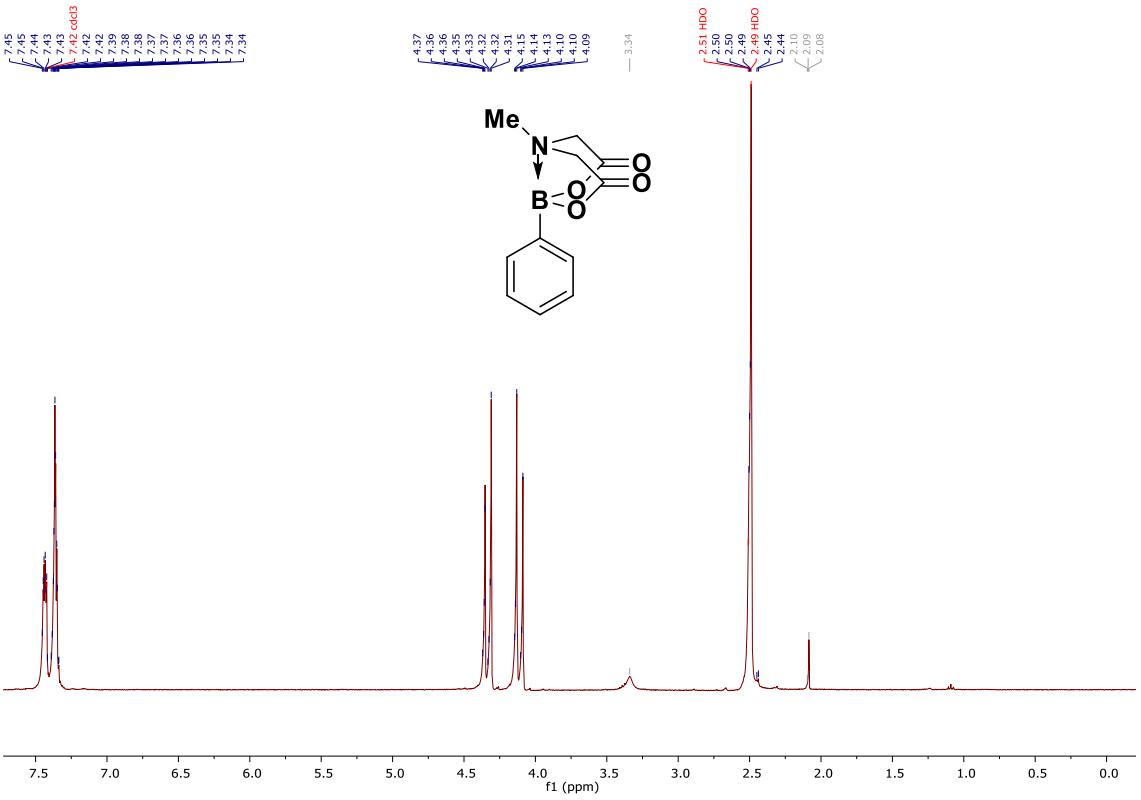
f1 (ppm)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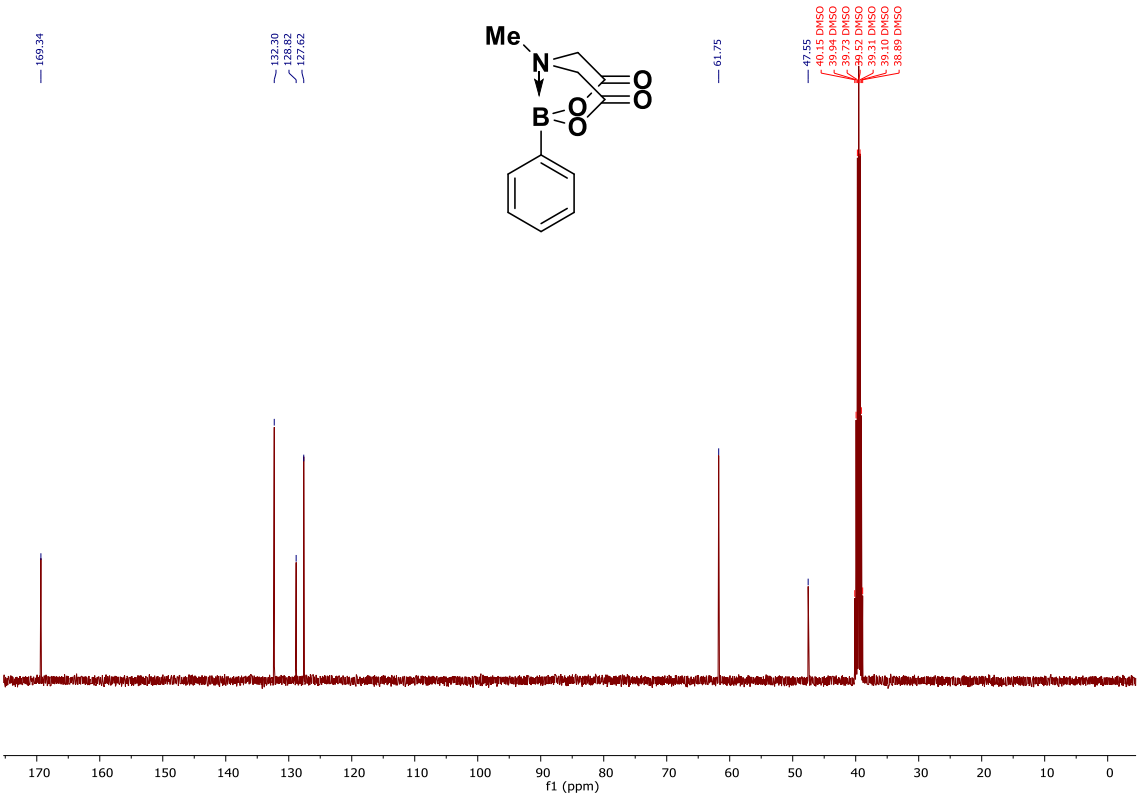
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39.10 DMSO
38.89 DMSO
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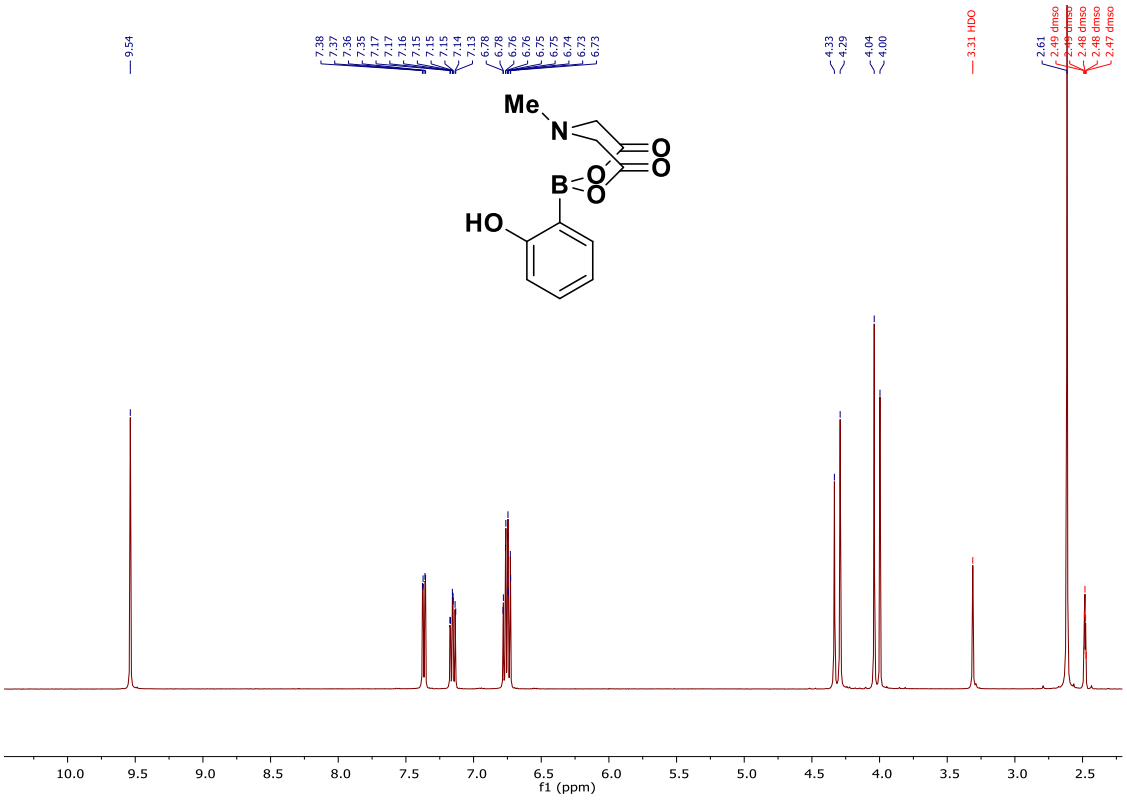
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4.29
4.04
4.00
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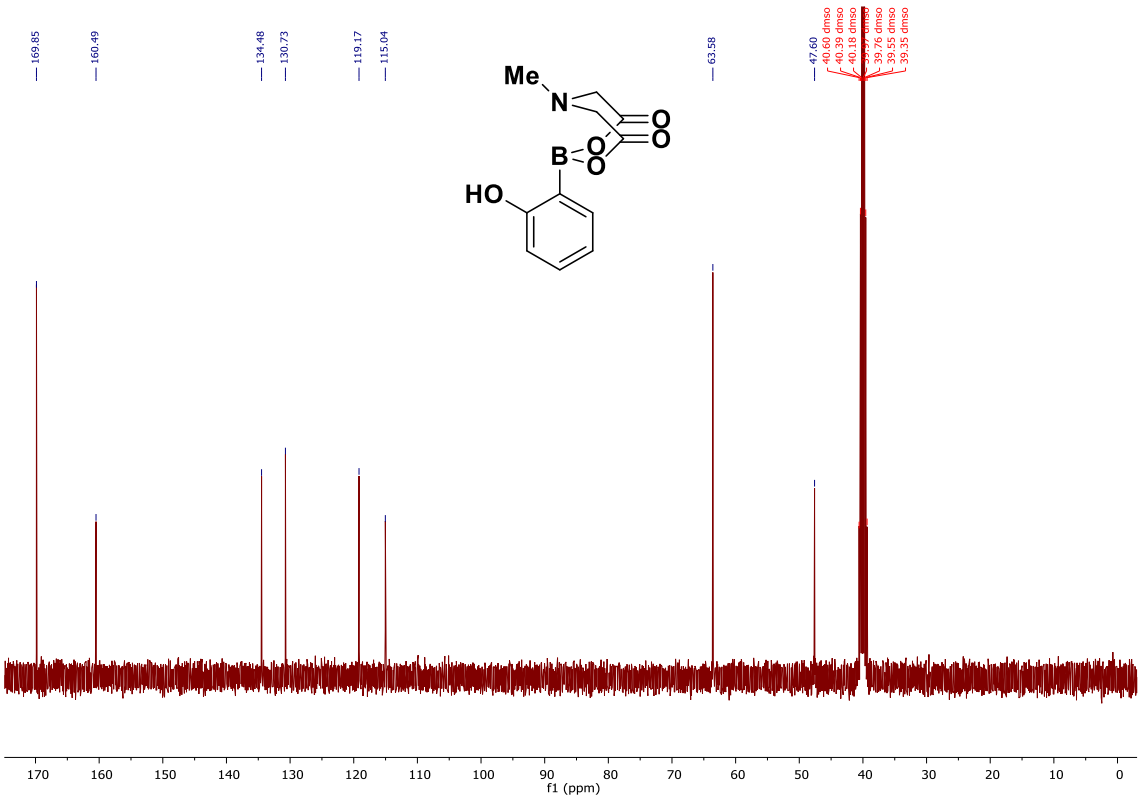
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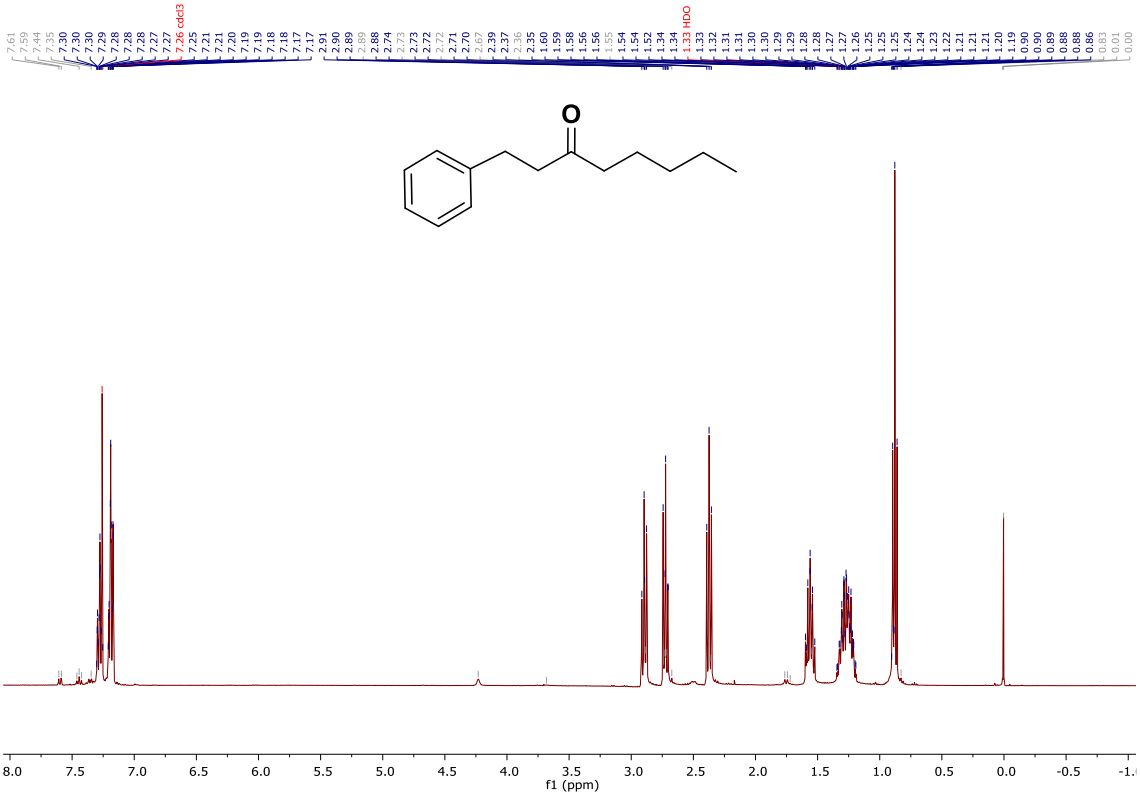
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O
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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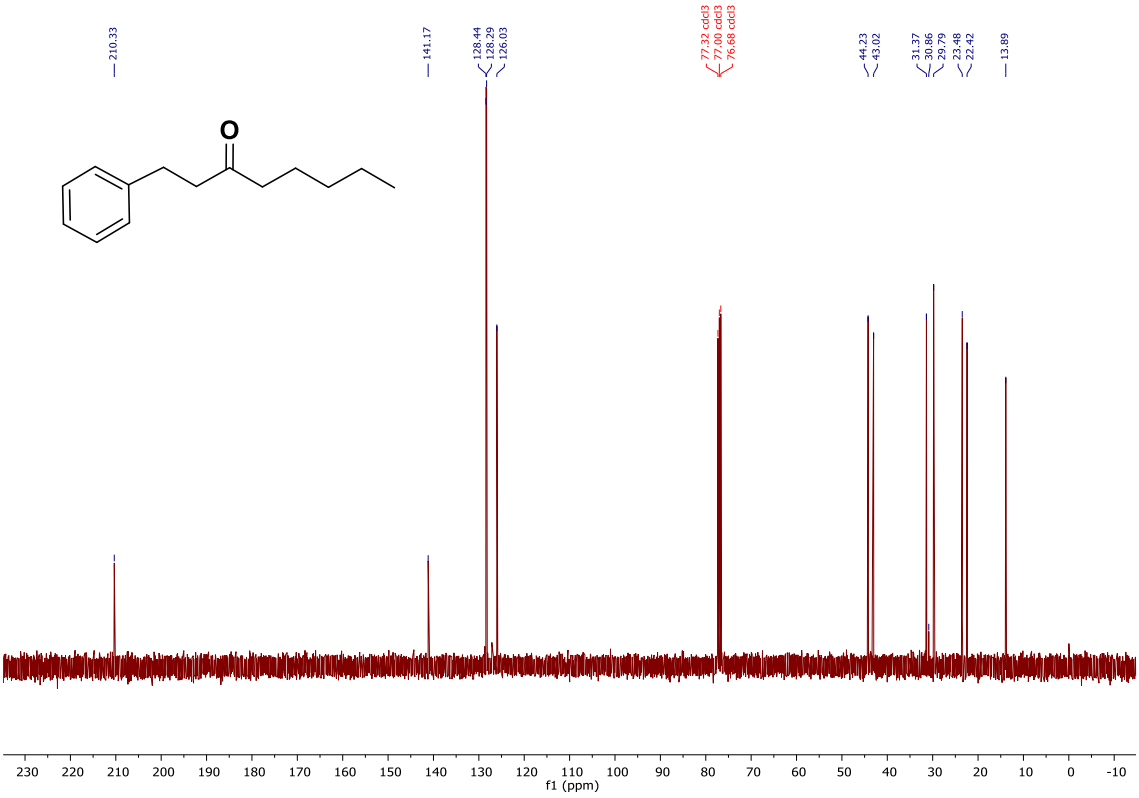
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O
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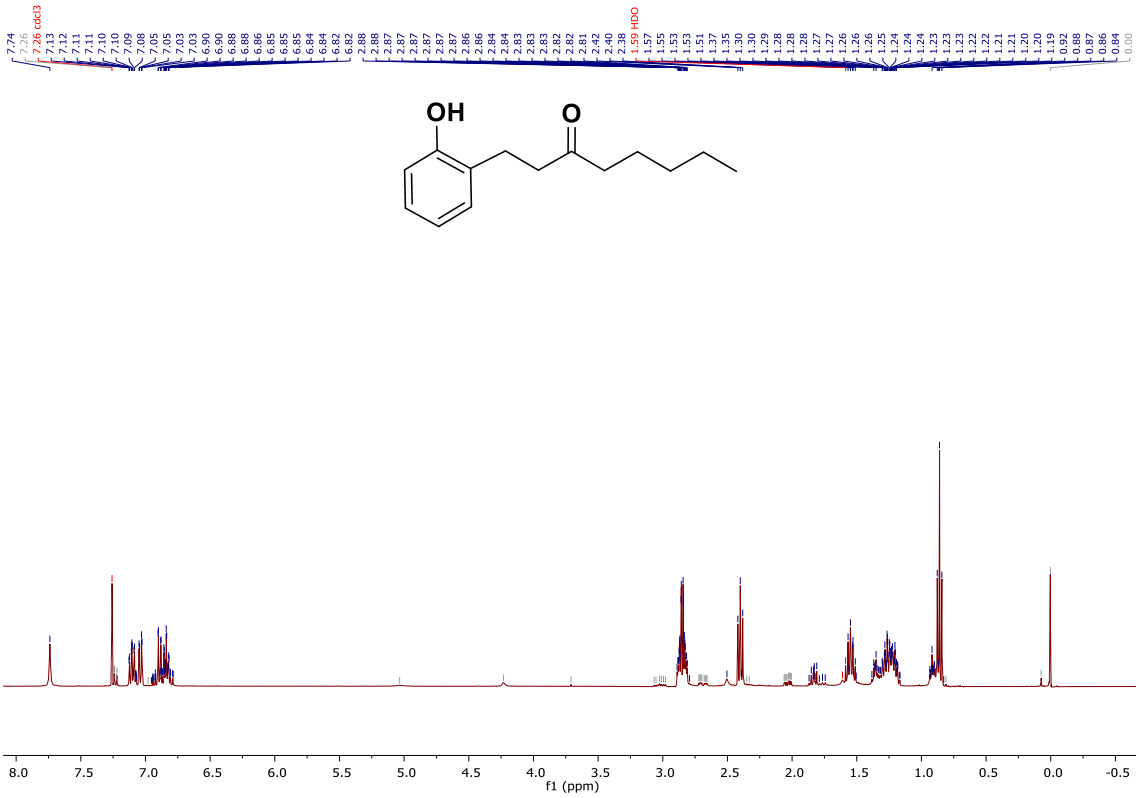
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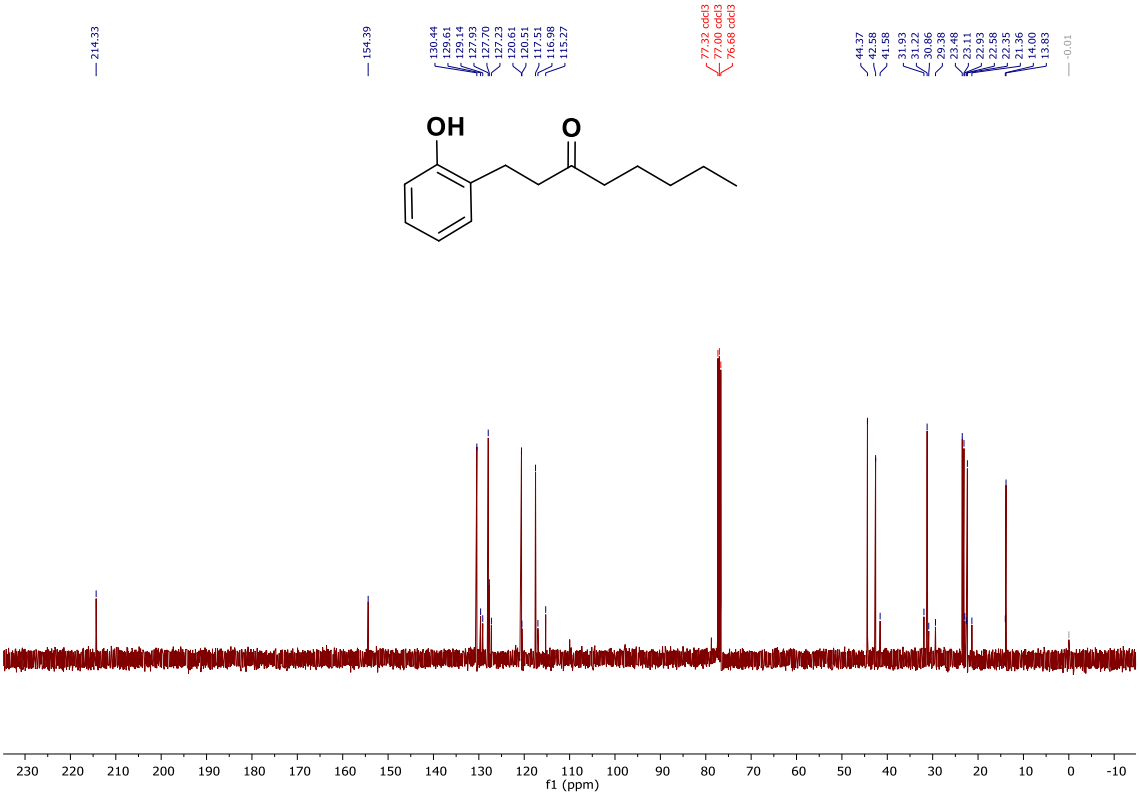
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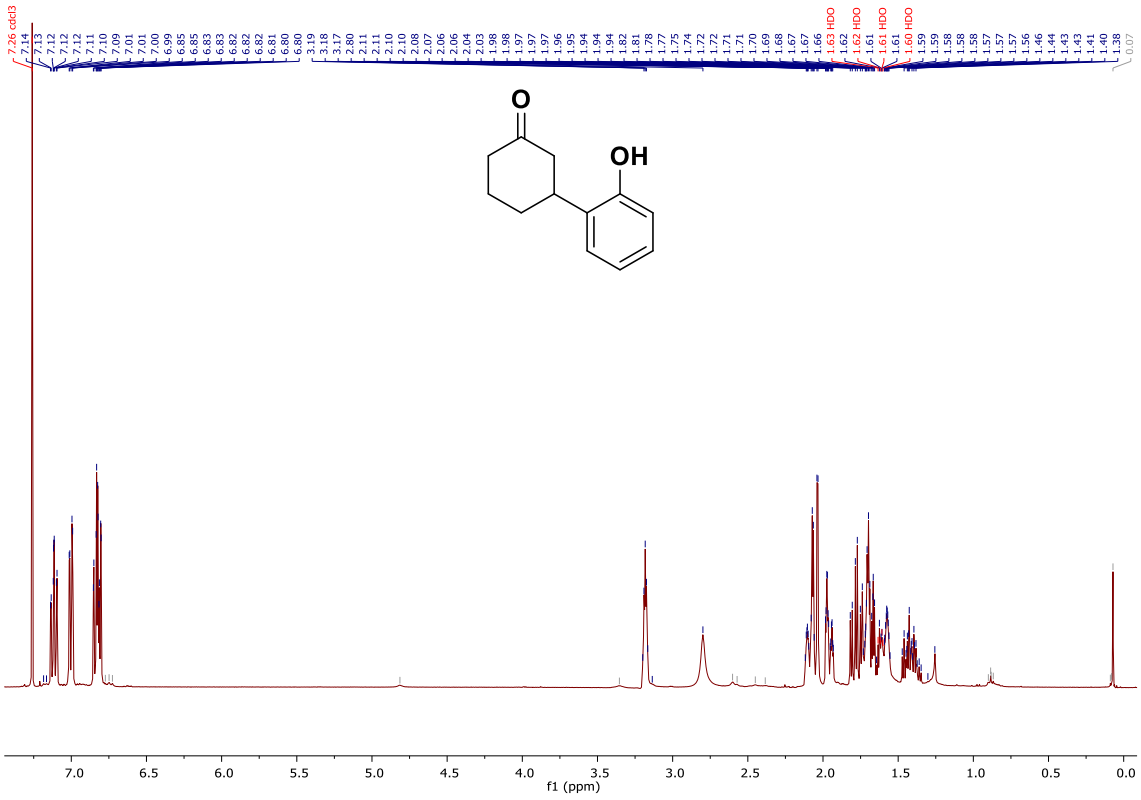
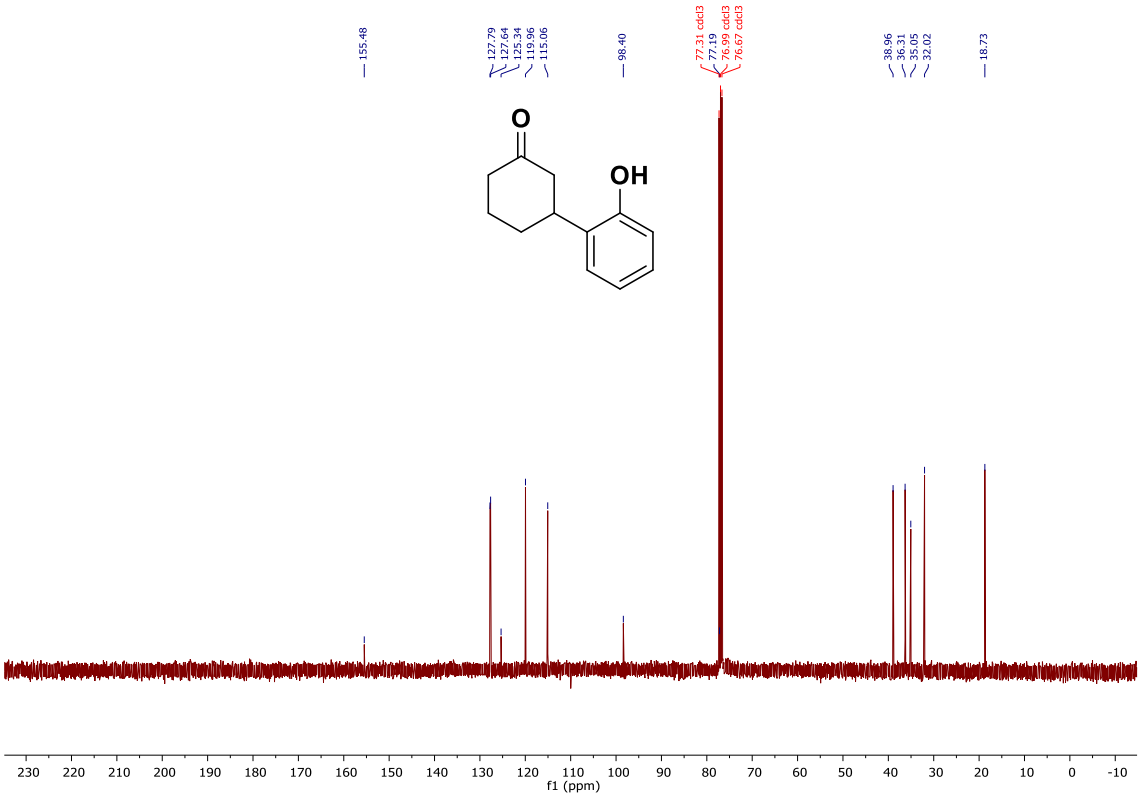
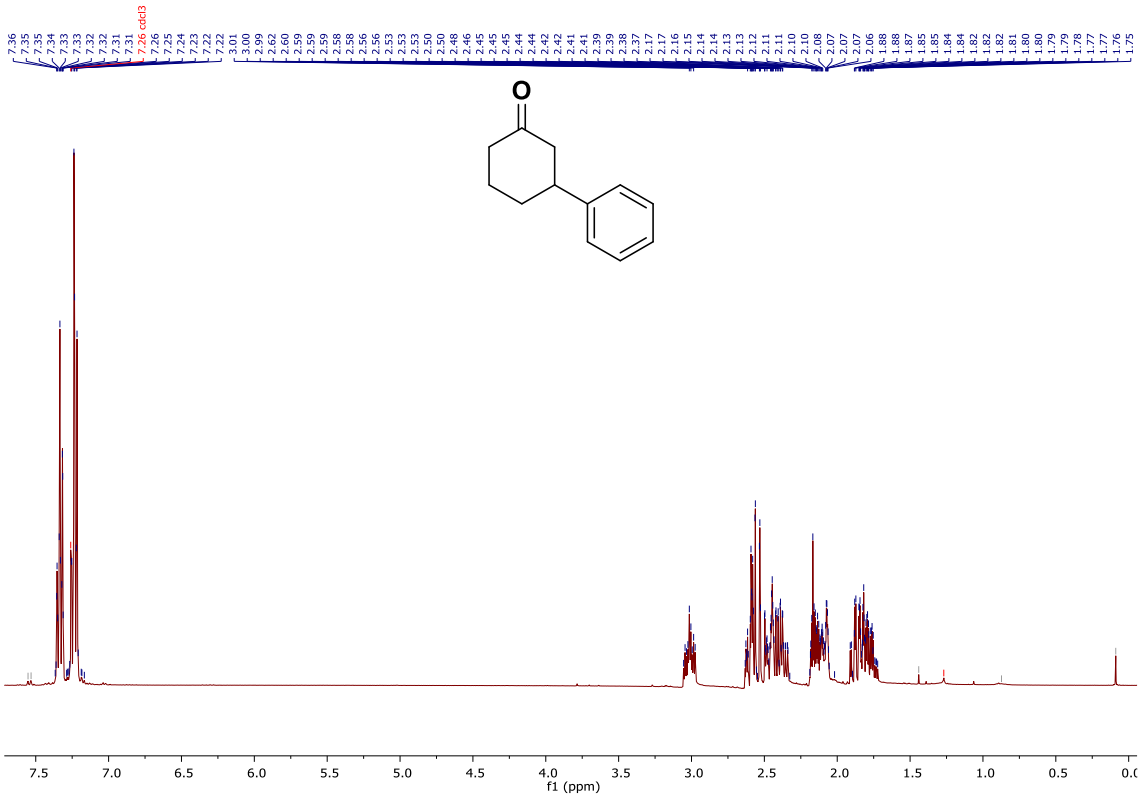
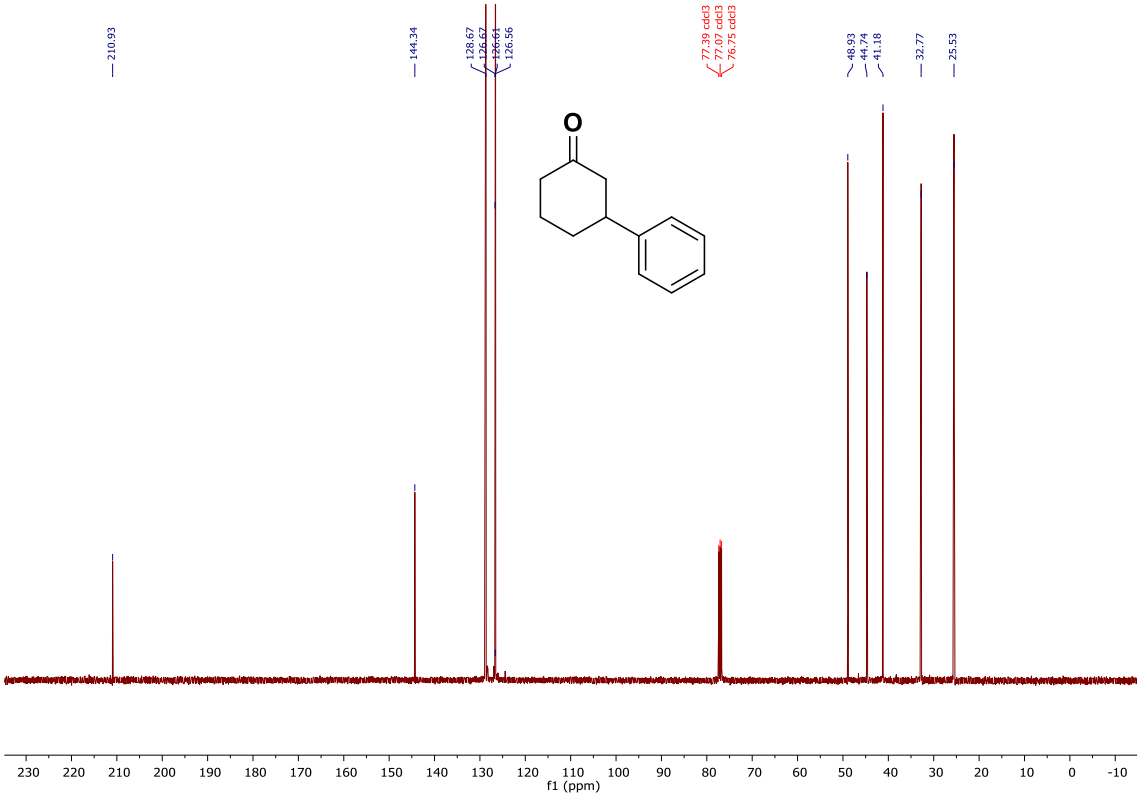
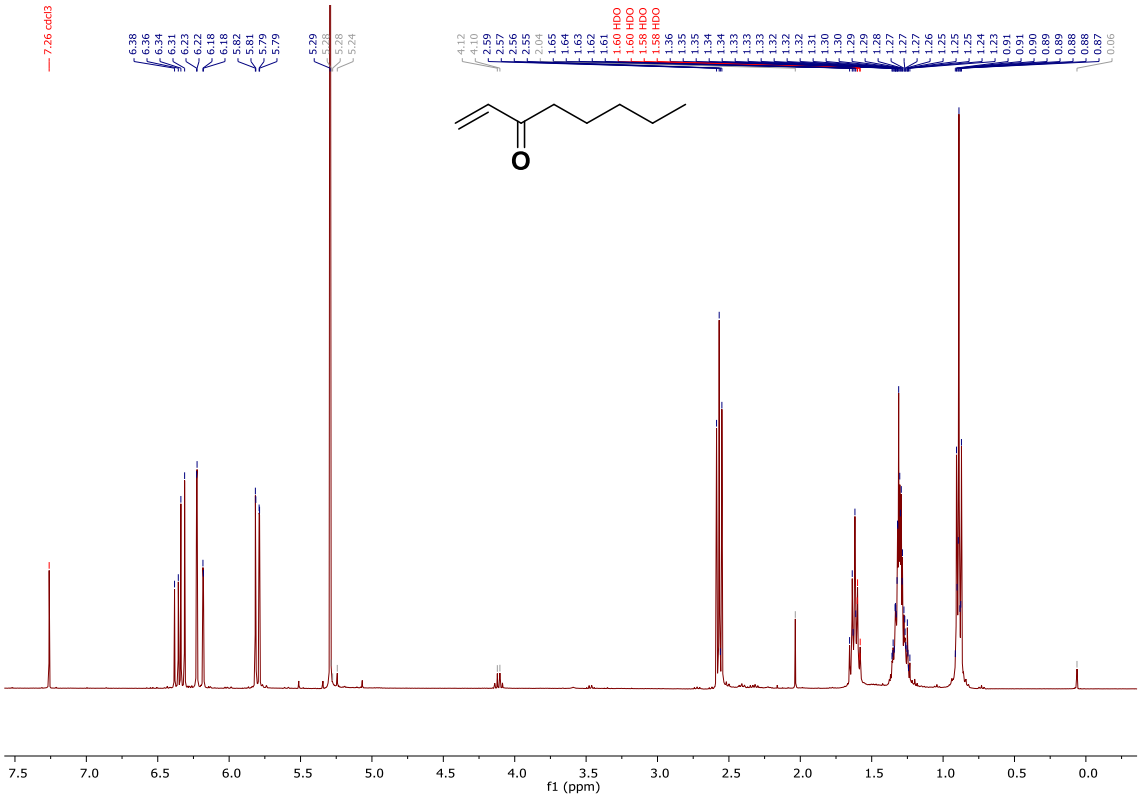
41.58
31.93
31.22
30.86
29.38
23.48
23.11
22.93
22.58
22.35
21.36
14.00
13.83
-0.01
OH
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

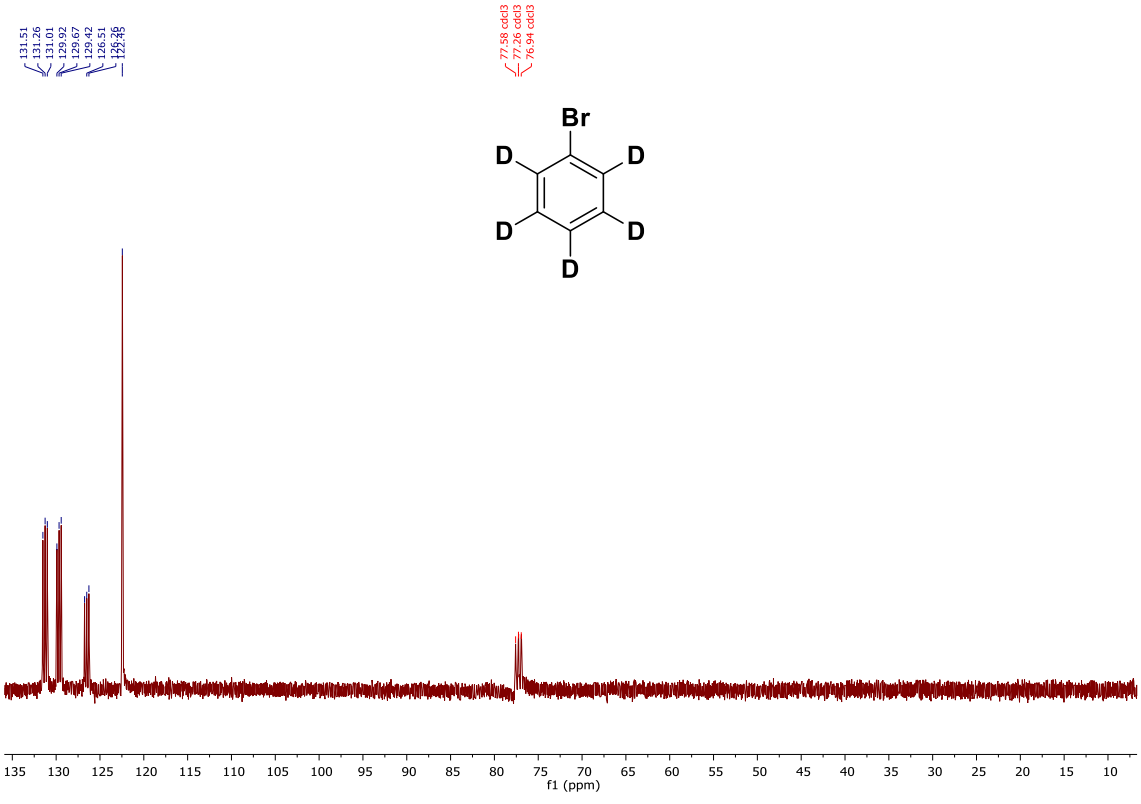

O
OH
f1 (ppm)


O
OH
f1 (ppm)


7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.26 cdcl3 7.25 7.24 7.23 7.22 7.22 3.01 3.00 2.99 2.62 2.60 2.59 2.59 2.59 2.58 2.56 2.56 2.53 2.53 2.50 2.50 2.48 2.46 2.45 2.45 2.45 2.44 2.44 2.42 2.42 2.41 2.41 2.39 2.39 2.38 2.37 2.17 2.17 2.16 2.15 2.14 2.13 2.12 2.11 2.11 2.10 2.10 2.08 2.07 2.07 2.07 2.06 1.88 1.88 1.87 1.85 1.85 1.84 1.84 1.82 1.82 1.82 1.81 1.80 1.80 1.79 1.79 1.78 1.77 1.77 1.76 1.75
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


210.93
144.34
128.67
126.62
126.61
126.56
77.39 cdcl3
77.07 cdcl3
76.75 cdcl3
48.93
44.74
41.18
32.77
25.53
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 cdcl3
6.38
6.36
6.34
6.31
6.23
6.22
6.18
5.82
5.81
5.79
5.79
5.29
5.28
5.24
4.12
4.10
2.59
2.57
2.56
2.55
2.04
1.65
1.64
1.63
1.62
1.61
1.60 HDO
1.60 HDO
1.58 HDO
1.58 HDO
1.36
1.35
1.35
1.34
1.34
1.33
1.33
1.32
1.32
1.32
1.31
1.30
1.29
1.29
1.28
1.27
1.27
1.27
1.26
1.25
1.25
1.25
1.24
1.23
0.91
0.90
0.89
0.89
0.88
0.88
0.87
0.06
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


131.51
131.26
131.01
129.92
129.67
129.42
126.51
77.58 cdcl3
77.26 cdcl3
76.94 cdcl3
Br
D
D
D
D
D
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

Chapter 7 – References

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