

# **Base-Free Suzuki acylation reactions of sodium (aryl trihydroxyborate) salts: A novel synthesis of substituted aryl ketones**

Submitted in fulfilment of the required for the degree of  
Master of Science



Faculty of Agriculture, Engineering and Science

School of Chemistry and Physics

University of KwaZulu-Natal

Pietermaritzburg Campus

South Africa

by

**Patience Snenhlanhla Sthembile Molefe**

BSc honours (UKZN)

**Supervisor: Dr S Sithebe**

December 2018

## **Thesis declaration**

The experimental work described in this dissertation was carried out in the School of Chemistry and Physics, University of KwaZulu-Natal, Pietermaritzburg campus, under the supervision of Dr S Sithebe.

These studies represent original work by the author and have not otherwise been submitted by any candidate for any degree.

Signed..... Patience Snehlanhla Sthembile Molefe (Candidate)

Signed..... Dr Siphamandla Sithebe (Supervisor)

## **List of seminar presentations**

1. Molefe P.S.S., Sithebe S. Base-Free Suzuki acylation reactions of sodium (aryl trihydroxyborate) salts: A novel synthesis of substituted aryl ketones. University of KwaZulu-Natal. College of Agriculture, Engineering and Science, Postgraduate research day, 26 October 2017, *poster presentation*.
2. Molefe P.S.S., Sithebe S. Base-Free Suzuki acylation reactions of sodium (aryl trihydroxyborate) salts: A novel synthesis of substituted aryl ketones. University of KwaZulu-Natal. Durban University of Technology, SACI Postgraduate Colloquium, 02 February 2018, *oral presentation*.

## **List of publication**

1. Sithebe S. and P. Molefe, Base-free Suzuki acylation reactions of sodium (aryl trihydroxyborate) salts: A novel synthesis of substituted aryl ketones. *Journal of Organometallic Chemistry*, 2017. **40**: p. 305-311. *published*.

## Abstract

Asymmetric biaryl ketones are important building block in organic chemistry since they occur in large number of biological active compounds, natural product, cosmetics as well as in organic synthesis. The aim of this project was to develop a novel base-free Suzuki-Miyaura cross-coupling of biaryl ketones from sodium (aryl trihydroxyborate) salts coupled with acyl chlorides catalysed by palladium precursor and investigate the electron effect of substituents attached to acyl chloride and sodium (aryl trihydroxyborate) salts on the yields of ketones produced. A novel synthesis of biaryl ketones was successfully developed in coupling of commercially available substituted acyl chlorides with easily accessible substituted sodium (aryl trihydroxyborate) salts catalysed by Pd(PPh<sub>3</sub>)<sub>4</sub> in aqueous toluene. A wide range of functional groups were accommodated including CF<sub>3</sub>, OMe, SMe, Br, F, NO<sub>2</sub>, OH, NH<sub>2</sub> yielding up to 96% in 24 hours.

Encouraged by successful cross-coupling reaction between sodium (aryl trihydroxyborate) salts and acyl chlorides under the Suzuki-Miyaura cross-coupling acylation reaction conditions, we thought it would be logical to extend the scope of the developed reaction condition to include carboxylic anhydrides as electrophiles. As a result, substituted benzoic anhydrides were first synthesised following previously published procedures giving the desired products in excellent yields (87-99%). The synthesised carboxylic anhydrides were subsequently cross-coupled with boronate salts under base-free and ligandless palladium catalysed cross-coupling reaction conditions to synthesise biaryl ketones in aqueous acetone. The developed method appears sensitive to electronic effects both on the electrophile and on the nucleophile and on the nucleophile furnishing the desired ketones in moderate yields.

Two novel methods have been developed to synthesise ketones from stable, easy to prepare and free flowing pure sodium (aryl trihydroxyborate) salts.

## **Acknowledgements**

I would like to highly appreciate the guidance, support, motivation with patience I got from my supervisor Dr Siphamandla Sithebe, ‘Ngithi ukwenze nakwabanye.’

Much gratitude to the following people:

- ❖ My family for the support, love, care and prayers.
- ❖ My friends for the support, laughter and motivation.
- ❖ Chemistry family at large, namely: technicians, research group and postgraduates for any contribution they had in my project.
- ❖ NRF for finance stability.

Above all, I thank God for everything!!!

# Table of contents

Thesis declaration .....	i
List of seminar presentations.....	ii
List of publication.....	ii
Abstract.....	iii
Acknowledgements.....	iv
Table of contents .....	v
List of Abbreviations .....	ix
List of tables .....	xii
List of figures.....	xii
Chapter 1.....	1
1.1 Introduction .....	1
1.2 References .....	4
Chapter 2.....	5
Literature Review.....	5
2.1 Introduction .....	5
2.2 Background of Suzuki-Miyaura Cross-Coupling .....	9
2.3 Coupling of arylboronic acid derivatives with acyl halides .....	10
2.3 Coupling of arylboronic acid derivatives with anhydrides.....	16
2.4 Suzuki-Miyaura Cross-Coupling mechanism.....	19
2.5 Aims and objectives .....	22
2.6 References .....	24
Chapter 3.....	28
Results and Discussion .....	28
3.1 The synthesis of sodium (aryl trihydroxyborate) salts.....	28
3.1.1 The synthesis of sodium (aryl trihydroxyborate) salts.....	29
3.2 The application of sodium (aryl trihydroxyborate) salts in Suzuki-Miyaura acylation reaction .	30
3.2.1 The synthesis of phenyl( <i>p</i> -tolyl)methanone (3).....	32
3.2.2 The synthesis of (4-bromophenyl)(phenyl)methanone (68).....	33
3.2.3 The synthesis of bis( <i>p</i> -tolyl)methanone (69) .....	35
3.2.4 The synthesis of (4-nitrophenyl)( <i>p</i> -tolyl)methanone (12) .....	36
3.2.5 The synthesis of (4-methylthiophenyl)(4-nitrophenyl)methanone (71).....	38

3.2.6	The synthesis of (4-methylthiophenyl)(4-methoxyphenyl)methanone (73) .....	39
3.2.7	The synthesis of (4-methylthiophenyl)(2-fluorophenyl)methanone (84).....	40
3.2.8	The synthesis of (4-methoxyphenyl)(4-chlorophenyl)methanone (87).....	41
3.2.9	The synthesis of (3-fluorophenyl)(4-trifluoromethylphenyl)methanone(95) .....	42
3.2.10	Attempted synthesis of 2 -Propen-1-one,1,3-diphenyl (97).....	43
3.2.11	The Mechanistic Study .....	46
3.2.12	Synthesis of 4-aminobenzophenone (106) .....	50
3.2.13	Synthesis of 4-hydroxybenzophenone (107) .....	52
3.3	Palladium-catalysed acylation of sodium (aryl trihydroxyborate) salts with carboxylic anhydrides .....	54
3.4	The synthesis of carboxylic anhydride compounds .....	57
3.4.1	The synthesis of benzoic anhydride (52) .....	57
3.4.2	The synthesis of 4-methylbenzoic anhydride (110).....	59
3.4.3	The synthesis of 4-nitrobenzoic anhydride (111) .....	59
3.4.4	The synthesis of 4-chlorobenzoic anhydride (112).....	61
3.4.5	The synthesis of 3-fluorobenzoic anhydride (113) .....	61
3.4.6	The synthesis of 2-fluorobenzoic anhydride (114) .....	61
3.4.7	Attempted synthesis of cinnamic anhydride (130).....	62
3.5	The synthesis of ketones from sodium (aryl trihydroxyborate) salts and carboxylic anhydride .....	63
3.5.1	The synthesis of phenyl( <i>p</i> -tolyl)methanone (3).....	64
3.5.2	The synthesis of (4-nitrophenyl)(phenyl)methanone (43).....	64
3.5.3	The synthesis of (4-chlorophenyl)(phenyl)methanone (115) .....	65
3.5.4	The synthesis of (4-methylphenyl)(4-trifluorophenyl)methanone (93) .....	66
3.6	Conclusion.....	71
3.7	References .....	72
Chapter 4.....		75
Experimental.....		75
4.1	Chemical and instrumental information.....	75
4.2	Synthesis of sodium aryl trihydroxyborate salts.....	75
4.2.1	General procedure A.....	75
4.2.2	Synthesis of sodium (phenyltrihydroxyborate) (60) .....	76
4.2.3	Synthesis of sodium (4-methylphenyltrihydroxyborate) (61).....	76
4.2.4	Synthesis of sodium (4-methylthiophenyltrihydroxyborate) (64) .....	76

4.2.5	Synthesis of sodium (4-methoxyphenyltrihydroxyborate) (63).....	77
4.3.6	Synthesis of sodium (4-trifluoromethylphenyltrihydroxyborate) (65) .....	77
4.3.7	Synthesis of sodium (4-chlorophenyltrihydroxyborate) (62).....	77
4.4	Synthesis of ketones .....	78
4.4.1	General procedure B.....	78
4.4.2	Synthesis of phenyl(p-tolyl)methanone (3) .....	78
4.4.3	Synthesis of (4-bromophenyl)(phenyl)methanone (68) .....	78
4.4.4	Synthesis of (4-methoxyphenyl)(phenyl)methanone (78).....	79
4.4.5	Synthesis of bis(p-tolyl)methanone (69).....	79
4.4.6	Synthesis of (4-methoxyphenyl)(p-tolyl)methanone (79) .....	79
4.4.7	Synthesis of (4-nitrophenyl)(p-tolyl)methanone (12).....	80
4.4.8	Synthesis of (4-methylthiophenyl)(p-tolyl)methanone (81).....	80
4.4.9	Synthesis of (4-methylthiophenyl)(3-fluorophenyl)methanone (82) .....	80
4.4.10	Synthesis of (4-methylthiophenyl)(4-nitrophenyl)methanone (71) .....	81
4.4.11	Synthesis of (4-methylthiophenyl)(4-methoxyphenyl)methanone (73).....	81
4.4.12	Synthesis of (4-methylthiophenyl)(phenyl)methanone (83) .....	81
4.4.13	Synthesis of (4-methylthiophenyl)(2-fluorophenyl)methanone (84) .....	82
4.4.14	Synthesis of (4-methoxyphenyl)(4-nitrophenyl)methanone (85).....	82
4.4.15	Synthesis of bis(4-methoxyphenyl)methanone (86).....	82
4.4.16	Synthesis of (4-methoxyphenyl)(4-chlorophenyl)methanone (87) .....	83
4.4.17	Synthesis of (4-methoxyphenyl)(3-fluorophenyl)methanone (88).....	83
4.4.18	Synthesis of (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone ( 89) .....	84
4.4.19	Synthesis of (4-bromophenyl)(4-(trifluoromethyl)phenyl)methanone (90).....	84
4.4.20	Synthesis of (4-nitrophenyl)(4-(trifluoromethyl)phenyl)methanone (91).....	84
4.4.21	Synthesis of (4-(trifluoromethyl)phenyl)methanone (92) .....	85
4.4.22	Synthesis of (p-tolyl)(4-(trifluoromethyl)phenyl)methanone (93) .....	85
4.4.23	Synthesis of (3-fluorophenyl)(4-(trifluoromethyl)phenyl)methanone (95).....	85
4.4.24	Synthesis of (4-chlorophenyl)(4-(trifluoromethyl)phenyl)methanone (94) .....	86
4.4.25	Synthesis of (4-Aminophenyl)phenyl-methanone (106).....	86
4.4.26	Synthesis of (4-Hydroxyphenyl)phenyl-methanone (107).....	87
4.5	Synthesis of anhydrides .....	87
4.5.1	General Procedure C.....	87
4.5.2	Synthesis of benzoic anhydride (52) .....	87
4.5.3	Synthesis of 4-methylbenzoic anhydride (110).....	88



4.5.4	Synthesis of 4-nitrobenzoic anhydride (111) .....	88
4.5.5	Synthesis of 4-chlorobenzoic anhydride (112).....	88
4.5.6	Synthesis of 3-fluorobenzoic anhydride (113) .....	88
4.5.7	Synthesis of 2-fluorobenzoic anhydride (114).....	89
4.6	Synthesis of biaryl ketones .....	89
4.6.1	General procedure D.....	89
4.6.2	Synthesis of phenyl( <i>p</i> -tolyl)methanone (3) .....	89
4.6.3	Synthesis of benzophenone (41).....	90
4.6.4	Synthesis of (4-chlorophenyl)(phenyl)methanone (115).....	90
4.6.5	Synthesis of phenyl(4-nitrophenyl)methanone (43).....	90
4.6.6	Synthesis of Bis( <i>p</i> -tolyl)methanone (69).....	91
4.6.7	Synthesis of Phenyl(3-fluorophenyl)methanone (116).....	91
4.6.8	Synthesis of (4-chlorophenyl)(4-methylphenyl)methanone (121) .....	91
4.6.9	Synthesis of (4-chlorophenyl)(3-fluorophenyl)methanone (122).....	92
4.6.10	Synthesis of (4-(trifluoromethyl)phenyl)(4-methylphenyl)methanone (93) .....	92
4.6.11	Synthesis of (4-(trifluoromethyl)phenyl)(phenyl)methanone (92).....	92
4.7	References .....	94
Appendix	.....	96

## List of Abbreviations

$\text{AlCl}_3$	Aluminium trichloride
Ar	Aryl
APSS	Active pharmaceutical ingredient
$\text{B}(\text{OMe})_3$	Trimethyl borate
$^{11}\text{B}$ NMR	Boron nuclear magnetic resonance
B-C	Boron-carbon bond
$\text{BF}_3$	Boron trifluoride
$^{13}\text{C}$ NMR	Carbon nuclear magnetic resonance
conc.	Concentration
$^\circ\text{C}$	Degrees Celsius
C-C	Carbon-carbon
$\text{CF}_3$	Trifluoromethyl
CO	Carbon monoxide
$\text{CHCl}_3$	Chloroform
C-O	Carbon-oxygen bond
cat	Catalyst
CuTC	Copper(I)-thiophene-2-carboxylate
$\text{Cs}_2\text{CO}_3$	Caesium carbonate
DMAP	4-dimethylaminopyridine
d	Doublet
DCM	Dichloromethane
DSC	Differential scanning calorimetry
$\text{Et}_3\text{N}$	Triethylamine
equiv	Equivalence
$\text{Et}_2\text{O}$	Diethyl ether
$\text{Fe}(\text{acac})_2$	Tris(acetylacetonate)iron(II)
$\text{H}_2\text{O}$	Water
$^1\text{H}$ NMR	Proton nuclear magnetic resonance
h	Hour
HCl	Hydrochloric acid

IR	Infrared spectroscopy
<i>J</i>	Coupling constant
KOH	Potassium hydroxide
K <sub>3</sub> PO <sub>4</sub>	Potassium phosphate
KF	Potassium fluoride
mmol	Millimoles
mol	Molar
mL	Millilitre
min	Minutes
MeNO <sub>2</sub>	Nitromethane
<i>m</i>	Meta
mol %	Molar percentage
m	Multiplet
m/z	Mass to charge ratio
MS	Mass spectrometry
NaOH	Sodium hydroxide
Na <sub>2</sub> CO <sub>3</sub>	Sodium carbonate
NH <sub>2</sub>	Amino
NO <sub>2</sub>	Nitro
Ni(acac) <sub>2</sub>	Nickel(II) acetylacetonate
Ni(PPh <sub>3</sub> ) <sub>4</sub>	Tetrakis(trisphenylphosphine)nickel(0)
NaHCO <sub>3</sub>	Sodium bicarbonate
OH	Hydroxyl
OTs	Tosylate
PPh <sub>3</sub>	Triphenylphosphine
PdCl <sub>2</sub>	Palladium chloride
Psi	Pound per square inch
P <sub>2</sub> O <sub>5</sub>	Phosphorus pentoxide
Ph	Phenyl
<i>p</i>	Para
Pd(COD) <sub>2</sub> Cl <sub>2</sub>	Dichloro(1,5-cyclooctadiene)palladium(II)
Pd(dba) <sub>2</sub>	Tris(dibenzylideneacetone)dipalladium(0)
Pd(OAc) <sub>2</sub>	Palladium acetate

Pd(PPh <sub>3</sub> ) <sub>4</sub>	Tetrakis(triphenylphosphine)palladium(0)
Pd(acac) <sub>2</sub>	Palladium acetylacetonate
Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Bis(triphenylphosphine)palladium(II)dichloride
PhMe	Toluene
PCy <sub>3</sub>	Tricyclohexylphosphine
r.t	Room temperature
R <sub>f</sub>	Retention factor
s	Singlet
TLC	Thin layer chromatography
THF	Tetrahydrofuran
SiO <sub>2</sub>	Silicon dioxide
W	Watt
Yb(OTf) <sub>3</sub>	Ytterbium(III) trifluoromethanesulfonate

## List of tables

Table 1: Initial optimisation of the reaction conditions <sup>a</sup> .....	30
Table 2: Base free palladium-catalyzed acylation reactions of sodium (aryl trihydroxyborate) salts with acyl chlorides <sup>a</sup> .....	43
Table 3: Synthesis of base sensitive diaryl ketones <sup>a</sup> .....	54
Table 4: Parameter screening for the cross-coupling of 4-methylbenzoic anhydride with sodium (phenyltrihydroxyborate) (60) <sup>a</sup> .....	56
Table 5: Summary of Palladium-Catalysed Suzuki-Miyaura Cross-Coupling Reaction .....	68

## List of figures

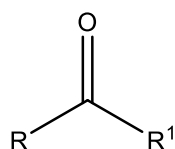
Figure 1.1: Ketone structure .....	1
Figure 1.2: Examples of biaryl ketones .....	1
Figure 1.3: Synthesised sodium (aryl trihydroxyborate) salts .....	3
Figure 2.1: Phosphine free palladium complex .....	15
Figure 2.2: NHC-Pd(II) complex .....	18
Figure 2.3: Cyclopalladated catalyst .....	18
Figure 2.4: Suzuki cross-coupling mechanism .....	19
Figure 3.1: Organoboron reagents .....	29
Figure 3.2: Sodium (aryl trihydroxyborate) salts prepared .....	30
Figure 3.3: <sup>1</sup> H NMR spectrum for compound 3 .....	32
Figure 3.4: <sup>13</sup> C NMR spectrum for compound 3 .....	33
Figure 3.5: <sup>1</sup> H NMR spectrum of compound 68 .....	34
Figure 3.6: <sup>13</sup> C NMR spectrum of compound 68 .....	34
Figure 3.7: <sup>1</sup> H NMR spectrum for compound 69 .....	35
Figure 3.8: <sup>1</sup> H NMR spectrum for (4-nitrophenyl)(p-tolyl)methanone 12 .....	37
Figure 3.9: <sup>13</sup> C NMR spectrum for (4-nitrophenyl)(p-tolyl)methanone 12 .....	37
Figure 3.10: The <sup>1</sup> H NMR spectrum of compound 71 .....	38
Figure 3.11: The <sup>1</sup> H NMR spectrum for compound 73 .....	40
Figure 3.12: The <sup>13</sup> C NMR spectrum for compound 73 .....	40
Figure 3.13: The <sup>1</sup> H NMR spectrum for the compound 84 .....	41
Figure 3.14: Suzuki-Miyaura Catalytic Cycle .....	46
Figure 3.15: Transmetalation analysis using ESI-MS .....	48

Figure 3.16: $^1\text{H}$ NMR spectrum for compound 106.....	51
Figure 3.17: $^{13}\text{C}$ NMR spectrum for compound 106.....	52
Figure 3.18: $^1\text{H}$ NMR spectrum for compound 107.....	53
Figure 3.19: $^{13}\text{C}$ NMR spectrum for compound 107.....	53
Figure 3.20: $^1\text{H}$ NMR spectrum for benzoic anhydride (52) .....	58
Figure 3.21: $^{13}\text{C}$ NMR spectrum for benzoic anhydride (52) .....	58
Figure 3.22: $^1\text{H}$ NMR spectrum of compound 111 .....	60
Figure 3.23: $^{13}\text{C}$ NMR spectrum for compound 111.....	60
Figure 3.24: $^1\text{H}$ NMR spectrum for compound 114.....	62
Figure 3.25: GC-MS spectrum for compound 101 and impurities .....	63
Figure 3.26: $^1\text{H}$ NMR spectrum for (4-nitrophenyl)(phenyl)methanone (43) .....	65
Figure 3.27: $^1\text{H}$ NMR spectrum for (4-chlorophenyl)(phenyl)methanone (115).....	66
Figure 3.28: $^1\text{H}$ NMR spectrum for (4-methylphenyl)(4-trifluorophenyl)methanone (93) .....	67

# Chapter 1

## 1.1 Introduction

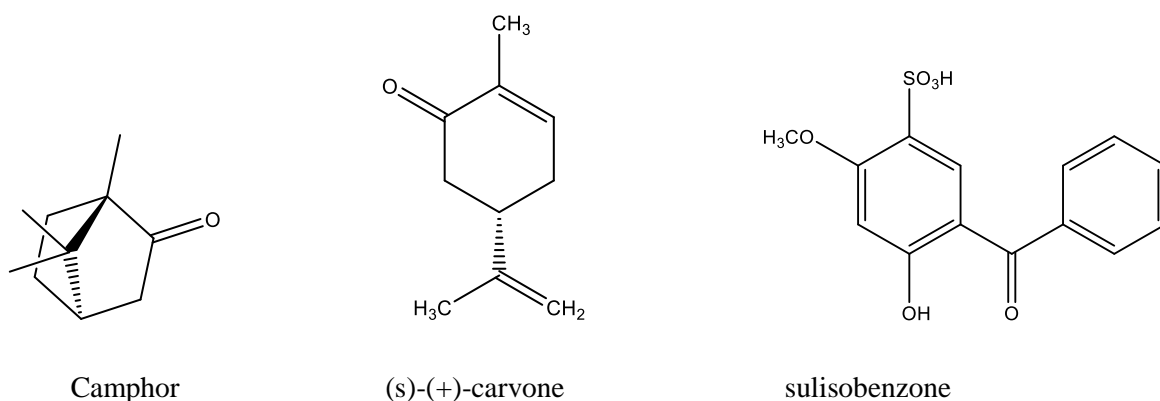
Ketones are organic compounds which consist of a carbonyl group (C=O) that is directly bonded to two hydrocarbons which can be alkyl, aromatic, saturated aliphatic or unsaturated aliphatic groups (**Figure 1.1**) [1, 2]. This class of organic compounds with the functional group consisting of a carbonyl is of central importance in organic chemistry because of its ubiquity. The synthesis of ketones is important in organic chemistry, more especially, unsymmetrical diaryl ketones because of their characteristic sweet odour [2].



R, R<sup>1</sup> = alkyl, aromatic, saturated aliphatic, unsaturated aliphatic

**Figure 1.1: Ketone structure**

Unsymmetrical ketone moieties play a big role in many natural products, biologically active compounds, and organic synthesis as well as in pharmaceuticals [3]. However, because of their characteristic sweet odour, they have found applications in fragrances as well as in the food industry as flavouring agents, for example, (S)-(+)-carvone is a ketone used in food as a flavouring agent and camphor is an aliphatic compound which is found in the camphor tree, spearmint leaves and caraway seeds, and is used in cosmetics. In addition, one of the pharmaceuticals unsymmetrical biaryl ketones is sulisobenzone which is used in some sunscreen as a UV absorber to protect the skin from UV light (**Figure 1.2**) [4].



**Figure 1.2: Examples of biaryl ketones**

However, because of the broad application of ketones, a lot of research has been focused on finding mild and convenient methods to synthesise ketones in high yields [5]. The conversion of carboxylic acid derivatives have been a traditional method applied to synthesise aryl ketones following different routes such as Friedel Crafts acylation[6], addition of organometallic reagents [7] and carbonylative [8]. These synthetic methods however, exhibit several drawbacks such as harsh reaction conditions, the use of toxic reagents, production of environmentally unfriendly by-products and low regioselectivity [9].

The most well-known and effective method to synthesise C-C bond is the palladium-catalysed Suzuki-Miyaura cross-coupling [10]. This method has brought a powerful shift in organic synthesis due to its mild reaction conditions, readily available organoboron reagents which are also easy to handle and removable as by-products especially in large-scale synthesis [11].

Suzuki cross-coupling involves boronic acid derivatives coupled with acyl chlorides or aryl halides in palladium, catalysed in the presence of a base to produce ketones (**Scheme 1.1**). This method has shown many advantages over direct acylation that have been mentioned above but has a drawback which is the addition of at least one equivalence of a base and that narrows the range of functionalities. In addition, the difficulties associated with isolation of boronic acids with their respective anhydrides complicates stoichiometric calculations [12].



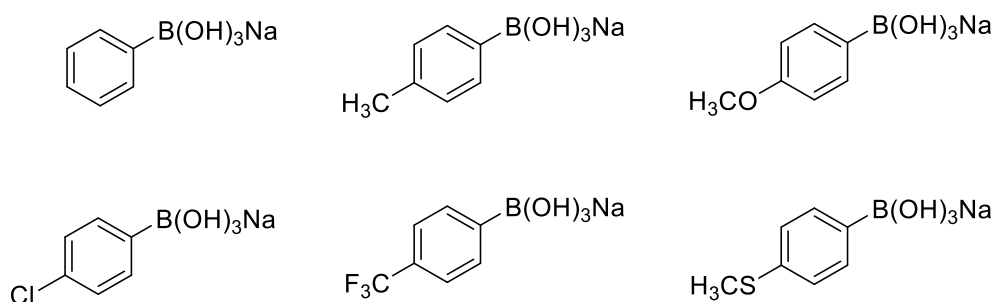
**Scheme 1.1**

Researchers have reported a number of different methods (reported in chapter 2) under Suzuki-Miyaura reactions. However, there have been no reports on the use of sodium (aryl trihydroxyborate) salts as nucleophiles in the synthesis of ketones. Trihydroxyborate salts have been reported by Cammidge and co-workers [13] as nucleophiles for the synthesis of biaryls and have shown many advantages over boronic acids. However, boronic acid requires addition of a base in order to promote the transmetalation step because tri-coordinated organoboron compounds do not induce enough nucleophilicity to the organic moiety directly bonded to it unlike trihydroxyborate salts which are already activated to transmetalate [14].



This has allowed us to investigate whether sodium (aryl trihydroxyborate) salts will transmetallate in Suzuki-Miyaura acylation without the addition of a base, therefore, accommodating base sensitive functional groups.

Different free flowing sodium (aryl trihydroxyborate) salts were synthesised following Cammidge's [13] method in chapter 3 (**Figure 1.3**) then coupled with acyl chloride bearing electron-donation, electron-neutral and electron-withdrawing substituents. Thereafter, another electrophilic partner was tried out, carboxylic anhydrides also reported in chapter 3.



**Figure 1.3: Synthesised sodium (aryl trihydroxyborate) salts**

With regards to electrophilic partners in Suzuki cross-coupling acylation reactions, the scope of acyl derivatives have been successfully expanded to acyl chlorides [15], acyl fluoride [16], anhydrides [17], carboxylic acids [18], carboxylic amides [19], thioesters and esters [20]. However, they all have different reactivity towards the palladium precursor in the oxidative addition step.

## 1.2 References

1. Lloyd, D., *The chemistry of simple organic chemistry compounds*. 1964: University of London Press.
2. Bezzant, R. J., *Basic organic chemistry*. 1967: McGraw-Hill. p.219-221
3. Jafarpour, F., P. Rashidi-Ranjbar, and A.O. Kashani, *Easy-to-execute carbonylative arylation of aryl halides using molybdenum hexacarbonyl: efficient synthesis of unsymmetrical diaryl ketones*. *European Journal of Organic Chemistry*, 2011. **11**: p. 2128-2132.
4. Ogawa, D., et al., *Palladium-catalyzed and copper-mediated cross-coupling reaction of aryl- or alkenylboronic acids with acid chlorides under neutral conditions: efficient synthetic methods for diaryl ketones and chalcones at room temperature*. *Tetrahedron*, 2013. **69**(12): p. 2565-2571.
5. Dieter, R.K., *Reaction of acyl chlorides with organometallic reagents: a banquet table of metals for ketone synthesis*. *Tetrahedron*, 1999. **55**(14): p. 4177-4236.
6. Ashdown, A.A., *Earliest history of the Friedel-Crafts reaction*. *Industrial & Engineering Chemistry*, 1927. **19**(9): p. 1063-1065.
7. Newman, M.S. and W.T. Booth Jr, *The preparation of ketones from Grignard reagents*. *Journal of the American Chemical Society*, 1945. **67**(1): p. 154-154.
8. Sharma, P., S. Rohilla, and N. Jain, *Palladium catalyzed carbonylative coupling for synthesis of arylketones and arylesters using chloroform as the carbon monoxide source*. *The Journal of Organic Chemistry*, 2017. **82**(2): p. 1105-1113.
9. Blangetti, M., et al., *Suzuki-Miyaura cross-coupling in acylation reactions, scope and recent developments*. *Molecules*, 2013. **18**(1): p. 1188-1213.
10. Lennox, A.J. and G.C. Lloyd-Jones, *Transmetalation in the Suzuki-Miyaura coupling: the fork in the trail*. *Angewandte Chemie International Edition*, 2013. **52**(29): p. 7362-7370.
11. Gujral, S.S., et al., *Suzuki cross coupling reaction-a review*. *Indo Global Journal of Pharmaceutical Sciences*, 2012. **2**: p. 351-367.
12. Bumagin, N.A. and D.N. Korolev, *Synthesis of unsymmetric ketones via ligandless Pd-catalyzed reaction of acyl chlorides with organoboranes*. *Tetrahedron Letters*, 1999. **40**(15): p. 3057-3060.
13. Cammidge, A.N., et al., *Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions*. *Organic Letters*, 2006. **8**(18): p. 4071-4074.
14. Lennox, A.J. and G.C. Lloyd-Jones, *Selection of boron reagents for Suzuki-Miyaura coupling*. *Chemical Society Reviews*, 2014. **43**(1): p. 412-443.
15. Bandgar, B. and A. Patil, *A rapid, solvent-free, ligandless and mild method for preparing aromatic ketones from acyl chlorides and arylboronic acids via a Suzuki-Miyaura type of coupling reaction*. *Tetrahedron Letters*, 2005. **46**(44): p. 7627-7630.
16. Ogiwara, Y., et al., *Acid Fluorides as Acyl Electrophiles in Suzuki-Miyaura Coupling*. *European Journal of Organic Chemistry*, 2017.
17. Kakino, R., et al., *Synthesis of unsymmetrical ketones by palladium-catalyzed cross-coupling reaction of carboxylic anhydrides with organoboron compounds*. *Bulletin of the Chemical Society of Japan*, 2002. **75**(1): p. 137-148.
18. Kakino, R., et al., *Palladium-catalyzed direct conversion of carboxylic acids into ketones with organoboronic acids promoted by anhydride activators*. *Bulletin of the Chemical Society of Japan*, 2002. **75**(6): p. 1333-1345.
19. Li, X. and G. Zou, *Acylative Suzuki coupling of amides: acyl-nitrogen activation via synergy of independently modifiable activating groups*. *Chemical Communications*, 2015. **51**(24): p. 5089-5092.
20. Kakino, R., I. Shimizu, and A. Yamamoto, *Synthesis of trifluoromethyl ketones by palladium-catalyzed cross-coupling reaction of phenyl trifluoroacetate with organoboron compounds*. *Bulletin of the Chemical Society of Japan*, 2001. **74**(2): p. 371-376.

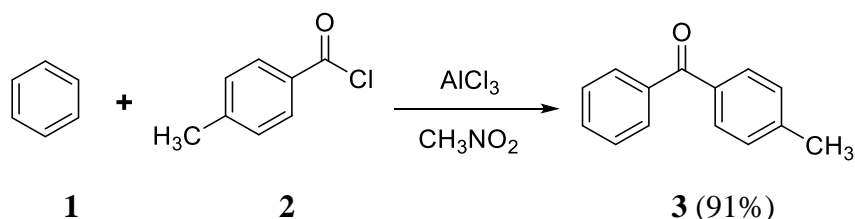
## Chapter 2

### Literature Review

#### 2.1 Introduction

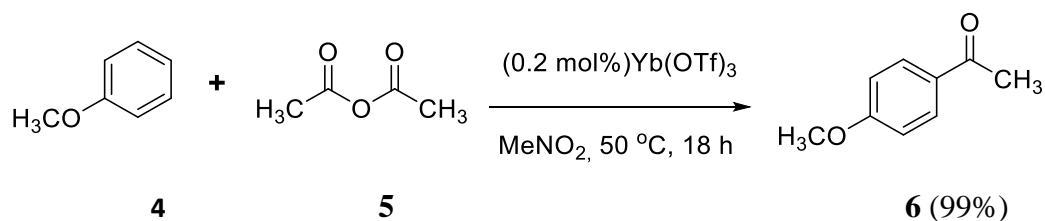
Transition metal catalyzed transformations are one of the most powerful bond forming strategies in organic chemistry [1]. The carbon-carbon bond formation reactions play an important role in the synthesis of aromatic ketones, which are crucial building blocks for the synthesis of complex natural products, active pharmaceutical ingredients (APIs) and small molecules for drug discovery [2, 3].

There are many procedures to prepare ketones reported in the literature. One of these methods is Friedel Crafts acylation [4] reaction of substituted acyl chloride (**2**) with benzene (**1**) in the presence of a Lewis acid [5] ( $\text{BF}_3$  or  $\text{AlCl}_3$ ) to produce the product (**3**) in excellent yield (**Scheme 2.1**) [6]. Regardless of the great impact this method brings to organic chemistry, this reaction entails drawbacks such as the use of stoichiometric amounts of a strong Lewis acid due to the formation of a strong complex between the product ketone and metal halide [7, 8], generation of toxic and corrosive acid ( $\text{HCl}$ ), harsh reaction conditions and low selectivity (meta substituted do not participate) [9].



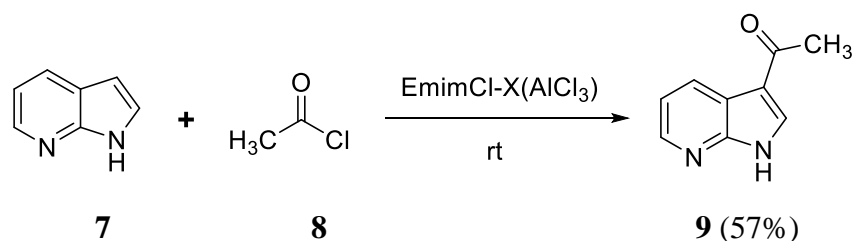
**Scheme 2.1**

To overcome the use of stoichiometric amounts of aluminium chloride, Kawada and co-workers [10] developed a novel methodology for the acylation of methoxybenzene (**4**) with acetic anhydride (**5**) in the presence of a catalytic amount of ytterbium trifluoromethanesulfonates in  $\text{MeNO}_2$ , providing the desired product in excellent yield (**Scheme 2.2**). The catalyst, ytterbium triflate was recovered and reused three times giving almost the same yield. The use of ytterbium as a catalyst is more attractive compared to  $\text{AlCl}_3$  because it is stable under aqueous media whereas aluminium trichloride cannot be reused due to its instability under aqueous workups. However,  $\text{Yb}(\text{OTf})_3$  was inefficient in the catalytic acylation of benzene and had relatively low activity [10].



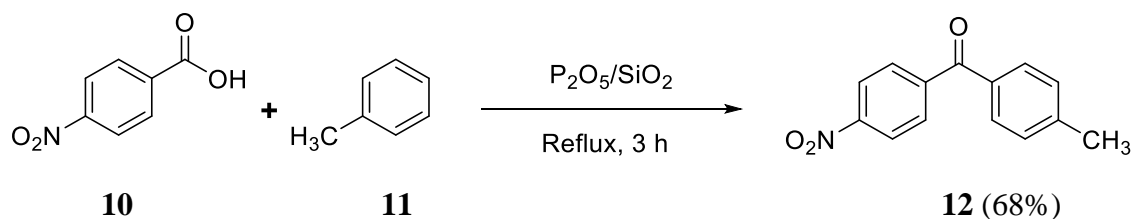
**Scheme 2.2**

On the other hand, the great application of ionic liquids as a solvent and as a catalyst was firstly performed in Friedel Craft reactions by Wilkes and co-workers [11]. Lewis acidic ionic liquids bring greater effect in Friedel Craft acylation reaction because it give high reaction rates, selectivity and conversion [12]. In 2002, Yeung and co-workers [13] reported a convenient Friedel Craft acylation procedure of indoles (**7**) in ionic liquid EmimCl-X(AlCl<sub>3</sub>) at room temperature producing ketones (**9**) in moderate to high yields (**Scheme 2.3**).



**Scheme 2.3**

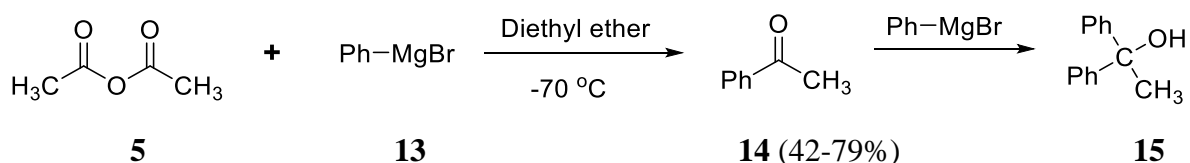
Due to the poor isolation of the product from ionic liquids, an alternative method was reported by Zarei and co-workers that involves the acylation of aromatic compounds in heterogeneous conditions [14]. This procedure describes the acylation of substituted benzene (**11**) with carboxylic acid (**10**) in the presence of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> to produce ketones in moderate to high yields (**Scheme 2.4**). The use of heterogeneous conditions improved the isolation of the catalyst from the product.



**Scheme 2.4**

The direct addition of organometallic reagents to carboxylic acid derivatives to construct a C-C bond achieves an important goal in organic synthesis. Friend [15] was the first to observe

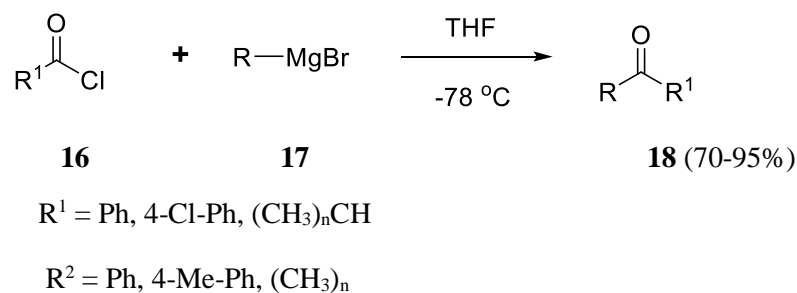
the formation of ketones from the addition of organozinc to acyl chloride in 1861. The mild nature of organometallic reagents, including, organozinc [16, 17], Grignard or organolithium [18], organotin [19] and organocadmium [20] make them useful nucleophiles for the synthesis of ketones. Newman *et al* [21] reacted the Grignard reagent (**13**) with anhydrides (**5**) to produce ketones in diethyl ether with moderate to high yields (**Scheme 2.5**).



**Scheme 2.5**

The limitation of this protocol is that allyl and benzyl Grignard reagents produce low yields of ketones due to the formation of tertiary alcohol (**15**) as a result of the reaction of the addition of Grignard reagent (**13**) to a product ketone (**14**) [21].

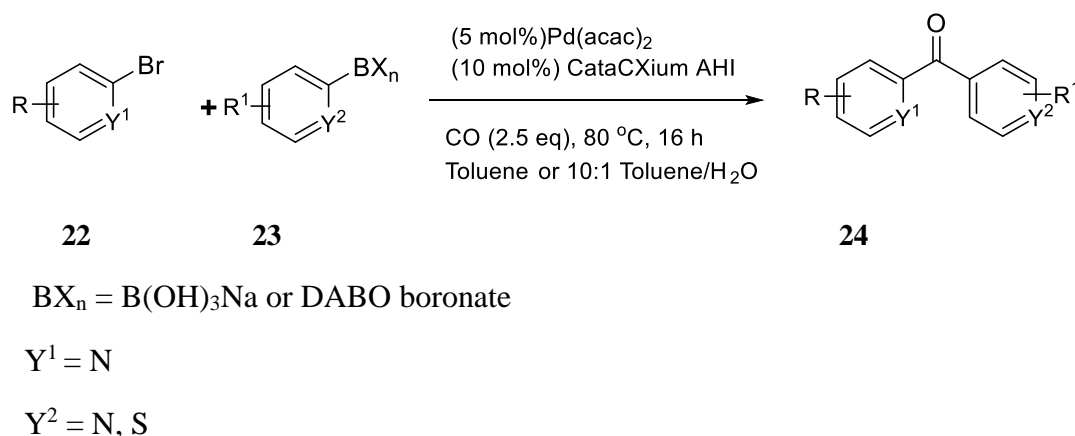
To overcome this obstacle, Sato and co-workers [22] reported that the slow addition of Grignard reagent (**17**) to an excess of acid chloride (**16**) in THF, suppresses the side reaction thus improving the yields of ketones (**Scheme 2.6**). Additionally, solvent also played a significant role in improving the yields because when Et<sub>2</sub>O was used, a high percentage of alcohol byproduct was produced as compared to when THF was used as a solvent.



**Scheme 2.6**

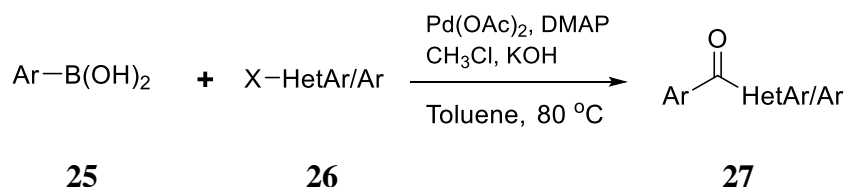
Even though the procedure reported by Sato and co-workers produced ketones in good to excellent yield (**Scheme 2.6**), this protocol must be conducted at -78 °C and excess acyl chloride must be added. An improved alternative method, in which the addition of 1:1 stoichiometric ratio of acyl chloride (**19**) to Grignard reagent (**20**) produced the desired ketones (**21**) in good to excellent yields under catalytic activity of Fe(acac)<sub>3</sub> at room temperature, was reported by Fiandanese (**Scheme 2.7**) [23].





**Scheme 2.8**

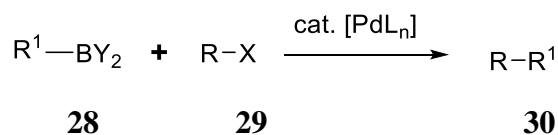
Most recently, a CO gas-free procedure was described by Jain and co-workers [31], where aryl(hetero)aryl halides (**26**) have been successfully coupled with boronic acids (**25**) in the presence of  $\text{Pd}(\text{OAc})_2$  as a catalyst and  $\text{CHCl}_3$  as the carbon monoxide source in toluene (**Scheme 2.9**). This methodology has proven to be an improvement on the existing carbonylative methods for the preparation of biaryl ketones (**27**) by circumventing the use and handling of CO gas. Instead of using direct CO, this method relies on generating CO *in situ* from chloroform and KOH.



**Scheme 2.9**

## 2.2 Background of Suzuki-Miyaura Cross-Coupling

In the 1970s, a new method for the synthesis of C-C bond was reported which was based on the palladium transition-metal catalysts. A remarkable palladium catalyzed cross coupling is the Suzuki-Miyaura reaction that involves the coupling of organoboron (**28**) with aryl or alkenyl halides and triflates (**29**) in the presence of the catalyst (palladium) to form a new carbon-carbon single bond [32]. This method is widely used in industries to synthesis biaryls, natural products as well as ketones. This reaction was first reported in 1979 by Akira Suzuki where he reacted aryl halide with aryl boronic acid in the presence of Pd catalyst and a base (**Scheme 2.10**) [33, 34].



R<sup>1</sup> = alkyl, alkynyl, aryl, vinyl

R = alkyl, alkynyl, aryl, benzyl, vinyl

X = Br, Cl, I, OP(=O)(OR)<sub>2</sub>, OTf, OTs

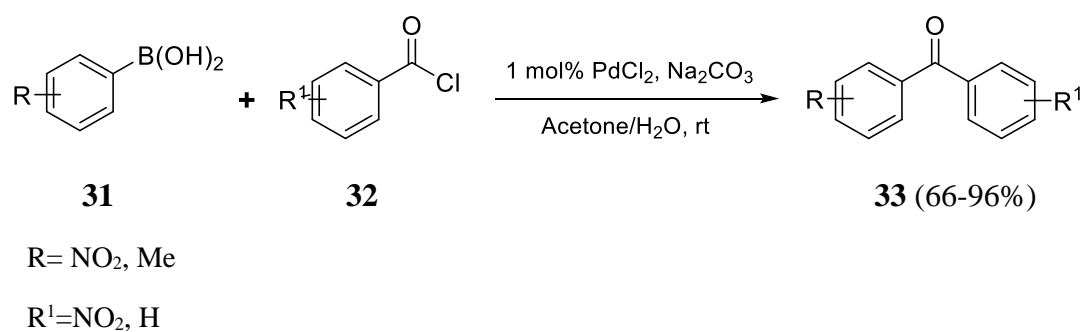
### Scheme 2.10

Compared to other coupling reactions such as the Heck and Stille cross-coupling reaction, Suzuki-Miyaura cross-coupling reactions have occupied a unique spot in the C-C bond cross-coupling reaction due to numerous advantages such as the use of commercially available boronic acid derivatives that are more environmentally friendly than the other organometallic reagents, mild reaction conditions, stable organoboron use in moist air conditions and the easy removal of less-toxic inorganic reagents as opposed to organometallic reagents even in large scale [35, 36]. Therefore, palladium-catalyzed Suzuki cross coupling has taken over other cross coupling reactions since it is not only limited to small molecules but can be used to synthesize large complex molecules [36]. In addition, the palladium-catalyzed Suzuki-Miyaura reaction is one of the few methodologies to form C-C bonds that have transformed from the research sector to manufacturing sector due to the above mentioned advantages.

## 2.3 Coupling of arylboronic acid derivatives with acyl halides

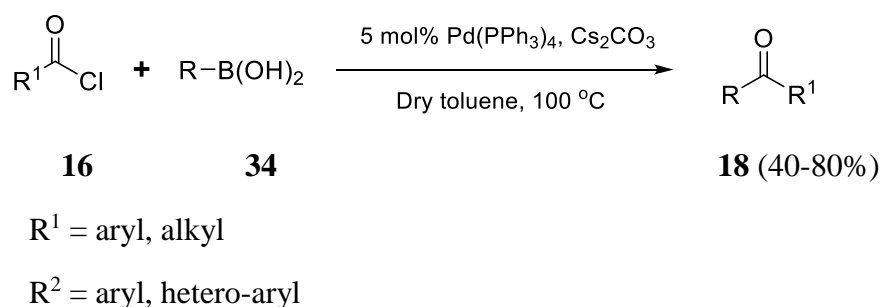
With these advantages in mind, Bumagin and co-worker [37] were the first to demonstrate that ketones can be prepared from acyl chloride (**32**) and boronic acids (**31**) under Suzuki-Miyaura cross-coupling conditions (**Scheme 2.11**). In this method, the authors reported the synthesis of ketones (**33**) in high yields using ligandless palladium catalyst in aqueous acetone where acyl chlorides (*m*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COCl) reacted smoothly with boronic acid in the present of Na<sub>2</sub>CO<sub>3</sub> as a base (**Scheme 2.11**).





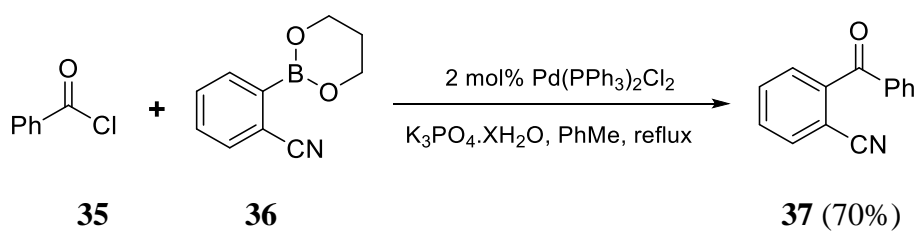
**Scheme 2.11**

Although the above reaction produced a ketone in good to excellent yields, ketones bearing electron withdrawing groups were produced in poor yield owing to the competitive hydrolysis of acyl chloride to the corresponding carboxylic acid as a result of the presence of H<sub>2</sub>O as a solvent. An alternative method was shown by Haddach and co-workers in 1999, where they reported an anhydrous reaction condition for the coupling of organoboronic acid (**34**) with acyl chloride (**16**) to produce ketones (**18**) in moderate to high yields (**Scheme 2.12**) [38].



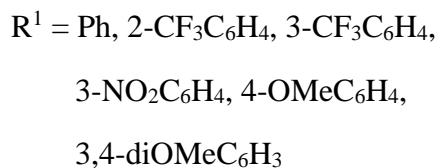
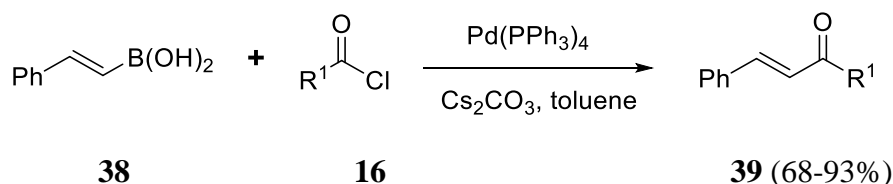
**Scheme 2.12**

Haddach's [38] and Bumagin's [37] reaction conditions were not suitable for the synthesis of cyanobenzophenone which are useful moieties for the synthesis of pharmaceuticals. As a result, in 2003, Urawa and Ogura demonstrated that the addition of K<sub>3</sub>PO<sub>4</sub> hydrate as a base in the coupling reaction of boronic acid (**36**) with acyl chloride (**35**) in toluene produced the desired cyanobenzophenone (**37**) in high yield (**Scheme 2.13**). This method furnished moderate to high yields of symmetric and asymmetric ketones [39].



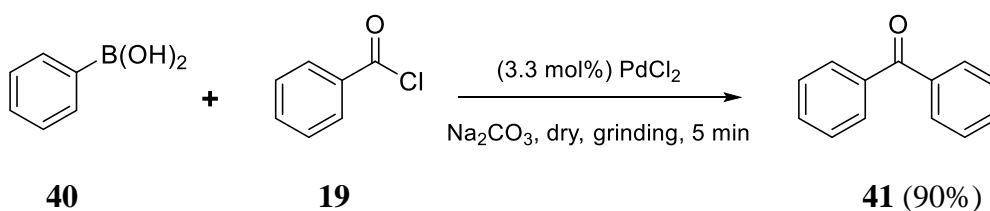
**Scheme 2.13**

Meanwhile, Haddach's [38] methodology was a success when it was applied by Rolando [40] to synthesise substituted chalcones (**39**) by cross-coupling phenylvinylboronic acids (**38**) with acyl chlorides or cinnamoyl chlorides (**16**) affording different chalcones in high yields (**Scheme 2.14**).



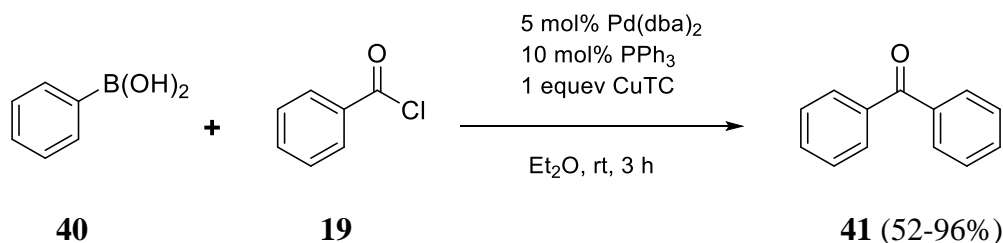
**Scheme 2.14**

Bandgar and co-workers [41] developed a ligandless and solvent free procedure for the synthesis of aromatic ketones by coupling arylboronic acids (**40**) with acyl chlorides (**19**) in the present of  $\text{PdCl}_2$  and dry  $\text{Na}_2\text{CO}_3$  at room temperature (**Scheme 2.15**). This procedure has overcome some disadvantages associated with other reported Suzuki reactions such as the addition of five equivalents of a base in the above-mentioned reaction as well as long reaction times. Despite all the good it brings, alkyl acyl chlorides are not accommodated by the reported conditions.



**Scheme 2.15**

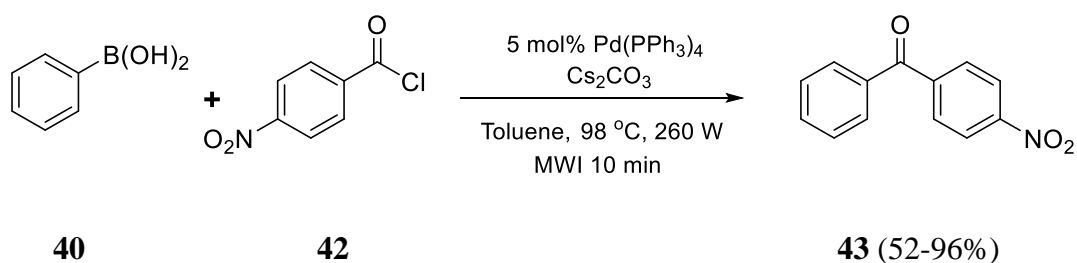
Simultaneously, a more convenient and neutral (base free) alternative method to synthesise ketones was developed by Nishihara and co-workers [42] when they use (CuTC) as an activator and Pd(dba)<sub>2</sub> as a catalyst in diethyl ether to produce unsymmetrical aromatic ketones (**41**) (**Scheme 2.16**).



**Scheme 2.16**

This method is advantageous over the other methods because (1) it doesn't use three equivalence of base (2) it is conducted at room temperature (3) it produces high yields of ketones. However, the problem with this procedure is that it uses an expensive CuTC as boronic acid activator which is lost after the reaction is completed and it also uses Pd(dba)<sub>2</sub> in conjunction with PPh<sub>3</sub> as a ligand. These metal-ligand combination is moisture and air sensitive and is also more expensive than other Pd sources such as Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub>.

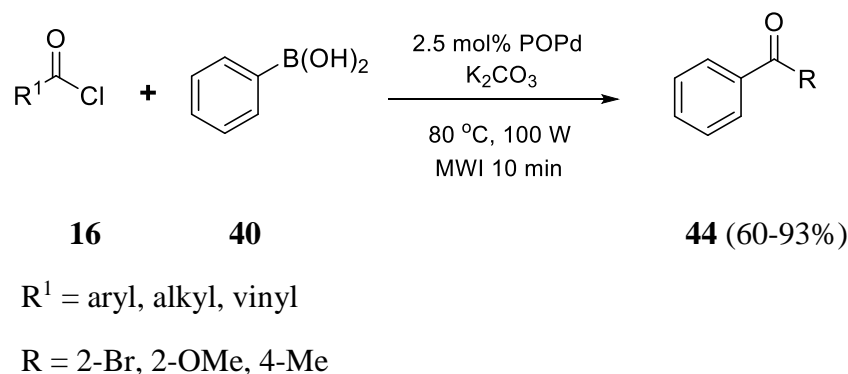
On the other hand, Palackova and co-workers [43] developed a catalytic procedure to produce ketones using aromatic acyl chloride (**42**) and arylboronic acids (**40**) in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst and Cs<sub>2</sub>CO<sub>3</sub> as a base in aqueous toluene under microwave irradiation (**Scheme 2.17**). This Suzuki-Miyaura cross-coupling procedure was developed in order to reduce reaction time while finishing substituted aromatic ketones in excellent yield although it could not accommodate aliphatic and cinnamic acyl chlorides (**Scheme 2.17**).



**Scheme 2.17**

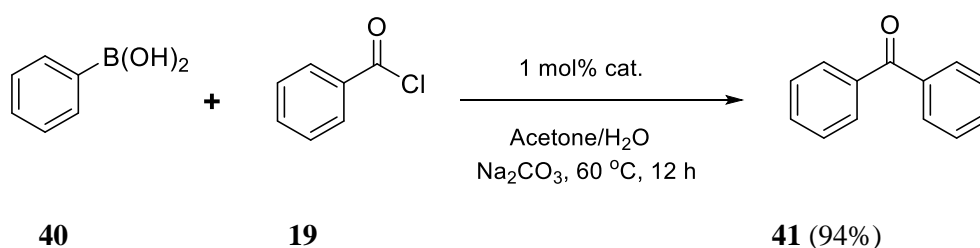
Alternatively, Wolf and co-workers [44] reported a microwave-assisted method which could accommodate aromatic and aliphatic acyl chlorides including cinnamic acyl chlorides (**16**)

coupling with arylboronic acids (**40**) in the presence of 2.5 mol% (t-Bu<sub>2</sub>POH)<sub>2</sub>PdCl<sub>2</sub> affording benzophenone and acetophenone (**44**) ketones in good to excellent yields in only 10 minutes (**Scheme 2.18**).

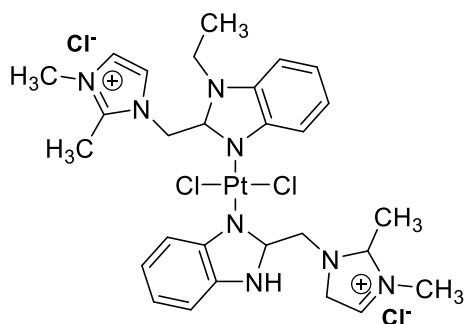


**Scheme 2.18**

Moreover, there have been many reported methodologies with phosphine ligands even though they are air and moist sensitive but they produce high yields of ketones. Li and co-workers [45] reported in 2011 a phosphine-free palladium complex (**Figure 2.1**) which catalyzed the synthesis of biaryl ketones from arylboronic acids coupling with acyl chlorides in the presence of Na<sub>2</sub>CO<sub>3</sub> as a base in aqueous acetone giving the desired products (ketones) in high yields (**Scheme 2.19**). The catalyst used was recyclable for about four times without a decrease in activity. Hajipour and co-workers [46] prepared a tetraalkylammonium salt containing palladium complex and used it to synthesise biaryl ketones in high yields coupling boronic acid with acyl chlorides at room temperature.

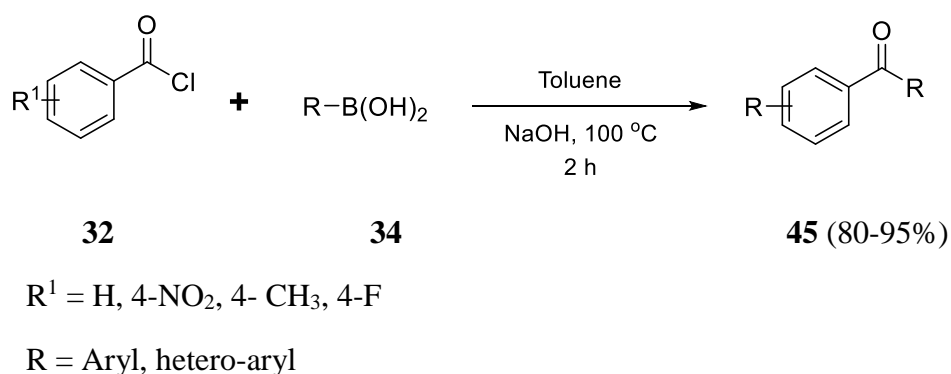


**Scheme 2.19**



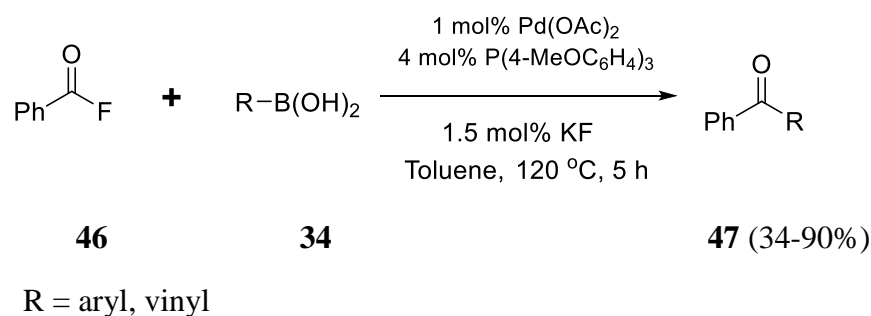
**Figure 2.1: Phosphine free palladium complex**

In 2017, the use of metal-free Suzuki cross-coupling reaction methodology had been reported by Salunkhe and coworkers [47] when they reacted acyl chlorides (**32**) with arylboronic acids (**34**) in the presence NaOH as a base in toluene (**Scheme 2.20**). This procedure seems to be environmentally friendly since it does not use additives, surfactants, metal and ligands to furnish the C-C bond formation.



**Scheme 2.20**

A vast number of acyl chlorides have been applied successfully as electrophilic coupling partners in the synthesis of biaryl ketones owing to their remarkable reactivity. To expand the scope of acyl halides electrophilic coupling partners, Ogiwara and co-workers recently developed a procedure for the synthesis of biaryl ketones from less reactive acyl fluorides as acylating agents. Aryl and acyl fluorides (**46**) were reacted with different boronic acids (**34**) in toluene affording the corresponding ketones in moderate to excellent yields (**Scheme 2.21**) [48]. A wide range of functional groups were tolerated affording desired products (**47**) in moderate to excellent yields.

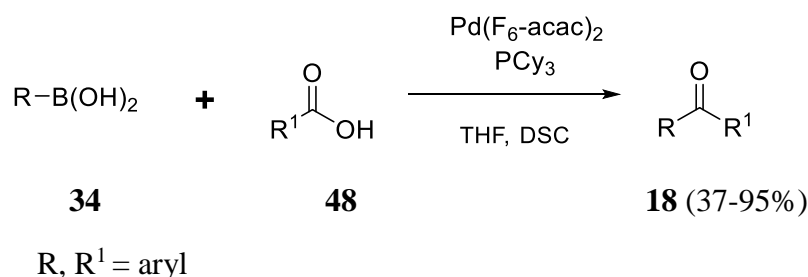


**Scheme 2.21**

### 2.3 Coupling of arylboronic acid derivatives with anhydrides

Regardless of the rich chemistry offered by acyl halides (acyl chloride) as efficient acylating agents which proceeds via C-X (X = Cl, F) bond cleavage, a recent protocol proceeding via C-O bond cleavage to effect acylation was independently developed by Yamamoto [49-51] and Gooben [52].

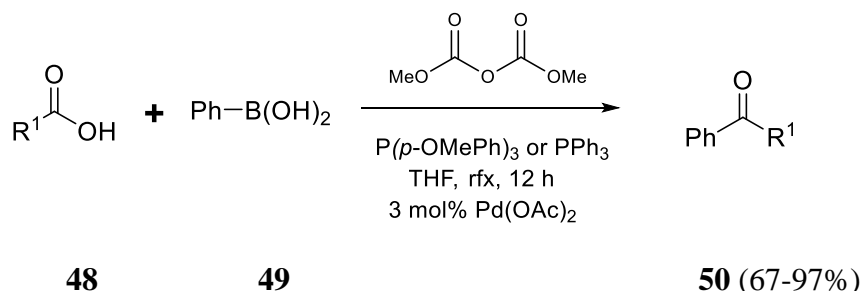
Gooben and co-workers were the first to report on the synthesis of ketones using carboxylic acid as an acylating agent under the Suzuki-Miyaura reaction conditions. In this method, carboxylic acids (**48**) bearing electron donating and electron withdrawing functionalities were efficiently coupled with aryl boronic acid (**34**) in the presence of di(N-succinimidyl) carbonate as acylating agents furnishing biaryl ketones (**18**) in good yield (**Scheme 2.22**). The developed procedure was mild and versatile tolerating a wide range of functionalities including nitro, cyano and amido functional groups. However, base sensitive functionalities such as hydroxyl and amino groups were not well catered [53].



**Scheme 2.22**

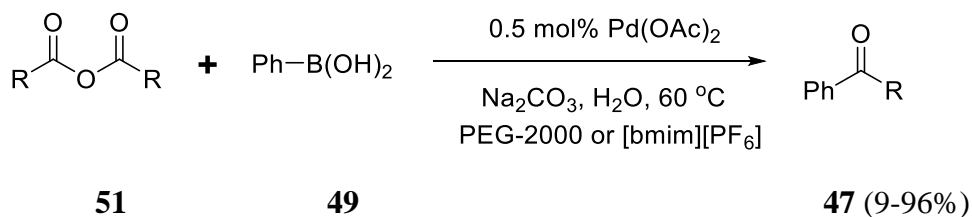
The above-mentioned challenge was resolved by using dimethyl carbonate as an acylating agent instead of a base. Thereafter, Gooben [54] was able to overcome the above-mentioned problems by using an activating agent (dimethyl dicarbonate). This was accomplished by

coupling arylboronic acids (**49**) with carboxylic acid (**48**) with dimethyl dicarbonate as an activating agent and Pd(OAc)<sub>2</sub> as a catalyst in THF (**Scheme 2.23**).



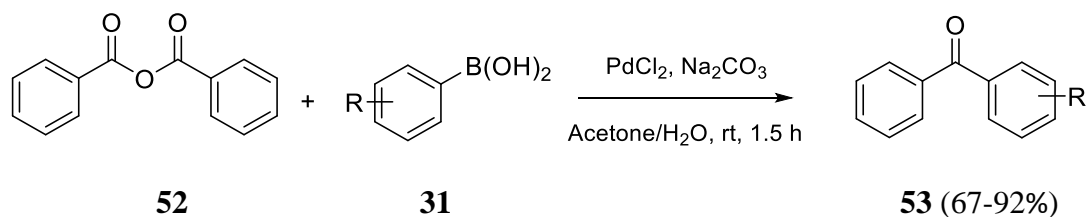
**Scheme 2.23**

Both Booben and Yamamotos' findings have revealed that phosphine ligands are vital for the efficient synthesis of ketones from carboxylic acids as acylating agents. Despite the necessity of phosphine ligands in these methodologies, phosphine-based ligands have been reported to be prone to protonation and oxidation under these reaction conditions thus lowering the efficiency of these protocols in the production of ketones [53]. As a result, Zhang *et al* have developed a phosphine free procedure with the aim of improving the above-mentioned challenge. In this procedure, Zhang and co-workers successfully coupled carboxylic anhydrides (**51**) with boronic acid (**49**) in ionic liquid [bmim][PF<sub>6</sub>] or PEG affording the desired ketone (**47**) in high yields (**Scheme 2.24**). The developed catalytic system is more attractive than previously reported procedures because PEG is not prone to oxidation and it can be recycled up to eight times without rendering it efficient [55]. A year later, the authors reported another method which makes use of surfactants as promoters instead of phosphine ligands in water, producing ketones in high yields [56].



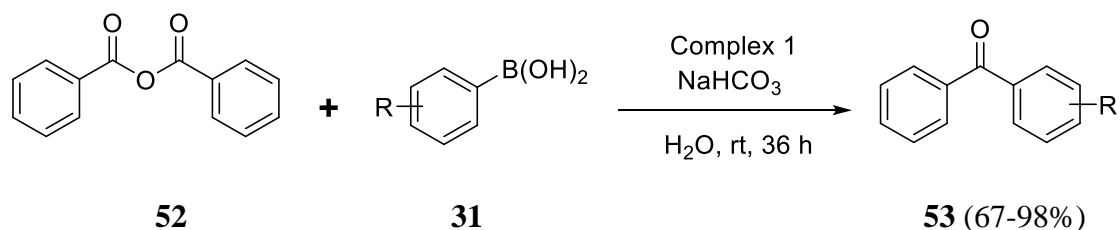
**Scheme 2.24**

In 2008, Xin [57] reported a cheaper procedure that showed that acetone had a remarkable effect in producing aryl ketones in water using ligandless palladium catalyst at room temperature in a short reaction time (**Scheme 2.25**).

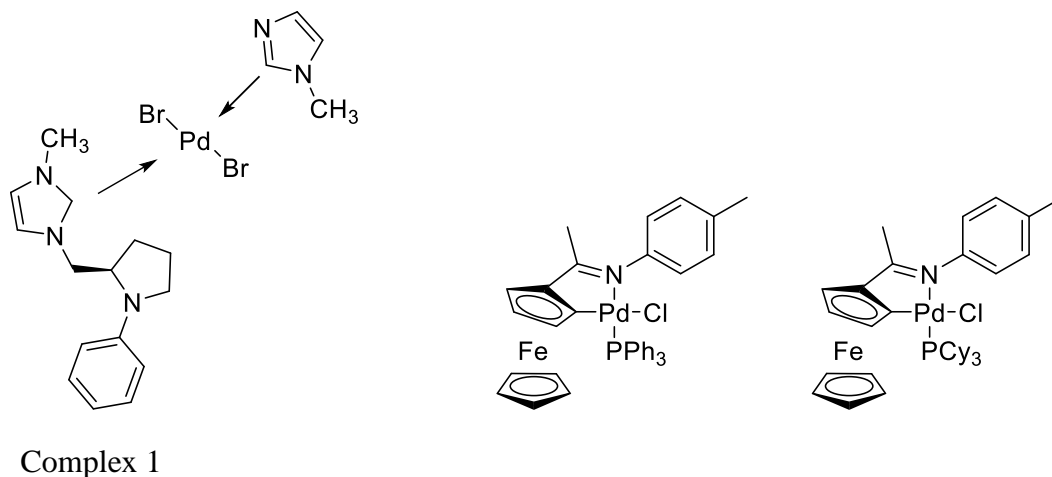


**Scheme 2.25**

The application of carboxylic anhydrides as acylating agents was further extended by Shao and co-workers when they developed a procedure to synthesise ketones which catalyzes with NHC-Pd(II) complex (**Figure 2.2**). In this procedure, aryl boronic acids (**31**) were successfully coupled with carboxylic anhydrides (**52**) in acidic conditions producing ketones (**53**) in moderate to excellent yield (**Scheme 2.26**) [58]. On the other hand, Wu and co-workers [59] developed cyclopalladated ferrocenylimine (**Figure 2.3**) catalysts that also finished the synthesis of biaryl ketones.



**Scheme 2.26**



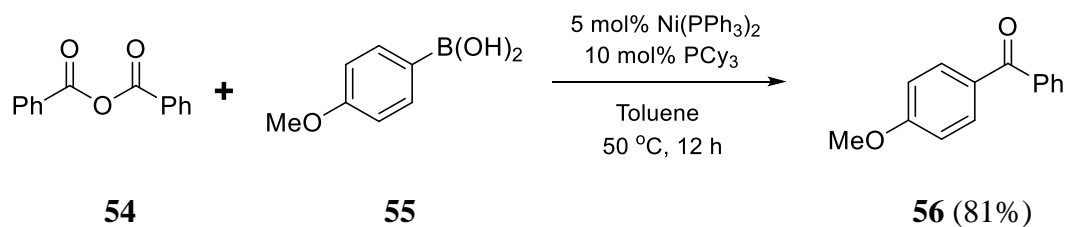
**Figure 2.2: NHC-Pd(II) complex**

**Figure 2.3: Cyclopalladated catalyst**

In 2014, a more attractive and economic procedure for the synthesis of ketones was developed by Yang and co-workers. Yang and his research group successfully coupled carboxylic anhydride with aryl boronic acids in the presence of catalytic amount of cheap  $\text{Ni}(\text{PPh}_3)_4$  providing a cheaper procedure to produce biaryl ketones in excellent yields



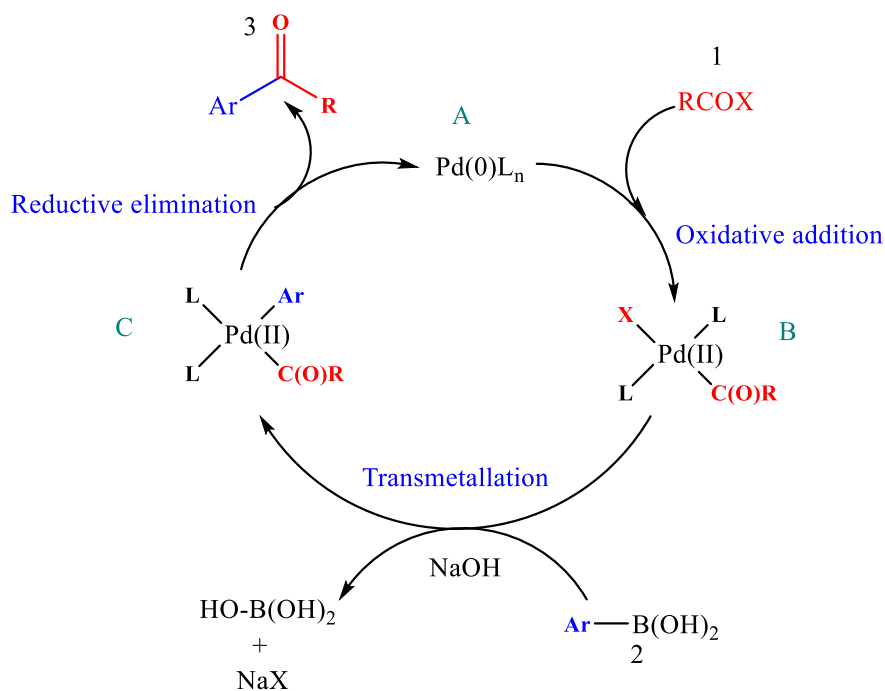
(Scheme 2.27). This protocol is attractive in the organic synthesis as nickel-based catalysts are cheaper than those of palladium, thus, increasing the potential utility of Yang's procedure in industrial settings [60].



Scheme 2.27

## 2.4 Suzuki-Miyaura Cross-Coupling mechanism

In order to understand how palladium-catalyzed Suzuki cross-coupling reactions form a new carbon-carbon bond, a mechanistic study was firstly proposed by Suzuki and Miyaura in 1985 [61].



Ar = Organic moiety

X = Cl, Br, I, OTf

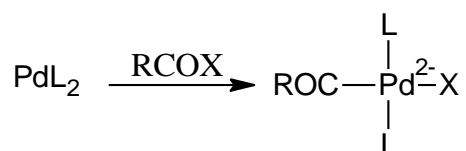
L = Ligand

R = Organic group

Figure 2.4: Suzuki cross-coupling mechanism

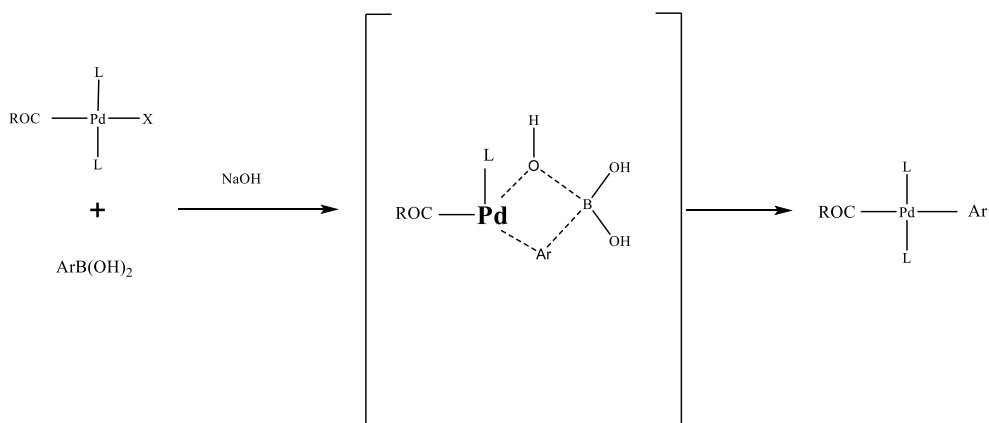
The Suzuki palladium-catalyzed reactions involve the cross coupling between organoboron species and organic electrophiles in the presence of a base expanding the spectrum of powerful methodologies to form new carbon-carbon bonds [62]. There are many advantages that come with such cross-coupling therefore, it is important to understand the path it takes to form carbon-carbon bonds [62]. The Suzuki-Miyaura cross-coupling catalytic cycle involves three steps, namely, oxidative addition, transmetallation and reductive elimination (**Figure 2.4**) [63]. Of the three steps that have been mentioned, the transmetallation step is the one that differentiates Suzuki coupling from all other transition metal cross-coupling reactions [64].

The oxidative addition step is said to be common to many transition- metal cross-coupling reactions and is a rate-determining step in the Suzuki catalytic cycle [65]. The oxidative addition of aryl halides or acyl halides or carboxylic derivatives to the Pd(0) species gives stable *trans*- $\sigma$ -palladium(II) complex (RPdXL<sub>n</sub>) (**Scheme 2.28**).



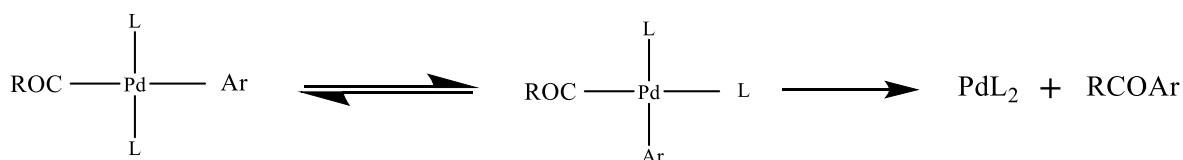
**Scheme 2.28**

The transmetallation step involves two pathways, namely, boronate pathway and oxo-palladium pathway [64]. Boronate pathway involves four coordinated active boron species that is preformed and in the oxo-palladium pathway, the alkyl or hydroxyl ligand acts as a Lewis acid on palladium that generates a four-coordinate species. The study that was done by Matos and Soderquist revealed that the pathway depends on the organoboron species involved [66]. The formation of an active oxo-palladium species allows the organic group bonded to boron to be transmetallated to the palladium center thus making the reductive elimination feasible (**Scheme 2.29**) [66].



**Scheme 2.29**

In the reductive elimination step, the organic moieties rearrange to *cis* position in palladium. The two organic groups undergo elimination from the metal center thereby regenerating Pd(0) for the next catalytic cycle (**Scheme 2.30**) [67].



**Scheme 2.30**

Organoboron compounds tolerate a broad spectrum of functionalities, are usually inexpensive to prepare, are generally environmentally friendly, easy to handle and stable which makes them industrially applicable. They transmetallate with different metals (copper, rhodium, gold etc.) under mild reaction conditions and are much better with palladium(II) complexes. The first application of boronic acids in Suzuki-Miyaura reactions was reported in 1981 [68] and has been widely-applied ever since to construct C-C bonds accommodating a variety of functional groups synthesised in mild reaction conditions. Despite the applications that boronic acids bring to the chemical society, there are still drawbacks that need to be overcome. The transmetallation step requires an active boron species and this was discovered by Suzuki and Miyaura, therefore, they added a base to activate a boron species which then excluded the base sensitive functionalities. Boronic acids require more than one equivalence of a base, form side reactions including oxidation [69], homocoupling [70] and protodeboronation [71], are difficult to isolate, produce the boroxide ring under anhydrous conditions and it tends to form wax solid.

Sodium (aryl trihydroxyborate) salts have showed to be versatile nucleophiles than boronic acids because they are coupled under base free Suzuki-Miyaura mild reaction conditions and are easy to isolate. In addition, they tolerate a wide range of functionalities since they do not require a base to be activated, therefore, undergo boronate pathway. Sodium (aryl trihydroxyborate) salts have shown to be better nucleophiles than boronic acids in Suzuki cross-coupling since they transmetallate with palladium in base free conditions which then make the cross coupling methodology economically feasible due to lower amount of chemicals required to form C-C bonds. Few reports have described the isolation of sodium (aryl trihydroxyborate) salts and directly applied in Suzuki cross-coupling reactions under mild reaction conditions to construct C-C bonds [72, 73].

To the best of our knowledge, there is no procedure in literature which describes the use of sodium (aryl trihydroxyborate) salts as nucleophilic coupling partners in Suzuki-Miyaura cross-coupling to form ketones. There are no reports which describes a base free Suzuki-Miyaura cross-coupling to synthesise ketones except by Nishihara and co-workers [42], however, they employed an expensive CuTC as an activator. As a result, the development of a base free synthesis of ketones using activated nucleophiles, sodium (aryl trihydroxyborates) salts, is highly desirable especially for ketones bearing base sensitive functionalities. Such developments will undoubtedly benefit the organic community at large and expand the scope of methodologies available, thus enriching the organic chemistry portal.

## **2.5 Aims and objectives**

There is a wide occurrence of biaryl ketone moieties in a large number of natural products, biological active compounds, cosmetics, pharmaceuticals, dye, agrochemical, fragrance and functional material industries bond. Due to the high demand of biaryl ketone moieties in our everyday life, therefore there is a need to find ways to synthesise them using mild reaction conditions using cheap, available and environmentally benign chemicals. Therefore, with a large pool of methods that has been published, a number of them use a base to promote a transmetallation step in Suzuki reactions, hence, we aim to use a base free methodology by using sodium (aryl trihydroxyborate) salts instead of boronic acid as a nucleophile.

- The first objective of this project was to develop a novel base-free Suzuki-Miyaura cross-coupling of activated sodium (aryl trihydroxyborate) salts with structurally

different acyl chlorides which would accommodate base sensitive functionalities thus enabling the preparation of hard to synthesise ketones.

- The second objective is to extend the scope of this newly developed procedure to include less reactive carboxylic anhydrides as electrophilic coupling partners in the synthesis of ketones. This was achieved by finding synthesised and fully characterised sodium (aryl trihydroxyborate) salts and carboxylic anhydrides using  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR and MS.
- With the above synthesised starting materials, sodium (aryl trihydroxyborate) salts and carboxylic anhydrides were coupled in palladium to produce ketones and also acyl chlorides will be coupled with sodium (aryl trihydroxyborate) salts to synthesise ketones in mild reaction conditions.

## 2.6 References

1. Nicolaou, K., P.G. Bulger, and D. Sarlah, *Palladium-catalyzed cross-coupling reactions in total synthesis*. Angewandte Chemie International Edition, 2005. **44**(29): p. 4442-4489.
2. Kumar, R. and E. Van der Eycken, *Recent approaches for C–C bond formation via direct dehydrative coupling strategies*. Chemical Society Reviews, 2013. **42**(3): p. 1121-1146.
3. Cooper, T.W., I.B. Campbell, and S.J. Macdonald, *Factors determining the selection of organic reactions by medicinal chemists and the use of these reactions in arrays (small focused libraries)*. Angewandte Chemie International Edition, 2010. **49**(44): p. 8082-8091.
4. Friedel, C. and J. Crafts, *A new general synthetical method of producing hydrocarbons*. Journal of the Chemical Society, 1877. **32**: p. 725.
5. Ashdown, A.A., *Earliest history of the Friedel-Crafts reaction*. Industrial & Engineering Chemistry, 1927. **19**(9): p. 1063-1065.
6. Olah, G.A. and S. Kobayashi, *Aromatic substitution. XXIX. Friedel-Crafts acylation of benzene and toluene with substituted acyl halides. Effect of substituents and positional selectivity*. Journal of the American Chemical Society, 1971. **93**(25): p. 6964-6967.
7. Hayashi, R. and G.R. Cook, *Remarkably mild and efficient intramolecular Friedel–Crafts cyclization catalyzed by In (III)*. Organic Letters, 2007. **9**(7): p. 1311-1314.
8. Sartori, G. and R. Maggi, *Use of solid catalysts in Friedel–Crafts acylation reactions*. Chemical Reviews, 2006. **106**(3): p. 1077-1104.
9. Rueping, M. and B.J. Nachtsheim, *A review of new developments in the Friedel–Crafts alkylation–From green chemistry to asymmetric catalysis*. Beilstein Journal of Organic Chemistry, 2010. **6**.
10. Kawada, A., S. Mitamura, and S. Kobayashi, *Lanthanide trifluoromethanesulfonates as reusable catalysts: catalytic Friedel-Crafts acylation*. Journal of the Chemical Society, Chemical Communications, 1993. **14**: p. 1157-1158.
11. Boon, J.A., et al., *Friedel-Crafts reactions in ambient-temperature molten salts*. The Journal of Organic Chemistry, 1986. **51**(4): p. 480-483.
12. Liu, Z., et al., *Friedel-Crafts acylation of aromatic compounds in ionic liquids*. Petroleum Science and Technology, 2009. **27**(2): p. 226-237.
13. Yeung, K.-S., et al., *Friedel–Crafts acylation of indoles in acidic imidazolium chloroaluminate ionic liquid at room temperature*. Tetrahedron Letters, 2002. **43**(33): p. 5793-5795.
14. Zarei, A., A.R. Hajipour, and L. Khazdooz, *Friedel–Crafts acylation of aromatic compounds with carboxylic acids in the presence of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> under heterogeneous conditions*. Tetrahedron Letters, 2008. **49**(47): p. 6715-6719.
15. Freund, A., *Ueber sg sauerstoffhaltige Radicale*. European Journal of Organic Chemistry, 1861. **118**(1): p. 33-43.
16. Reddy, C.K. and P. Knochel, *New cobalt-and iron-catalyzed reactions of organozinc compounds*. Angewandte Chemie International Edition in English, 1996. **35**(15): p. 1700-1701.
17. Seyferth, D., *Zinc alkyls, Edward Frankland, and the beginnings of main-group organometallic chemistry*. 2001, ACS Publications.
18. Eberle, M.K. and G.G. Kahle, *Preparation of functionalized ketones via low temperature grignard reaction*. Tetrahedron Letters, 1980. **21**(24): p. 2303-2304.
19. Labadie, J.W. and J.K. Stille, *Stereochemistry of transmetalation in the palladium-catalyzed coupling of acid chlorides and organotins*. Journal of the American Chemical Society, 1983. **105**(3): p. 669-670.
20. Wu, T.C., H. Xiong, and R.D. Rieke, *Organocalcium chemistry: preparation and reactions of highly reactive calcium*. The Journal of Organic Chemistry, 1990. **55**(17): p. 5045-5051.
21. Newman, M.S. and W.T. Booth Jr, *The preparation of ketones from Grignard reagents*. Journal of the American Chemical Society, 1945. **67**(1): p. 154-154.

22. Sato, F., et al., *Preparation of ketones by direct reaction of grignard reagents with acid chlorides in tetrahydrofuran*. Tetrahedron Letters, 1979. **20**(44): p. 4303-4306.
23. Fiandanese, V., et al., *Iron catalyzed cross-coupling reactions of acyl chlorides with Grignard reagents. A mild, general, and convenient synthesis of aliphatic and aromatic ketones*. Tetrahedron Letters, 1984. **25**(42): p. 4805-4808.
24. Lee, P.H., S.W. Lee, and K. Lee, *Pd-catalyzed carbonylative cross-coupling reactions by triorganoindiums: Highly efficient transfer of organic groups attached to indium under atmospheric pressure*. Organic Letters, 2003. **5**(7): p. 1103-1106.
25. Wu, X.F., H. Neumann, and M. Beller, *Palladium-catalyzed oxidative carbonylation reactions*. ChemSusChem, 2013. **6**(2): p. 229-241.
26. Gadge, S.T. and B.M. Bhanage, *Recent developments in palladium catalysed carbonylation reactions*. RSC Advances, 2014. **4**(20): p. 10367-10389.
27. Heck, R. and J. Nolley Jr, *Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides*. The Journal of Organic Chemistry, 1972. **37**(14): p. 2320-2322.
28. Negishi, E. and J.A. Miller, *Selective carbon-carbon bond formation via transition metal catalysis. 37. Controlled carbometalation. 16. Novel syntheses of. alpha.,. beta.-unsaturated cyclopentenones via allylzincation of alkynes*. Journal of the American Chemical Society, 1983. **105**(22): p. 6761-6763.
29. Negishi, E.-i. and J.M. Tour, *Complete reversal of regiochemistry in cyclic acylpalladation. Novel synthesis of quinones*. Tetrahedron Letters, 1986. **27**(40): p. 4869-4872.
30. Bjerglund, K.M., T. Skrydstrup, and G.A. Molander, *carbonylative Suzuki couplings of aryl bromides with boronic acid derivatives under base-free conditions*. Organic Letters, 2014. **16**(7): p. 1888-1891.
31. Sharma, P., S. Rohilla, and N. Jain, *Palladium catalyzed carbonylative coupling for synthesis of arylketones and arylesters using chloroform as the carbon monoxide source*. The Journal of organic chemistry, 2017. **82**(2): p. 1105-1113.
32. Suzuki, A., *Organoborates in new synthetic reactions*. Accounts of Chemical Research, 1982. **15**(6): p. 178-184.
33. Miyaura, N., K. Yamada, and A. Suzuki, *A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides*. Tetrahedron Letters, 1979. **20**(36): p. 3437-3440.
34. Miyaura, N. and A. Suzuki, *Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst*. Journal of the Chemical Society, Chemical Communications, 1979. **19**: p. 866-867.
35. Gujral, S.S., et al., *Suzuki cross coupling reaction-a review*. Indo Global Journal Pharmeceutical Sciences, 2012. **2**: p. 351-367.
36. Johansson Seechurn, C.C., et al., *Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize*. Angewandte Chemie International Edition, 2012. **51**(21): p. 5062-5085.
37. Bykov, V., D. Korolev, and N. Bumagin, *Palladium-catalyzed reactions of organoboron compounds with acyl chlorides*. Russian Chemical Bulletin, 1997. **46**(9): p. 1631-1632.
38. Haddach, M. and J.R. McCarthy, *A new method for the synthesis of ketones: The palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids*. Tetrahedron Letters, 1999. **40**(16): p. 3109-3112.
39. Urawa, Y. and K. Ogura, *A convenient method for preparing aromatic ketones from acyl chlorides and arylboronic acids via Suzuki-Miyaura type coupling reaction*. Tetrahedron Letters, 2003. **44**(2): p. 271-273.
40. Eddarir, S., et al., *An efficient synthesis of chalcones based on the Suzuki reaction*. Tetrahedron Letters, 2003. **44**(28): p. 5359-5363.

41. Bandgar, B. and A. Patil, *A rapid, solvent-free, ligandless and mild method for preparing aromatic ketones from acyl chlorides and arylboronic acids via a Suzuki–Miyaura type of coupling reaction*. Tetrahedron Letters, 2005. **46**(44): p. 7627-7630.
42. Nishihara, Y., et al., *Room-temperature palladium-catalyzed and copper (I)-mediated coupling reactions of acid chlorides with boronic acids under neutral conditions*. Synlett, 2005. **2005**(15): p. 2309-2312.
43. Poláčková, V., Š. Toma, and I. Augustínová, *Microwave-promoted cross-coupling of acid chlorides with arylboronic acids: a convenient method for preparing aromatic ketones*. Tetrahedron, 2006. **62**(50): p. 11675-11678.
44. Ekoue-Kovi, K., H. Xu, and C. Wolf, *Palladium-phosphinous acid-catalyzed cross-coupling of aliphatic and aromatic acyl chlorides with boronic acids*. Tetrahedron Letters, 2008. **49**(40): p. 5773-5776.
45. Zhang, L., et al., *Ionicly tagged benzimidazole palladium (II) complex: preparation and catalytic application in cross-coupling reactions*. Tetrahedron Letters, 2011. **52**(30): p. 3897-3901.
46. Hajipour, A.R. and R. Pourkaveh, *Efficient and Fast Method for the Preparation of Diaryl Ketones at Room Temperature*. Synlett, 2014. **25**(08): p. 1101-1105.
47. Jadhav, S., et al., *Transition metal-free Suzuki type cross-coupling reaction for the synthesis of dissymmetric ketones*. Tetrahedron Letters, 2017. **58**(33): p. 3201-3204.
48. Ogiwara, Y., et al., *Acid Fluorides as Acyl Electrophiles in Suzuki-Miyaura Coupling*. European Journal of Organic Chemistry, 2017.
49. Kakino, R., I. Shimizu, and A. Yamamoto, *Synthesis of trifluoromethyl ketones by palladium-catalyzed cross-coupling reaction of phenyl trifluoroacetate with organoboron compounds*. Bulletin of the Chemical Society of Japan, 2001. **74**(2): p. 371-376.
50. Kakino, R., et al., *Palladium-catalyzed direct conversion of carboxylic acids into ketones with organoboronic acids promoted by anhydride activators*. Bulletin of the Chemical Society of Japan, 2002. **75**(6): p. 1333-1345.
51. Kakino, R., et al., *Synthesis of unsymmetrical ketones by palladium-catalyzed cross-coupling reaction of carboxylic anhydrides with organoboron compounds*. Bulletin of the Chemical Society of Japan, 2002. **75**(1): p. 137-148.
52. Gooßen, L.J. and K. Ghosh, *Palladium-catalyzed synthesis of aryl ketones from boronic acids and carboxylic acids or anhydrides*. Angewandte Chemie, 2001. **113**(18): p. 3566-3568.
53. Gooßen, L.J. and K. Ghosh, *Palladium-catalyzed synthesis of aryl ketones from boronic acids and carboxylic acids activated in situ by pivalic anhydride*. European Journal of Organic Chemistry, 2002. **(19)**: p. 3254-3267.
54. Goossen, L.J., et al., *Pd-catalyzed synthesis of functionalized arylketones from boronic acids and carboxylic acids activated in situ with dimethyl dicarbonate*. Synlett, 2002. **(08)**: p. 1237-1240.
55. Xin, B., Y. Zhang, and K. Cheng, *Phosphine-free Cross-Coupling reaction of arylboronic acids with carboxylic anhydrides or acyl chlorides in aqueous media*. The Journal of Organic Chemistry, 2006. **71**(15): p. 5725-5731.
56. Xin, B., Y. Zhang, and K. Cheng, *The surfactant-promoted cross-coupling reactions of arylboronic acids with carboxylic anhydrides or acyl chlorides in water*. Synthesis, 2007. **(13)**: p. 1970-1978.
57. Xin, B.-W., *Synthesis of aryl ketones by cross-coupling reaction of arylboronic acids with carboxylic anhydrides in aqueous phase*. Synthetic Communications®, 2008. **38**(16): p. 2826-2837.
58. Shen, X.B., et al., *Imidazole-coordinated monodentate NHC–Pd (II) complex derived from proline and its application to the coupling reaction of arylboronic acids with carboxylic acid anhydrides in water at room temperature*. Applied Organometallic Chemistry, 2011. **25**(7): p. 497-501.
59. Yu, A., et al., *Palladacycle-catalyzed cross-coupling reactions of arylboronic acids with carboxylic anhydrides or acyl chlorides*. Tetrahedron, 2012. **68**(10): p. 2283-2288.

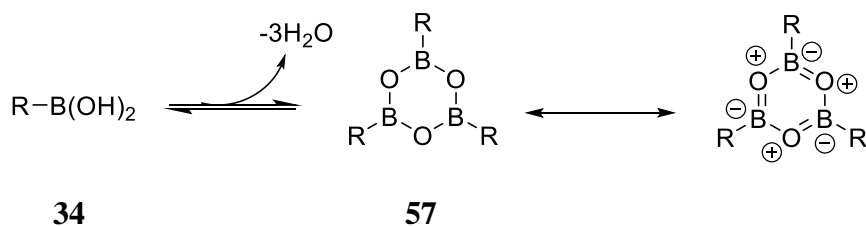


60. Chen, Q., et al., *Nickel-catalyzed cross-coupling of carboxylic anhydrides with arylboronic acids*. RSC Advances, 2014. **4**(96): p. 53885-53890.
61. Miyaura, N., et al., *Novel and convenient method for the stereo- and regioselective synthesis of conjugated alkenes and alkynes via the palladium-catalyzed cross-coupling reaction of 1-alkenylboranes with bromoalkenes and bromoalkynes*. Journal of the American Chemical Society, 1985. **107**(4): p. 972-980.
62. Suzuki, A., *Cross-coupling reactions of organoboranes: an easy way to construct C-C bonds (Nobel Lecture)*. Angewandte Chemie International Edition, 2011. **50**(30): p. 6722-6737.
63. Miyaura, N. and A. Suzuki, *Palladium-catalyzed cross-coupling reactions of organoboron compounds*. Chemical Reviews, 1995. **95**(7): p. 2457-2483.
64. Lennox, A.J. and G.C. Lloyd-Jones, *Transmetalation in the Suzuki-Miyaura coupling: The fork in the trail*. Angewandte Chemie International Edition, 2013. **52**(29): p. 7362-7370.
65. Li, X. and G. Zou, *Palladium-catalyzed acylative cross-coupling of amides with diarylboronic acids and sodium tetraarylborates*. Journal of Organometallic Chemistry, 2015. **794**: p. 136-145.
66. Matos, K. and J.A. Soderquist, *Alkylboranes in the Suzuki-Miyaura coupling: Stereochemical and mechanistic studies*. The Journal of Organic Chemistry, 1998. **63**(3): p. 461-470.
67. Mondal, M. and U. Bora, *Eco-friendly Suzuki-Miyaura coupling of arylboronic acids to aromatic ketones catalyzed by the oxime-palladacycle in biosolvent 2-MeTHF*. New Journal of Chemistry, 2016. **40**(4): p. 3119-3123.
68. Miyaura, N., T. Yanagi, and A. Suzuki, *The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases*. Synthetic Communications, 1981. **11**(7): p. 513-519.
69. Adamo, C., et al., *Mechanism of the palladium-catalyzed homocoupling of arylboronic acids: Key involvement of a palladium peroxo complex*. Journal of the American Chemical Society, 2006. **128**(21): p. 6829-6836.
70. Butters, M., et al., *Aryl trifluoroborates in Suzuki-Miyaura coupling: the roles of endogenous aryl boronic acid and fluoride*. Angewandte Chemie, 2010. **122**(30): p. 5282-5286.
71. Kuivila, H.G., J.F. Reuwer Jr, and J.A. Mangravite, *Electrophilic displacement reactions: XV. Kinetics and mechanism of the base-catalyzed protodeboronation of areneboronic acids*. Canadian Journal of Chemistry, 1963. **41**(12): p. 3081-3090.
72. Cammidge, A.N., et al., *Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions*. Organic Letters, 2006. **8**(18): p. 4071-4074.
73. Basu, B., et al., *Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki-Miyaura coupling reaction*. Green Chemistry, 2010. **12**(10): p. 1734-1738.

## Chapter 3

### Results and Discussion

The wide occurrence of asymmetric biaryl ketone moieties in many natural products, biologically active compounds as well as pharmaceutical drugs has encouraged and persuaded many researchers to find mild methods to synthesise biaryl ketones in high yields [1]. The synthesis of biaryl ketones via transition metal catalysed cross-coupling reactions has been vastly exploited; however, many of these methodologies employ harsh reaction conditions, toxic and environmentally unfriendly as well as unstable reagents. One of the most frequently used methods to synthesise ketones is the Suzuki-Miyaura cross-coupling reaction of organoboron (sodium tetraarylboronates [2] and boronic acids [3]) with different electrophiles (usually carboxylic acid derivatives) in the presence of a base and a catalyst. Quite often, the reaction conditions used in these methods do not accommodate base sensitive substrates. In addition, organoborons (boronic acid and tetraarylboronates) have been reported to decompose via dehydration to form cyclic anhydrides (**57**) (**Scheme 3.1**) which are less reactive than boronic acid and make it difficult to accurately calculate the stoichiometric amount required. In the interest of developing a mild reaction procedure that will accommodate base sensitive substrates while using ultra-stabilised nucleophiles which are not prone to decomposition, we developed and investigated the scope of novel base-free Suzuki-Miyaura cross-coupling reactions of freshly synthesised sodium (aryl trihydroxyborate) salts with structurally diverse acyl chlorides bearing electron-donating, electron-withdrawing as well as electron neutral functionalities.

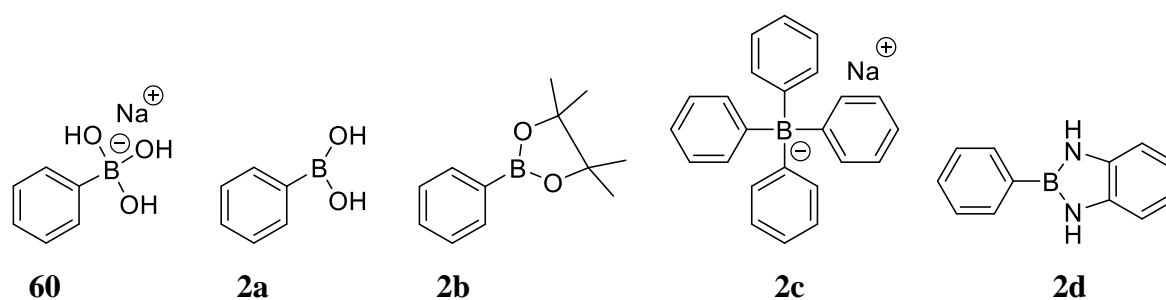


**Scheme 3.1**

### 3.1 The synthesis of sodium (aryl trihydroxyborate) salts

Initially, sodium (aryl trihydroxyborate) salts were synthesised from cheap and easily accessible aryl halides following previously reported methods [4-6]. In 2006, Cammidge and co-workers [4] synthesised and demonstrated the application of sodium (aryl trihydroxyborate) salts as efficient nucleophiles in Suzuki-Miyaura cross-coupling to

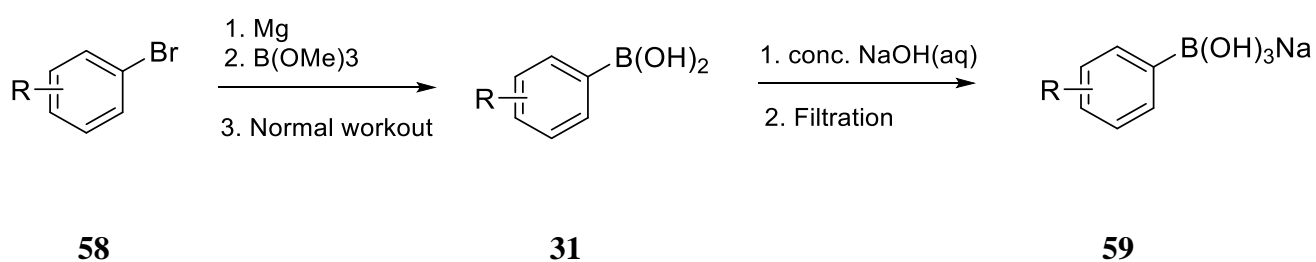
synthesise substituted biaryls. In his study, Cammidge showed that sodium (aryl trihydroxyborate) salts are more stable and more reactive than other organoboron compounds owing to the fact that the central boron atom is electron rich because it has four bonds as opposed to three bonds. This attribute made sodium (aryl trihydroxyborate) compounds very reactive because they are already ‘activated’ i.e not requiring a base activation. With this background information we thought it would be logical to apply this system to the synthesis of ketones. To the best of our knowledge, there were no reports in the literature reporting on base-free synthesis of ketones using sodium (aryl trihydroxyborate) salts.



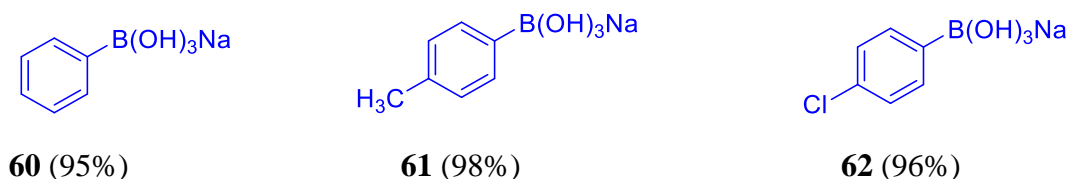
**Figure 3.1: Organoboron reagents**

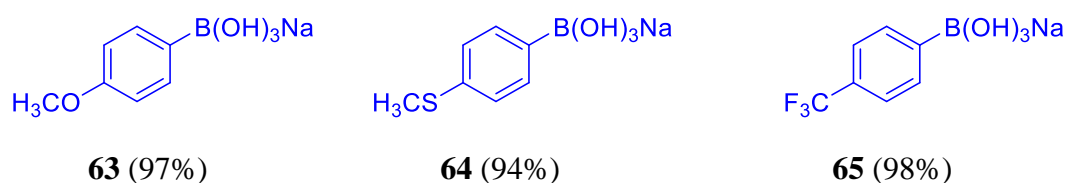
### 3.1.1 The synthesis of sodium (aryl trihydroxyborate) salts

Following the procedure reported by Cammidge *et al.* [4], sodium (aryl trihydroxyborate) salts (**59**) were successfully isolated as pure white powder with 94-98% yields (**Scheme 3.2**) (**Figure 3.2**). The pure products were just obtained without any purification, where  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{11}\text{B}$  and  $^{23}\text{Na}$  NMR spectra were consistent with the desired products showing expected peaks (See appendix A).



**Scheme 3.2**

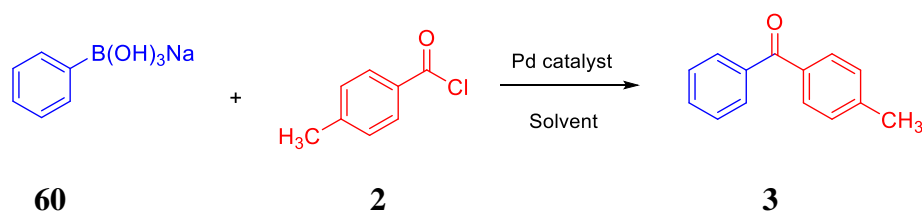




**Figure 3.2: Sodium (aryl trihydroxyborate) salts prepared**

### 3.2 The application of sodium (aryl trihydroxyborate) salts in Suzuki-Miyaura acylation reaction

With sodium (aryl trihydroxyborate) salts in hand, our next step was to find optimal reaction conditions to synthesise ketones. In order to find suitable reaction conditions, we studied the effect of solvent, temperature and a catalyst simultaneously in cross-coupling reactions. The initial investigation was done between sodium (phenyltrihydroxyborate) salt (**60**) and toluoyl chloride (**2**) under different reaction conditions as the model reaction (**Scheme 3.3**).



**Scheme 3.3**

**Table 1: Initial optimisation of the reaction conditions<sup>a</sup>**

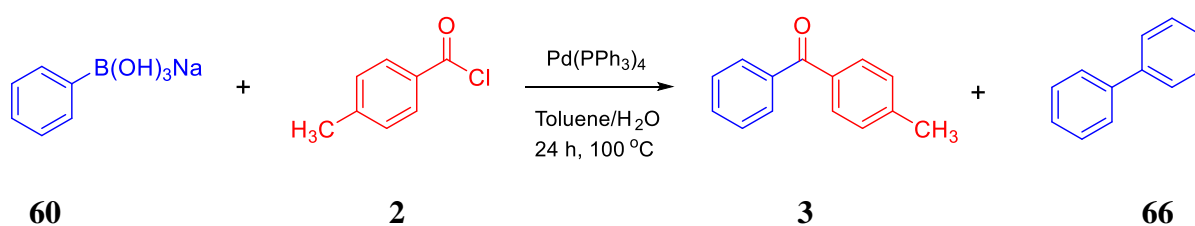
Entry	Catalyst	Solvent	Yield (%) <sup>b</sup>
1	-	Toluene (r.t)	0
2	PdCl <sub>2</sub> /PPh <sub>3</sub>	Toluene (r.t)	27
3	PdCl <sub>2</sub> /dppf	Toluene (r.t)	19
4	PdCl <sub>2</sub> /dppf	Toluene/H <sub>2</sub> O (r.t)	48
5	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> /PPh <sub>3</sub>	Toluene/H <sub>2</sub> O (r.t)	51
6	Pd(OAc) <sub>2</sub> /dppf	Toluene/H <sub>2</sub> O (r.t)	31
7	Pd(COD) <sub>2</sub> Cl <sub>2</sub> /PPh <sub>3</sub>	Toluene/H <sub>2</sub> O (r.t)	Trace
8	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> /dppf	Toluene/H <sub>2</sub> O (60 °C)	55
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Acetone/H <sub>2</sub> O (60 °C)	79
10	Ni(dppf) <sub>2</sub> /dppf	Toluene/H <sub>2</sub> O (60 °C)	23
11	Ni(acac) <sub>2</sub> /PPh <sub>3</sub>	Toluene/H <sub>2</sub> O (60 °C)	Trace
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Toluene/H <sub>2</sub> O (r.t)	71
<b>13</b>	<b>Pd(PPh<sub>3</sub>)<sub>4</sub></b>	<b>Toluene/H<sub>2</sub>O (60 °C)</b>	<b>88</b>
14	Pd(PPh <sub>3</sub> ) <sub>4</sub>	THF/H <sub>2</sub> O (60 °C)	67
15	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Toluene/H <sub>2</sub> O (100 °C)	52 <sup>c</sup>

The bold text indicates the optimized reaction conditions for the developed acylative procedure.

<sup>a</sup> Reaction conditions: sodium (phenyltrihydroxyborate) (1 mmol), toluoyl chloride (1.1 mmol), Pd catalyst (0.01 mmol), ligand (0.02 mmol), 0.5 mL (water), 24 h. <sup>b</sup> isolated yields after column and radial chromatography. <sup>c</sup> Microwave reactor was used, 100 W, 100Psi, Closed vessel, 10 min.

Deletion of palladium catalyst yielded no product formation, verifying the necessity of the catalyst in this cross-coupling reaction (Table 1, entry 1). Haddach [7] also had similar observations when he obtained no 4-chlorobenzophenone in the absence of  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst. The application of palladium chloride with monodentate and bidentate ligands such as  $\text{PPh}_3$  and dppf afforded product (**3**) in poor yields (Table 1, entry 2 and 3). This might be due to the excess binding of the ligands to the metal centre which then hinders the catalytic cycle [8]. The addition of water as a co-solvent increased the yield slightly to 48%; this may be attributed to better solubility of sodium (aryl trihydroxyborate) salts in water as compared to toluene (Table 1, entry 4). The application of other palladium(II) species produced the desired product (**89**) with poor yields (Table 1, entries 5-8).

An increase in yield (79%) of the desired product (**3**) was observed when  $\text{Pd}(\text{PPh}_3)_4$  was used as a catalyst in aqueous acetone (Table 1, entry 9). Low yields were obtained when nickel catalysts ( $\text{Ni}(\text{dppf})_2/\text{dppf}$  and  $\text{Ni}(\text{acac})_2/\text{PPh}_3$ ) were investigated, despite the popularity of Ni catalyst in Suzuki-Miyaura cross-coupling reactions [9] (Table 1, entry 10 and 11). Motivated by the good yield obtained when  $\text{Pd}(\text{PPh}_3)_4$  was used as a catalyst at room temperature, an increase in temperature to 60 °C gave the desired product in 88% yield in aqueous toluene as solvent (Table 1, entry 13). However, a decrease in yield of (**3**) was observed when the temperature was increased above 60 °C due to the formation of homo-coupling by-products (**66**) (Table 1, entry 15) (**Scheme 3.4**).

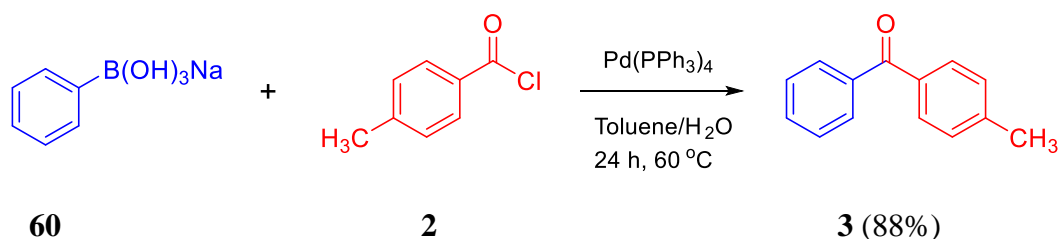


**Scheme 3.4**

With the optimised reaction condition in hand (Table 1, entry 13), the scope of sodium (aryl trihydroxyborate) salts and acyl chlorides bearing electron withdrawing and/or electron-donating substituents were investigated and the results are summarized in Table 2.

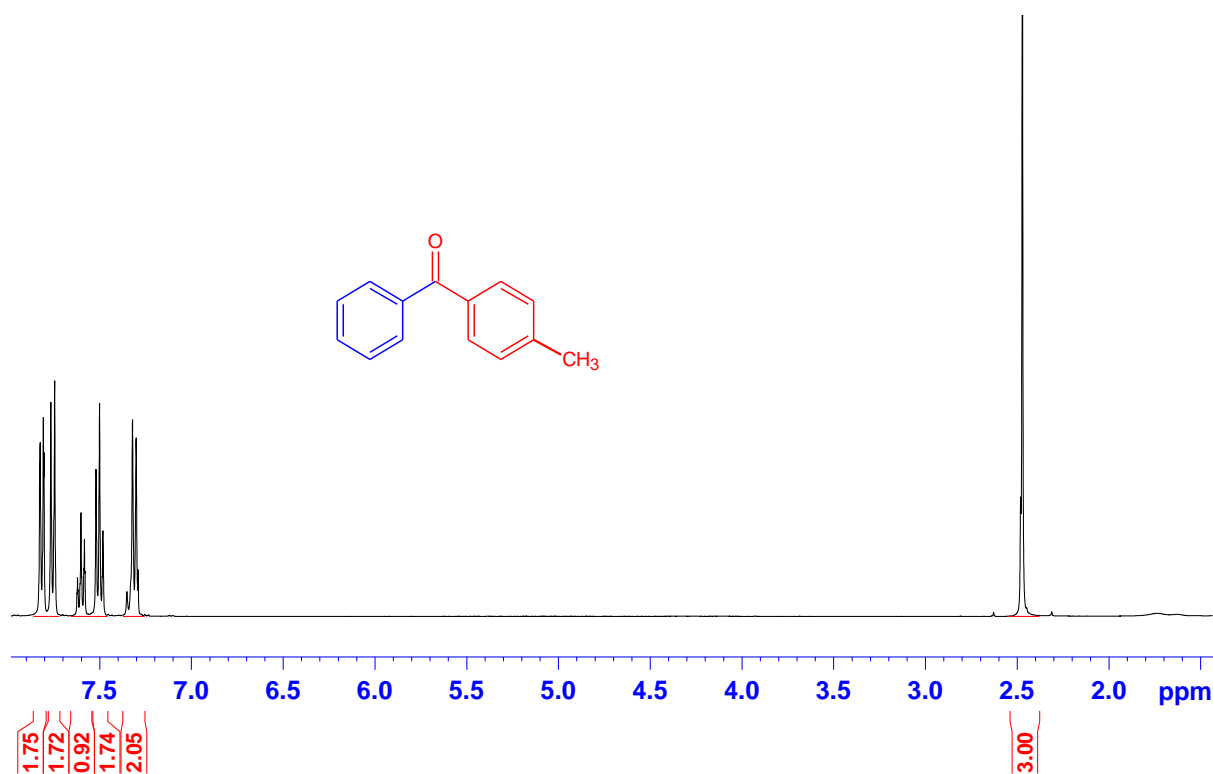
### 3.2.1 The synthesis of phenyl(p-tolyl)methanone (3)

Phenyl(p-tolyl)methanone (**3**) was prepared in an isolated yield of 88% as white crystalline solid from the reaction of sodium (phenyltrihydroxyborate) (**60**) and toluoyl chloride (**2**) (**Scheme 3.5**). The yield obtained was higher than that reported by Haddach and McCarthy [7] when they used a corresponding boronic acid as a coupling partner.



**Scheme 3.5**

The structure of the product was confirmed with  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. The  $^1\text{H}$  NMR spectrum showed a singlet at  $\delta_{\text{H}}$  2.43 which integrated to 3 protons, indicating that a methyl is attached to the ring. Signals resonating in the region  $\delta_{\text{H}}$  7.27-7.81 were due to the aromatic protons (**Figure 3.3**). The  $^{13}\text{C}$  NMR spectrum has 10 signals as expected because some of them are overlapping (**Figure 3.4**).



**Figure 3.3:**  $^1\text{H}$  NMR spectrum for compound **3**

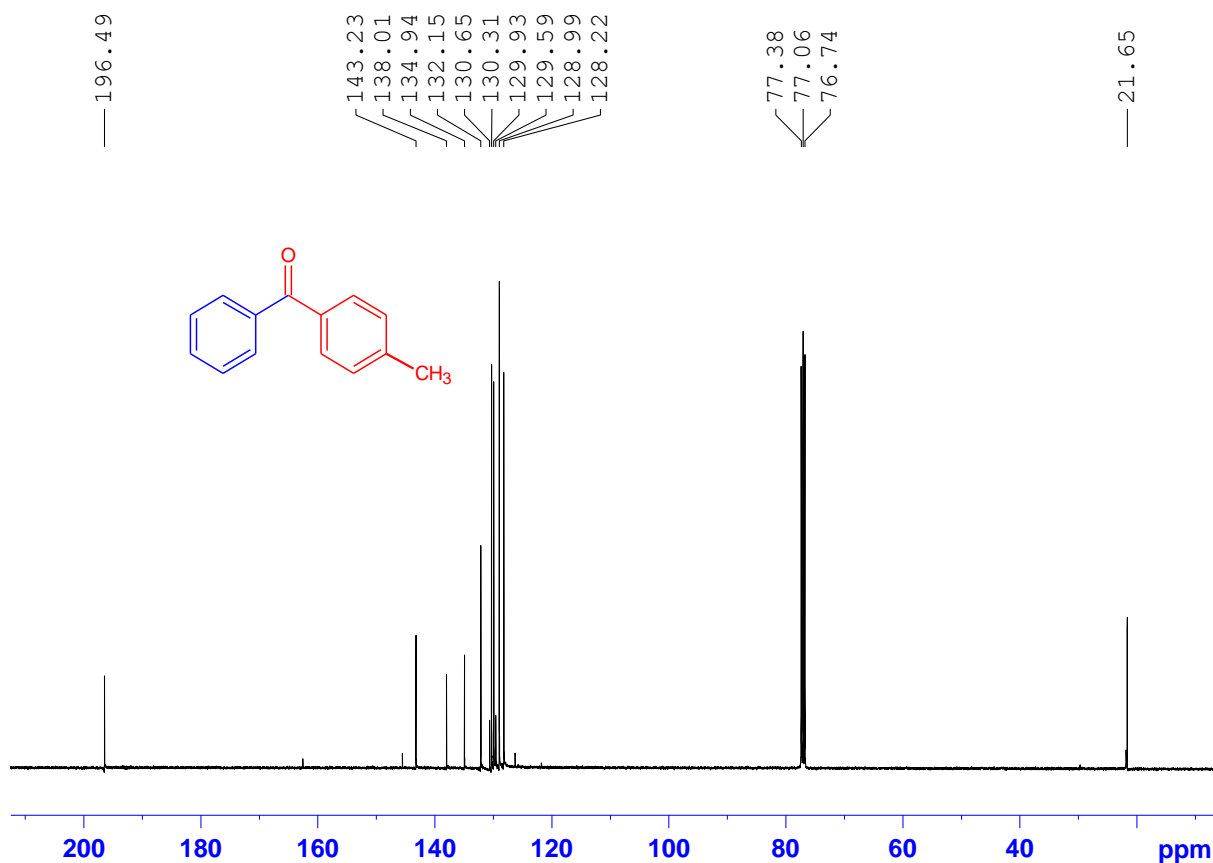
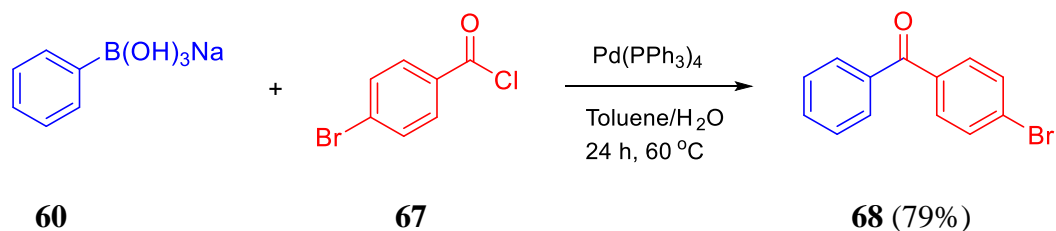


Figure 3.4:  $^{13}\text{C}$  NMR spectrum for compound 3

### 3.2.2 The synthesis of (4-bromophenyl)(phenyl)methanone (**68**)

(4-Bromophenyl)(phenyl)methanone (**68**) was successfully synthesised from the cross-coupling of sodium (phenyltrihydroxyborate) (**60**) and 4-bromobenzoyl chloride (**67**) in aqueous toluene at 60 °C for 24 hours (**Scheme 3.6**). The compound was achieved in 79% yield as crystalline solid which is slightly lower than the yield reported by Bumagin and co-workers [10].



Scheme 3.6

The successful synthesis of (4-bromophenyl)(phenyl)methanone (**68**) was confirmed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra showing expected peaks that correspond with the structure (**Figure 3.5**). It was noted that 4-bromobenzoyl chloride only reacted at the acyl functionality and not on the bromine site as it is well known that aryl bromides are good electrophiles

under Suzuki-Miyaura cross-coupling reactions [11]. This indicated high selectivity of the developed method as confirmed by the  $^1\text{H}$  NMR spectrum that only showed nine signals at the aromatic region for (4-bromophenyl)(phenyl)methanone (**68**) not for biaryls.

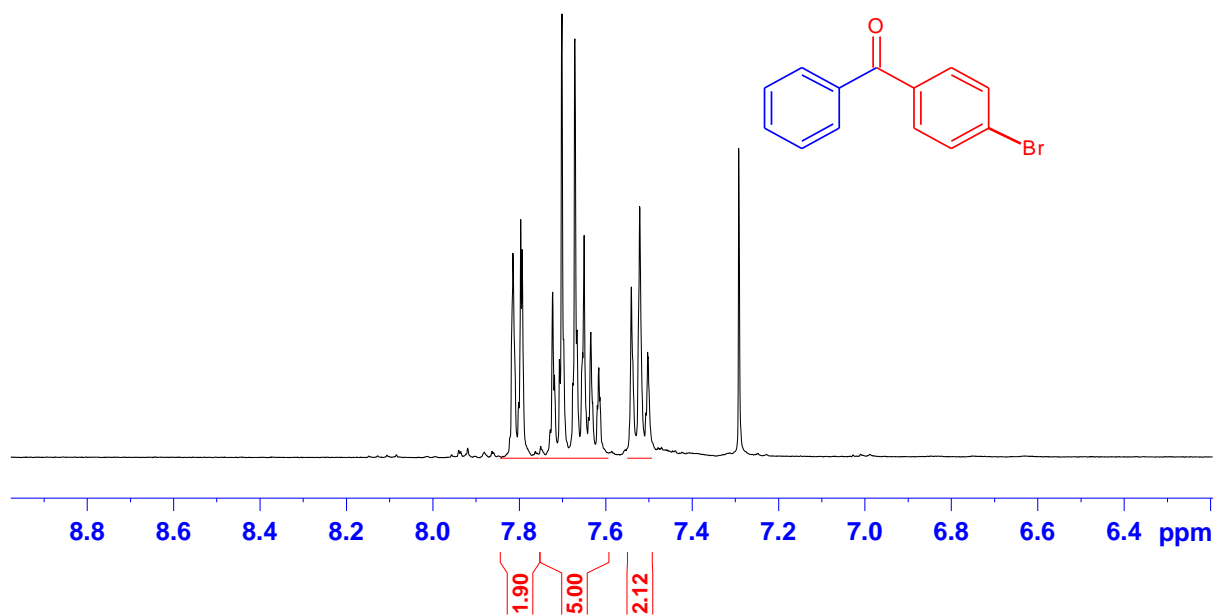


Figure 3.5:  $^1\text{H}$  NMR spectrum of compound **68**

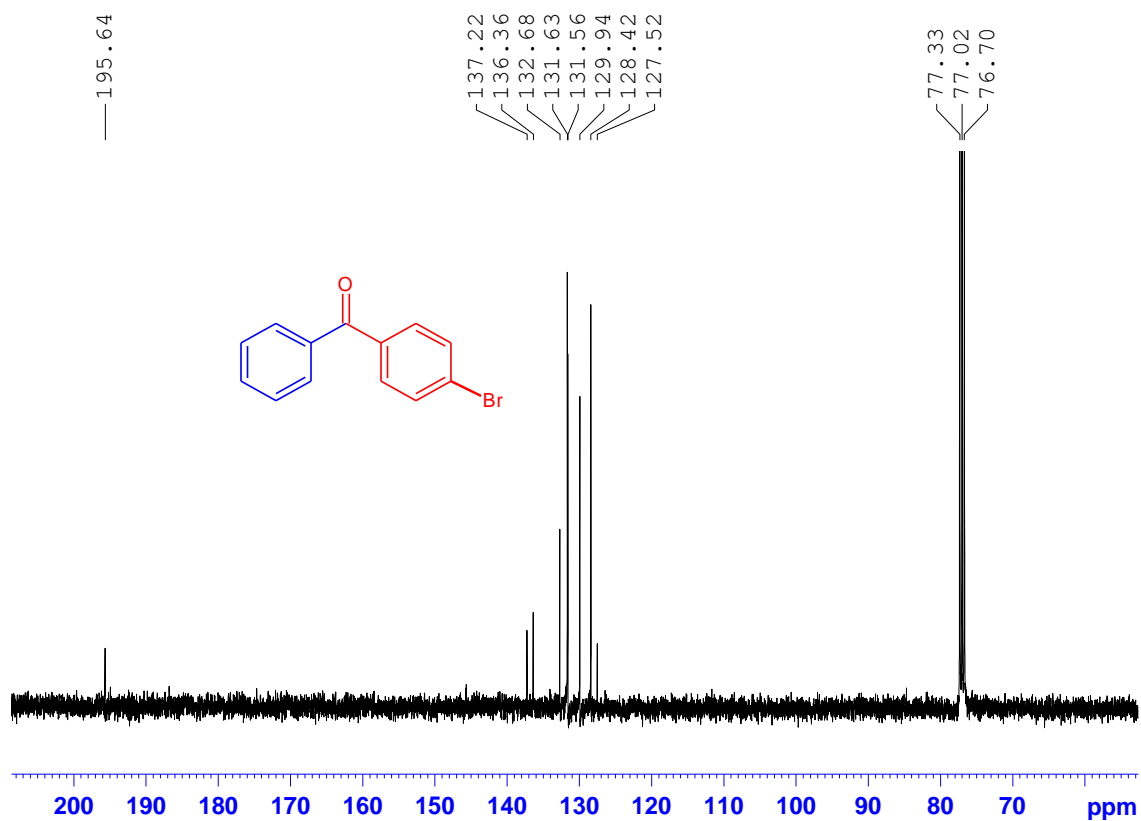
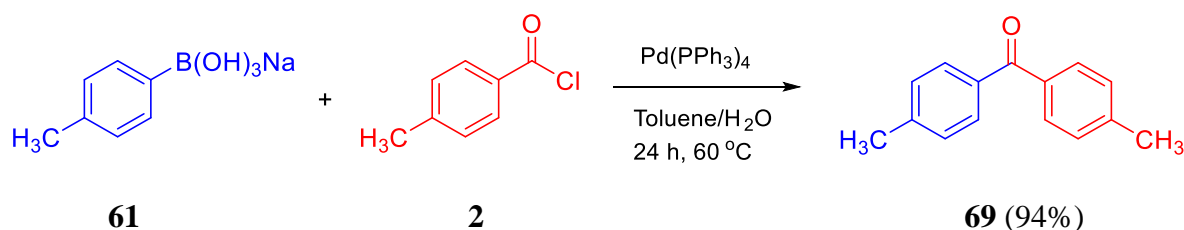


Figure 3.6:  $^{13}\text{C}$  NMR spectrum of compound **68**



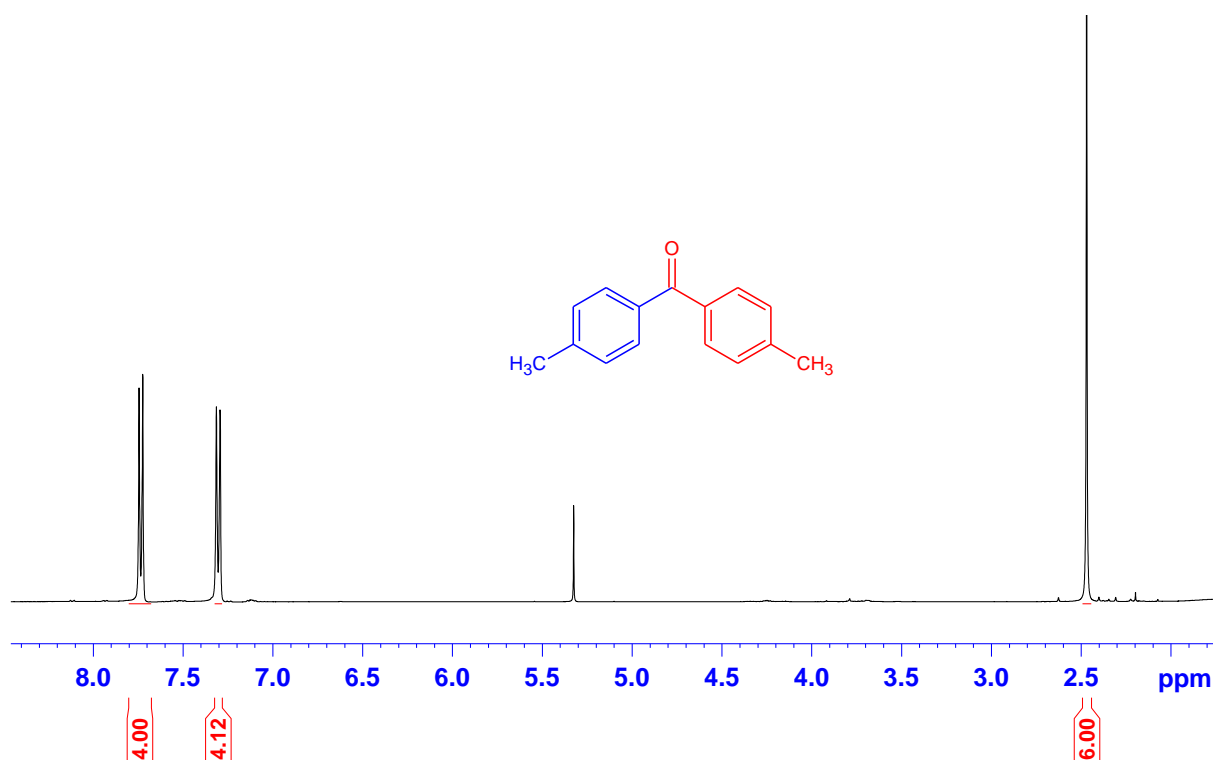
### 3.2.3 The synthesis of bis(*p*-tolyl)methanone (**69**)

An acyl chloride bearing an electron-donating methyl reacted efficiently with sodium (4-methylphenyl)trihydroxyborate (**61**) (Table 2, entry 4) furnishing a substituted ketone (**69**) in excellent yield (**Scheme 3.7**). Bis(*p*-tolyl)methanone (**69**) was synthesised in excellent yield (94%), a yield which is higher than the one reported by Wang and co-workers [12].



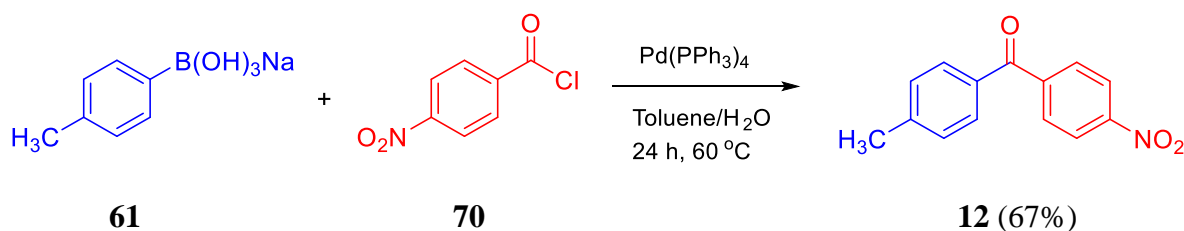
**Scheme 3.7**

The titled compound was furnished as white powder and the spectroscopic techniques confirmed its successful synthesis. The  $^1\text{H}$  NMR spectrum revealed that the singlet resonating at 2.49 ppm integrated for 6 protons which are two methyls that overlap and the two doublets that integrated to four protons are both for the aromatic ring protons (**Figure 3.7**).



### 3.2.4 The synthesis of (4-nitrophenyl)(*p*-tolyl)methanone (**12**)

A great coupling was observed when sodium (4-methylphenyltrihydroxyborate) was coupled with electron-donation substrates in acyl chloride but a notable decrease was observed when 4-nitro was introduced as a substituent in the acyl chloride. (4-Nitrophenyl)(*p*-tolyl)methanone (**12**) was synthesised in 67% isolated yield from the cross-coupling reaction of 4-nitrobenzoyl chloride (**70**) with sodium (4-methylphenyltrihydroxyborate) (**61**) (**Scheme 3.8**). A comparable yield of 68% was reported by Zaire and co-workers [13] after 5 hours of reflux.



**Scheme 3.8**

Generally, the acylative cross-coupling of 4-nitrobenzoyl chloride (**70**) with all sodium (aryl trihydroxyborate) salts produced unsatisfactory yields, probably due to competitive hydrolysis reactions because of the unfavourable oxidative addition of 4-nitrobenzoyl chloride to the metal centre since nitro is a deactivating group (Table 2, entry 6, 9, 13 and 19). Moderate yields were also obtained in the synthesis of (4-nitrophenyl)(*p*-tolyl)methanone (**12**) from 4-nitrobenzoyl chloride (**70**) reported by Charvatova and co-workers [14], Haddach and McCarthy [7] and Li and Zou [15]. The successful synthesis of (4-nitrophenyl)(*p*-tolyl)methanone (**12**) as white solid was confirmed using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic techniques (**Figure 3.8 and 3.9**).

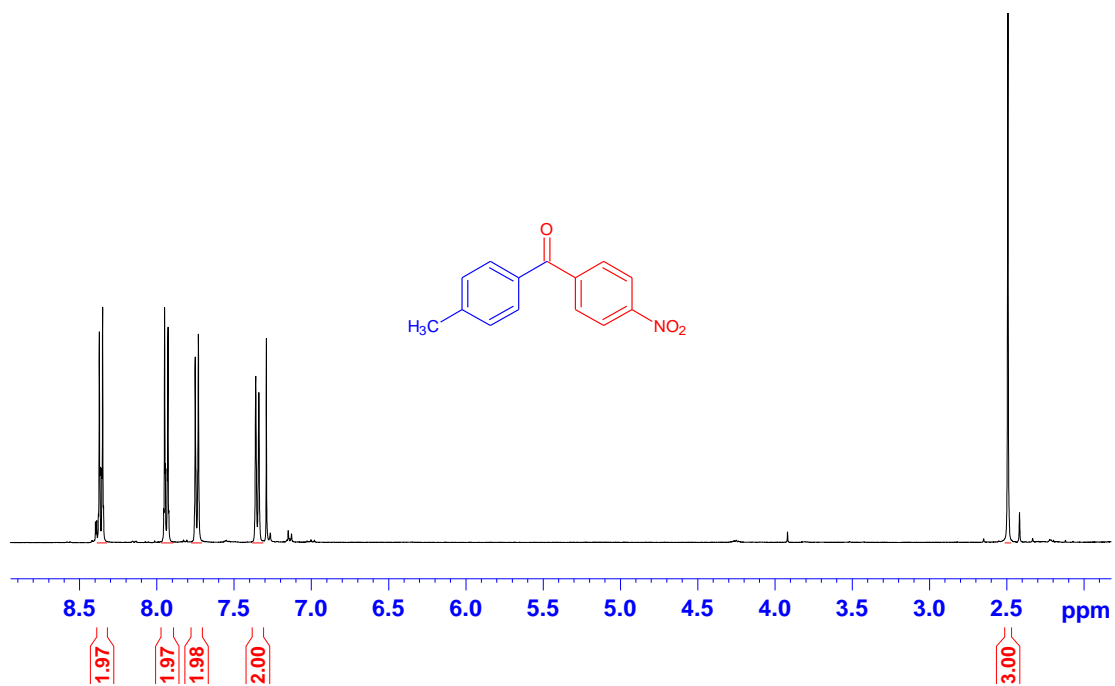


Figure 3.8: <sup>1</sup>H NMR spectrum for (4-nitrophenyl)(p-tolyl)methanone 12

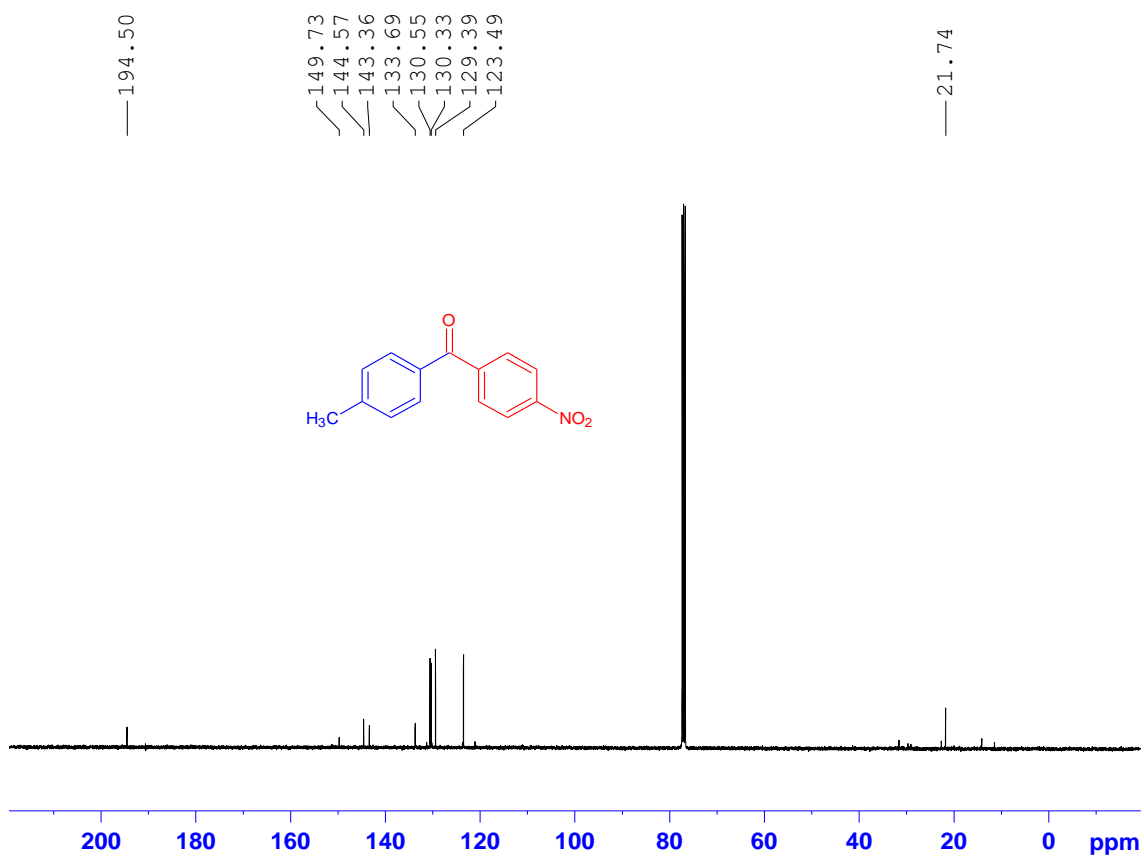
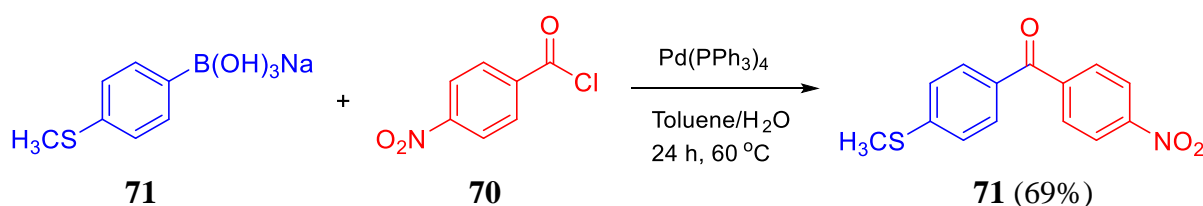


Figure 3.9: <sup>13</sup>C NMR spectrum for (4-nitrophenyl)(p-tolyl)methanone 12

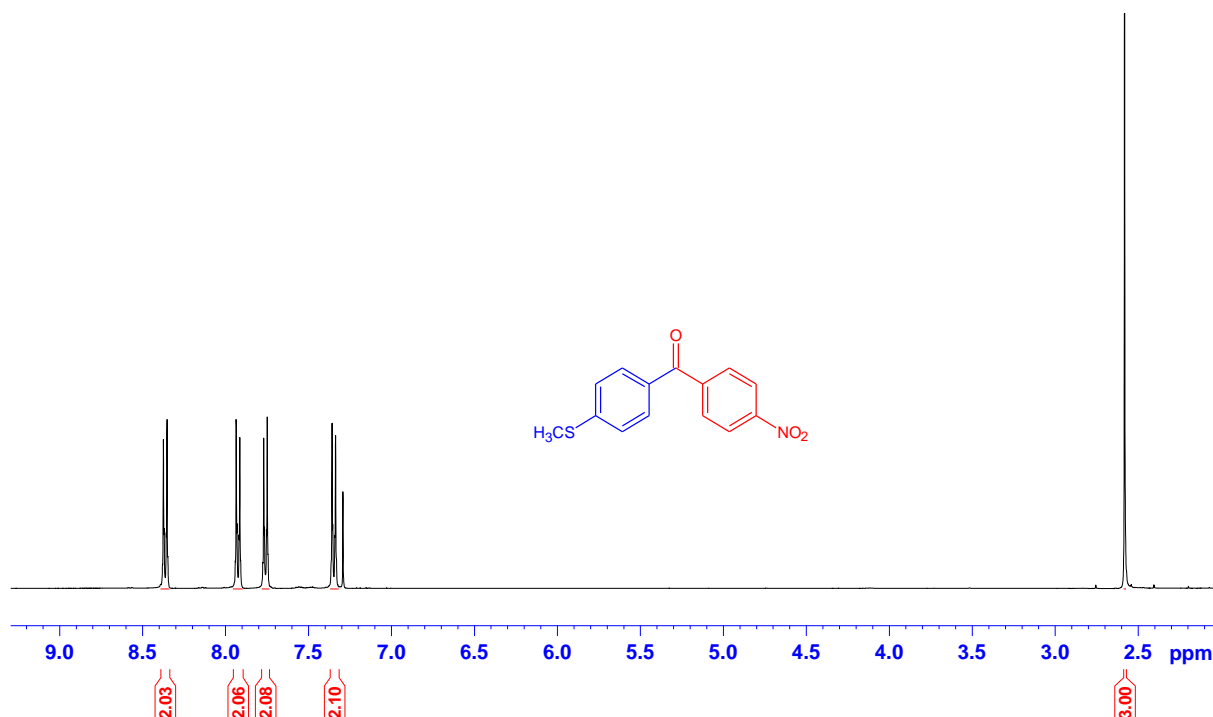
### 3.2.5 The synthesis of (4-methylthiophenyl)(4-nitrophenyl)methanone (71)

Sodium (4-methylthiophenyltrihydroxyborate) (**64**) participated efficiently with different acyl chlorides producing a range of different substituted biaryl ketones in good to excellent yields (Table 2, entry 7-11). As in the previous reactions, the participation of an acyl chloride bearing a strongly deactivating nitro functionality afforded the desired ketones in only moderate 69% yield. (4-Methylthiophenyl)(4-nitrophenyl)methanone (**71**) was obtained from the reaction of sodium (4-methylthiophenyltrihydroxyborate) (**64**) and 4-nitrobenzoyl chloride (**70**) (Scheme 3.9).



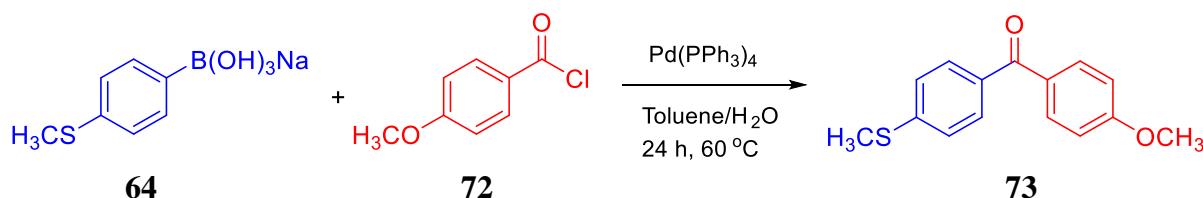
**Scheme 3.9**

(4-Methylthiophenyl)(4-nitrophenyl)methanone (**71**) was obtained as yellow crystals whose  $^1\text{H}$  NMR spectrum elucidation confirmed that it was indeed the desired product as evidenced by the expected peaks with the integral ratio completely matching the number of protons (Figure 3.10).



### 3.2.6 The synthesis of (4-methylthiophenyl)(4-methoxyphenyl)methanone (73)

The cross-coupling reaction of sodium (4-methylthiophenyltrihydroxyborate) (**64**) with 4-methoxybenzoyl chloride (**72**) afforded (4-methylthiophenyl)(4-methoxyphenyl)methanone (**73**) as white crystals in 94% isolated yield after 24 hours (**Scheme 3.10**). The yield of the product (**73**) is higher compared to 74% yield reported by Parella and co-workers [16] using the corresponding boronic acid as a nucleophile after 24 hours at 80 °C.



**Scheme 3.10**

The <sup>1</sup>H and <sup>13</sup>C NMR spectra confirmed the purity and structure of the desired product by showing the corresponding signal ratio with the structure. The <sup>1</sup>H NMR spectrum showed two different singlets, one resonating at 2.56 ppm integrating to 3 protons indicating a methylthio and the other singlet resonating at 3.91 ppm integrating for three protons indicate a methoxy group; the other signals resonating between 6.99-7.82 ppm indicate the proton attached to the benzene ring (**Figure 3.11**). The <sup>13</sup>C NMR spectrum also shows all expected carbons in the structure and especially the appearance of distinct methylthio and the methoxy signals resonating at 14.9 and 55.4 ppm, respectively (**Figure 3.12**). It is noteworthy that electron-donating substrates had a good effect on the yield compared to electron-withdrawing substrates on the electrophile coupling with sodium (4-methylthiophenyltrihydroxyborate) (**64**). It is noteworthy that electron-donating substrates on the electrophile had a good effect on the yield when compared to deactivating functionalities.

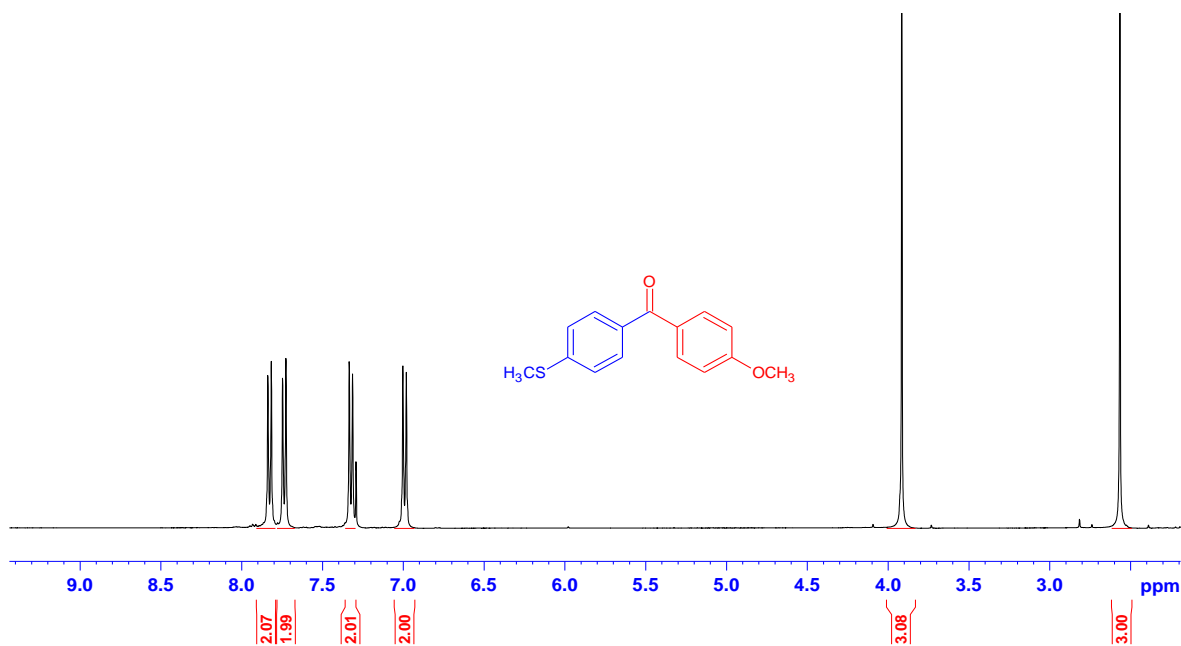


Figure 3.11: The  $^1\text{H}$  NMR spectrum for compound 73

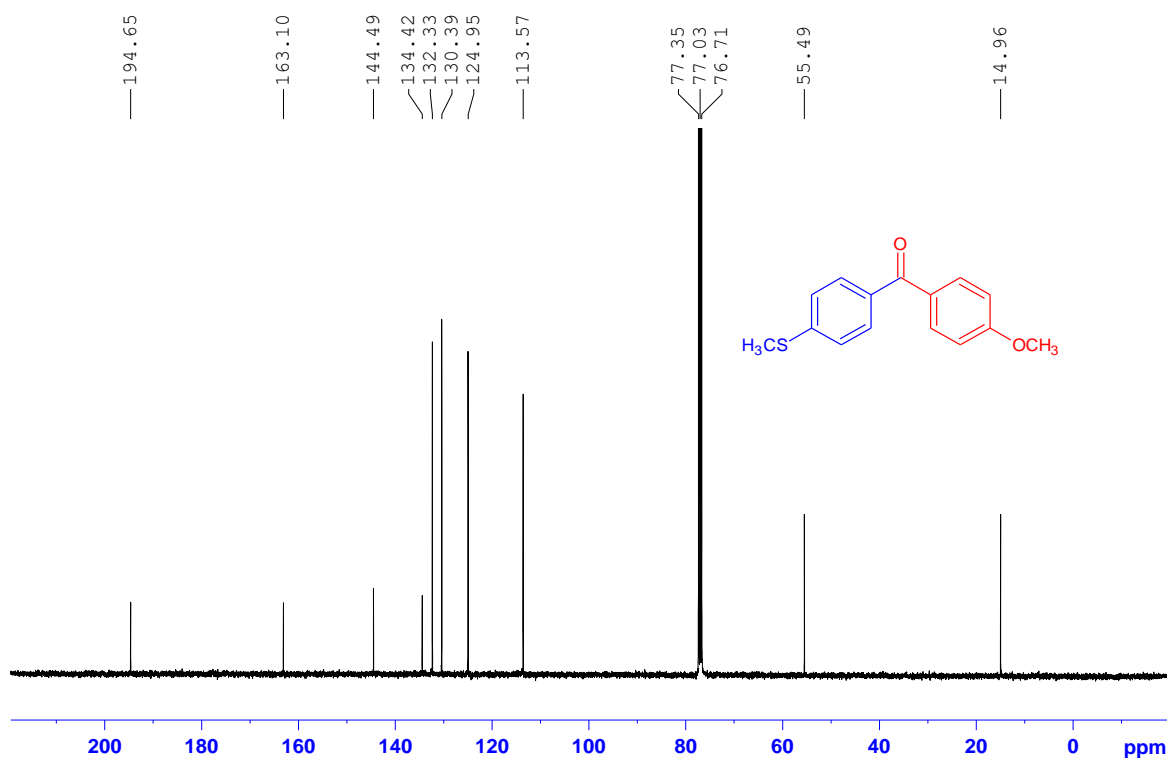
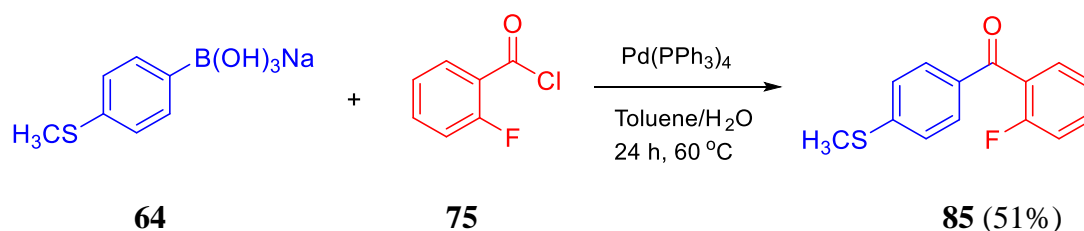


Figure 3.12: The  $^{13}\text{C}$  NMR spectrum for compound 73

### 3.2.7 The synthesis of (4-methylthiophenyl)(2-fluorophenyl)methanone (84)

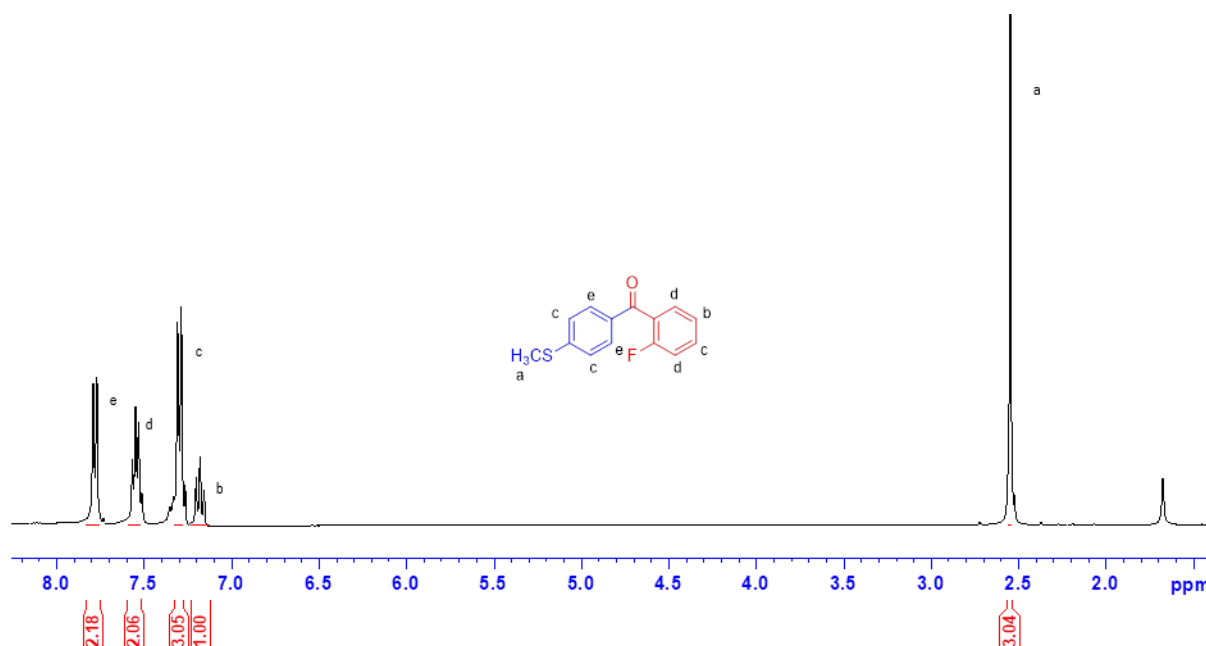
The significant decrease in the yield of the coupled product was noted when *ortho*-substituted acyl chloride was coupled with sodium (4-methylthiophenyl)trihydroxyborate) (**64**) (Scheme 3.11). The colourless crystals isolated were produced in 51% yield, which may be attributed to steric hindrance at the *ortho*-position. Low yields of 46% were observed when 2-

fluorobenzoic acid was used as an electrophile as reported by Tran and co-worker [17], confirming a negative effect of the *ortho*-substituent.



**Scheme 3.11**

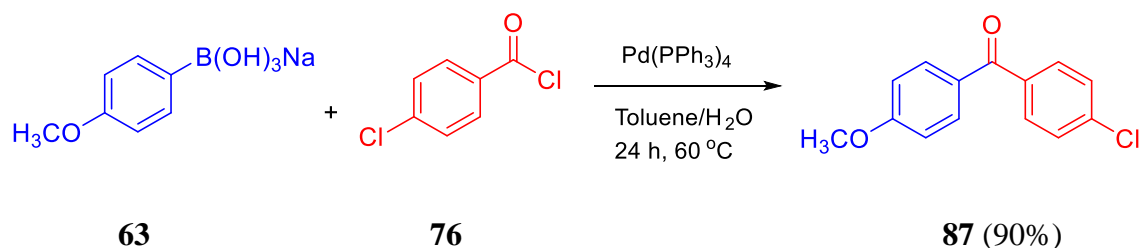
The coupled-product was proven to be clean using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic techniques showing peaks with consistent the structure. The methylthio group signal appeared in the <sup>1</sup>H NMR spectrum resonating at 2.54 ppm integrating to three protons and also the aromatic signals integrating to eight protons proving that the desired-product was synthesised (**Figure 3.13**).



**Figure 3.13: The <sup>1</sup>H NMR spectrum for the compound 84**

### 3.2.8 The synthesis of (4-methoxyphenyl)(4-chlorophenyl)methanone (87)

The nucleophilic coupling partner bearing an electron rich methoxy group reacted efficiently with a variety of acyl chlorides (Table 2, entry 13-16) affording biaryl ketones in good to excellent yields (64-93%). The synthesis of (4-methoxyphenyl)(4-chlorophenyl)methanone (**87**) from sodium (4-methoxyphenyltrihydroxyborate) (**63**) appeared to be more effective compared to its synthesis from the corresponding boronic acid (**Scheme 3.12**) [16].

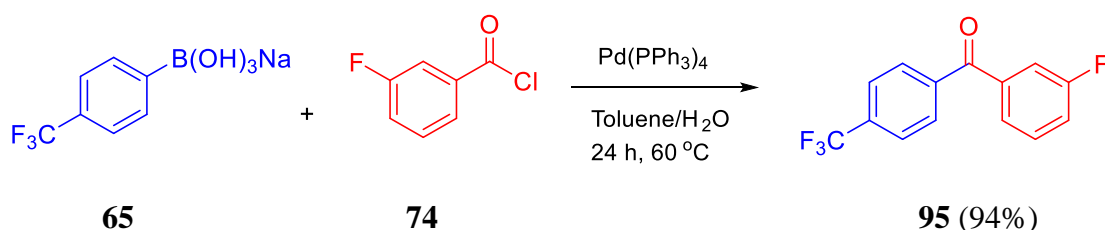


**Scheme 3.12**

The titled compound (**87**) was obtained as a colourless solid with excellent yield of 90% which is higher than 73% obtained from the corresponding boronic acids [18].  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were consistent with the expected structure of the desired product. It is also notable that the presence of the less reactive C-Cl and C-F as a substrate (Table 2, entry 8, 15, 16, 22 and 23) did not affect the yield of the desired products unless it was *ortho*-substituted (Table 2, entry 12).

### 3.2.9 The synthesis of (3-fluorophenyl)(4-trifluoromethylphenyl)methanone(**95**)

The reactivity of nucleophilic bearing electron-withdrawing groups was favourable compared to nucleophiles bearing electron-donating functionalities. For example, the cross-coupling reactions of sodium (4-trifluorophenyltrihydroxyborate) (**65**) with different acyl chlorides afforded ketones in moderate to excellent yields. *Meta*-substituted acyl chlorides also reacted efficiently with (4-trifluorophenyltrihydroxyborate) (**65**) furnishing (3-fluorophenyl)(4-trifluoromethylphenyl)methanone (**95**) in excellent (94%) isolated yield (**Scheme 3.13**).



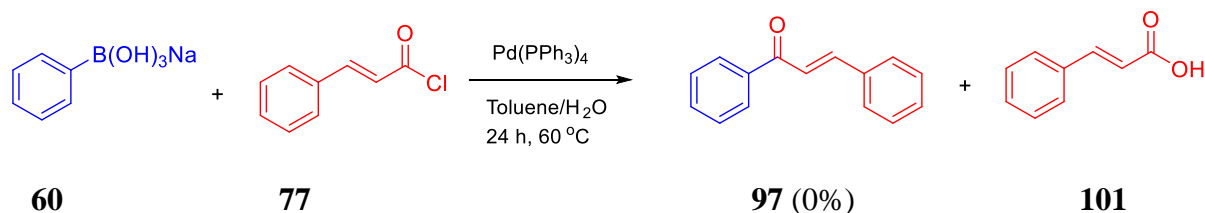
**Scheme 3.13**

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the white needle-like crystals of the coupled product confirmed the successful synthesis of the anticipated structure.



### 3.2.10 Attempted synthesis of 2-Propen-1-one,1,3-diphenyl (97)

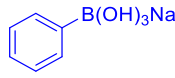
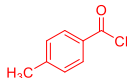
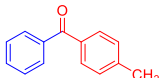
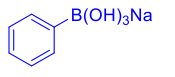
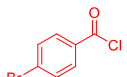
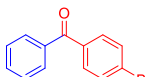
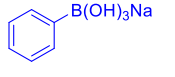
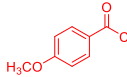
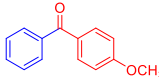
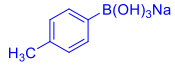
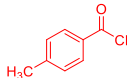
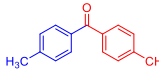
To further test the scope and limitations of the developed method, cinnamoyl chlorides (**77**) were reacted with sodium (aryl trihydroxyborate) salts (Table 2, entry 24-28) under optimal reaction conditions, however, no product was obtained and only the starting material was detected together with the hydrolysis product (cinnamic acid) (**101**) (Scheme 3.14). This observation was also noted by Polackova and co-workers [19] under microwave assisted synthesis.

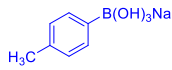
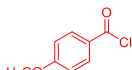
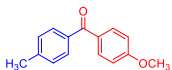
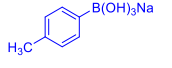
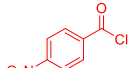
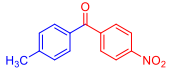
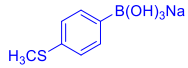
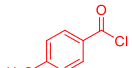
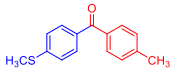
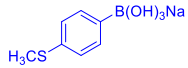
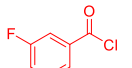
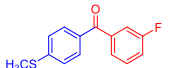
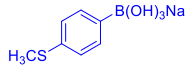
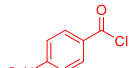
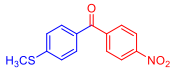
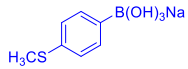
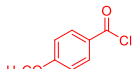
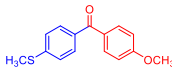
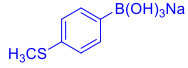
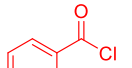
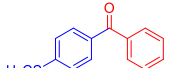
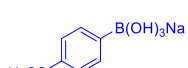
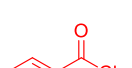
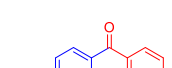
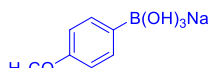
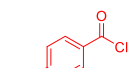
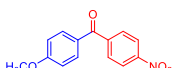
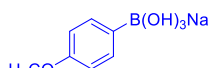
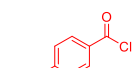
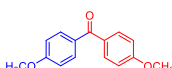
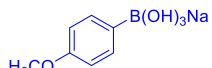
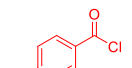
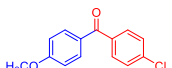


**Scheme 3.14**

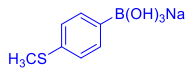
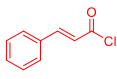
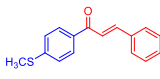
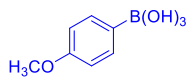
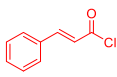
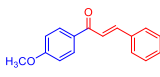
The scope and limitation of palladium-catalysed Suzuki-Miyaura cross-coupling reactions between acyl chlorides and sodium (aryl trihydroxyborate) salts is summarised in **Table 2** below.

**Table 2:** Base free palladium-catalyzed acylation reactions of sodium (aryl trihydroxyborate) salts with acyl chlorides <sup>a</sup>

Entry	Sodium (aryl trihydroxyborate)	Acyl chloride	Product	Yield (%)
1	 <b>60</b>	 <b>2</b>	 <b>3</b>	88
2	 <b>60</b>	 <b>67</b>	 <b>68</b>	74
3	 <b>60</b>	 <b>70</b>	 <b>78</b>	79
4	 <b>61</b>	 <b>2</b>	 <b>69</b>	94

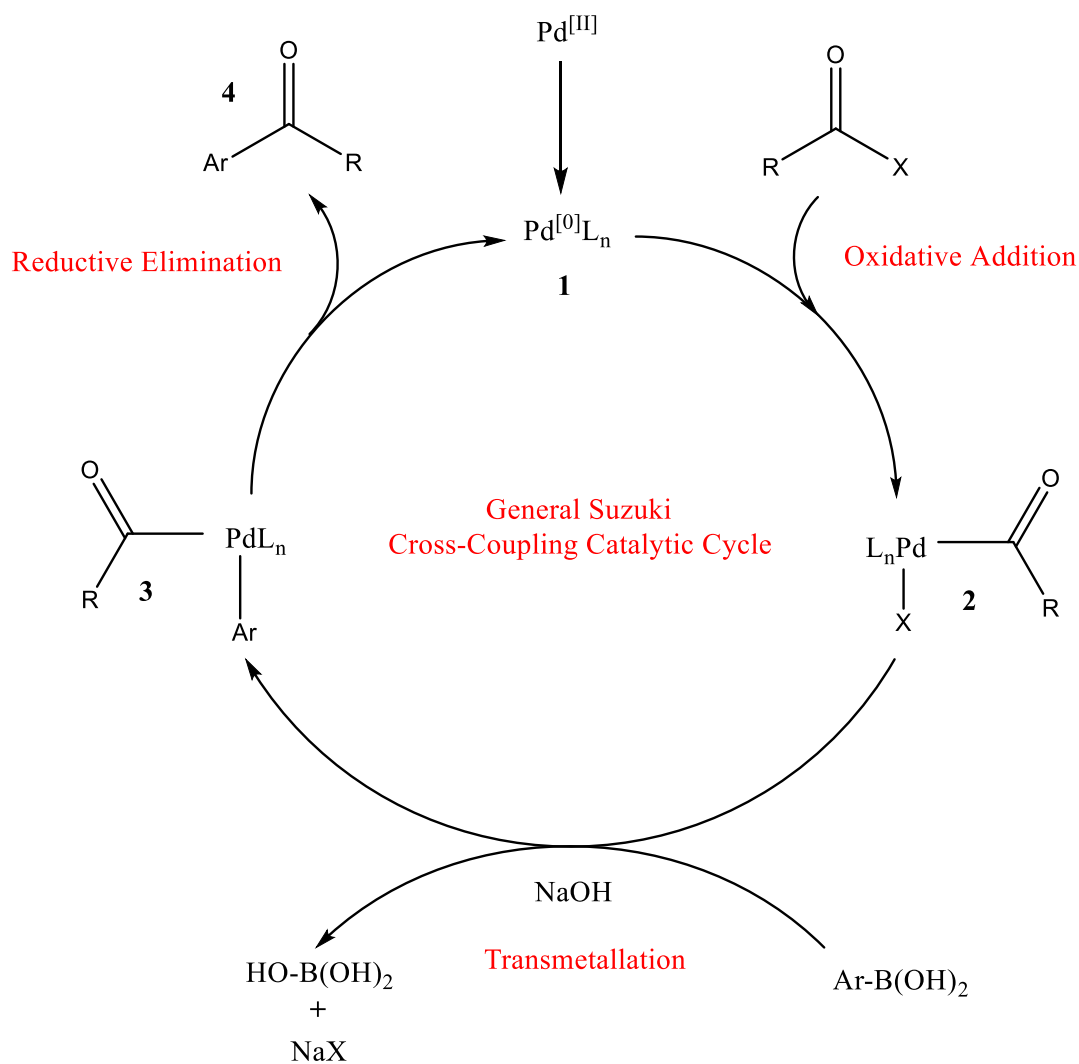
Entry	Sodium (aryl trihydroxyborate)	Acyl chloride	Product	Yield (%)
5	 <b>61</b>	 <b>72</b>	 <b>79</b>	86
6	 <b>61</b>	 <b>70</b>	 <b>80</b>	67
7	 <b>64</b>	 <b>2</b>	 <b>81</b>	74
8	 <b>64</b>	 <b>74</b>	 <b>82</b>	86
9	 <b>64</b>	 <b>70</b>	 <b>71</b>	69
10	 <b>64</b>	 <b>72</b>	 <b>73</b>	94
11	 <b>64</b>	 <b>19</b>	 <b>83</b>	89
12	 <b>64</b>	 <b>75</b>	 <b>84</b>	51
13	 <b>63</b>	 <b>70</b>	 <b>85</b>	64
14	 <b>63</b>	 <b>72</b>	 <b>86</b>	93
15	 <b>63</b>	 <b>76</b>	 <b>87</b>	90

Entry	Sodium (aryl trihydroxyborate)	Acyl chloride	Product	Yield (%)
16	<b>63</b>	<b>74</b>	<b>88</b>	73
17	<b>65</b>	<b>72</b>	<b>89</b>	82
18	<b>65</b>	<b>67</b>	<b>90</b>	91
19	<b>65</b>	<b>70</b>	<b>91</b>	70
20	<b>65</b>	<b>19</b>	<b>92</b>	86
21	<b>65</b>	<b>2</b>	<b>93</b>	81
22	<b>65</b>	<b>76</b>	<b>94</b>	89
23	<b>65</b>	<b>74</b>	<b>95</b>	94
24	<b>65</b>	<b>77</b>	<b>96</b>	0
25	<b>60</b>	<b>77</b>	<b>97</b>	0
26	<b>61</b>	<b>77</b>	<b>98</b>	0

Entry	Sodium (aryl trihydroxyborate)	Acyl chloride	Product	Yield (%)
27	 <b>64</b>	 <b>77</b>	 <b>99</b>	0
28	 <b>63</b>	 <b>77</b>	 <b>100</b>	0

<sup>a</sup> Reaction conditions: Acyl chloride (1.1 mmol), nucleophile (1.0 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 mmol), toluene (2.0 mL) and water (0.5 mL). All reactions were conducted under an argon atmosphere to avoid premature oxidation of Pd(PPh<sub>3</sub>)<sub>4</sub> at 60 °C, 24 h. All yields were isolated using column and/or radial chromatography.

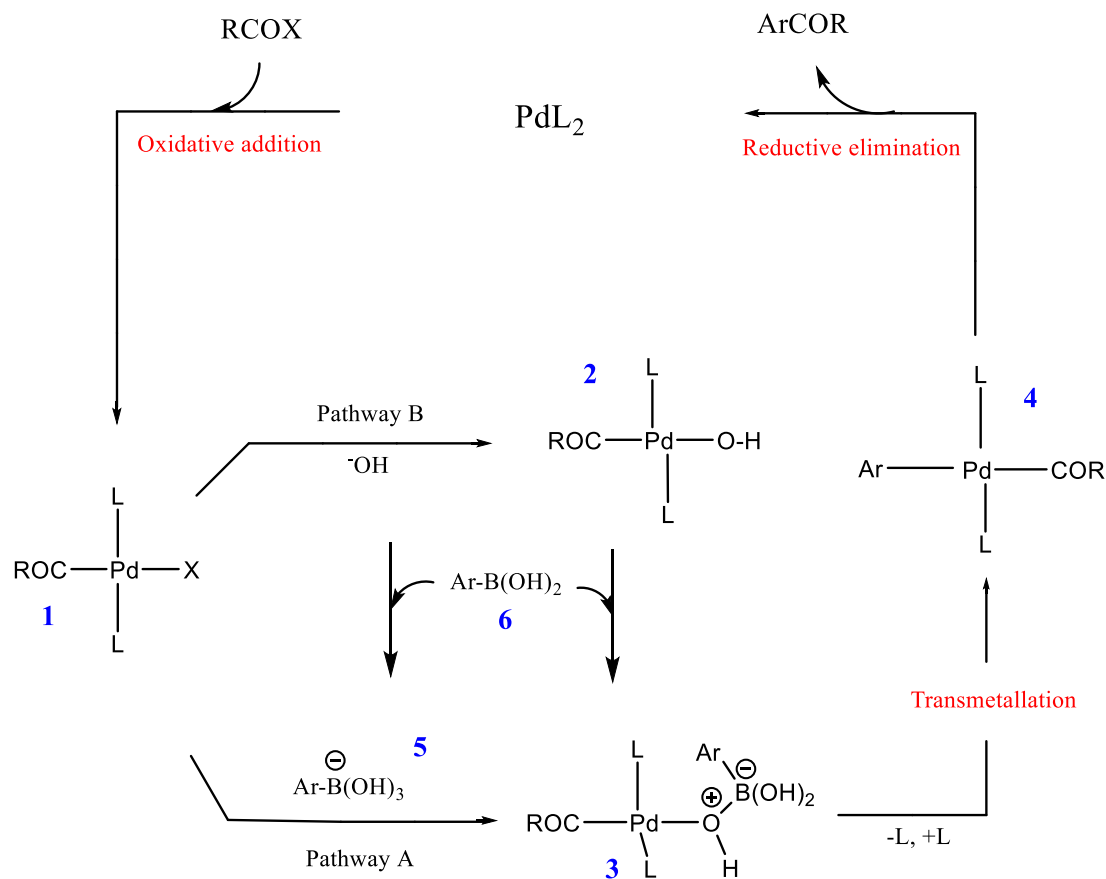
### 3.2.11 The Mechanistic Study



**Figure 3.14: Suzuki-Miyaura Catalytic Cycle**

The general mechanism of the palladium-catalysed Suzuki-Miyaura cross-coupling reaction involves three steps, namely: oxidative addition, transmetallation and reductive elimination. The oxidative addition step involves the addition of an acyl and the halide species on the zerovalent Pd centre **1** to form the Pd(II) complex **2**. This step is eventually followed by transmetallation, in which, the organic moiety directly bonded to the boron atom, is transmetallated to the Pd(II) complex **2** to form complex **3** in the presence of a base. The rearrangement of the acyl and an organic moiety to *cis*-isomer facilitates the reductive elimination of the product (**4**) and regeneration of the zerovalent Pd complex **1** (**Figure 3.14**) [20]. The key question that led to the development of Suzuki-Miyaura cross-coupling reactions was why the organoboron reagents with three coordinated species were not nucleophilic enough to induce transmetallation step [21, 22]. Therefore, the addition of a base accelerated the cross-coupling by converting the neutral organoboron reagents to a more nucleophilic four-coordinated species [23]. The general mechanism describes the use of three coordinated organoboron reagents such as boronic acids with the addition of a negatively charged base to promote transmetallation. There has been a debate on the role of a base and the rate of the active palladium intermediate with the active transmetallating agent [24].

Suzuki and Miyaura conducted mechanistic studies on alkenylborates coupled with bromoalkenes in the presence of alkoxide bases [23]. The authors considered two roles of the base, where the base reacts with palladium to form a more active alkoxo-palladium intermediate **2** (Pathway B) or where it reacts with the boronate to form a more nucleophilic tetrahedral boronate species (Pathway A) [24]. These two pathways are called oxo-palladium pathway and boronate pathway, respectively (**Figure 3.15**).



**Figure 3.15: Transmetalation analysis using ESI-MS**

Many computational and experimental studies have been conducted by different authors in order to explain each pathway and clearly indicate the importance of a base in each pathway [25-27]. Xue and Lin [28] reported a theoretical energy barrier of more than 44 kcal/mol that has to be overcome in transmetalation when using trivalent organoboron species (**6**) in the absence of a base. Whereas, in the addition of a base or  $\text{OH}^-$  anions, tetravalent organoboron species (**5**) is required to overcome a barrier of less than 21 kcal/mol (Pathway A). Hence, both experimental and theoretical studies revealed the importance of a base in Suzuki-Miyaura cross-coupling reactions. As for the replacement of a halide (**1**) by  $\text{OH}^-$  anion (**2**), this was not consistent with the theoretical studies (Pathway B) [28].

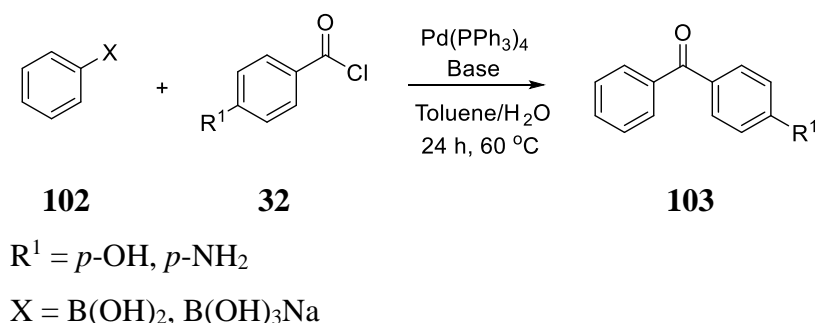
On the other hand, Mato and co-workers' showed that the transmetalation pathway depends on the organoboron reagent used [29]. Theoretical studies emphasised that the species involved in the transmetalation step are organoborate species through the boronate pathway (Pathway A). This theory was proven by the successful application of trihydroxyborate salts in base-free Suzuki reactions with aryl halides [4]. Nunes and co-workers conducted a study that proved that transmetalation was via the boronate pathway irrespective of the organoboron

reagent used because when boronic acid or boronic pinacol ester was used with a base, similar tetra-coordinated intermediates were detected in ESI-MS [30].

As the mechanism proved that trihydroxyborate salts (**5**) can couple efficiently in a base-free environment and transmetallate via boronate pathway (Pathway A), our work has also proven that trihydroxyborate requires no base to transmetallate which brings many advantages. One of them is that the mechanism pathway is shortened especially the transmetalation step because there is no need to generate tetra-coordinated boronate species *in-situ*. Therefore, they can easily accommodate base-sensitive functionalities. In addition, aryl trihydroxyborate salts seem to be more convenient organoboron reagents compared to others because of their stability, solubility, easy isolation and high reactivity which makes working with them convenient in the laboratory. This emphasises the excellent application of sodium (aryl trihydroxyborate) salts as nucleophilic partners in Suzuki-Miyaura acylation reactions.

As it was mentioned before, trihydroxyborate salts are ‘activated nucleophiles’ there is no need for the addition of the three equivalents of a base as was done in traditional Suzuki cross-coupling. This is advantageous, not only in an economic point of view but it is advantageous in the sense that it allows the synthesis of ketones bearing base sensitive functionalities which are otherwise difficult to prepare following traditional Suzuki-Miyaura cross-coupling.

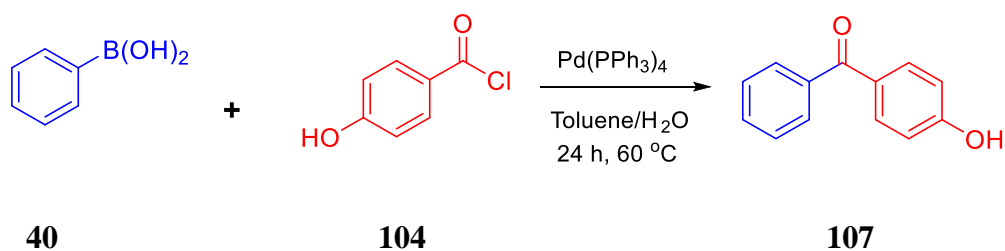
In order to prove that sodium (aryl trihydroxyborate) salts brings many benefits in Suzuki-Miyaura cross-coupling as a nucleophile, ketones bearing base sensitive functionalities were synthesised using boronic acid following traditional Suzuki cross-coupling reactions (**Scheme 3.15**) (Table 3).



**Scheme 3.15**

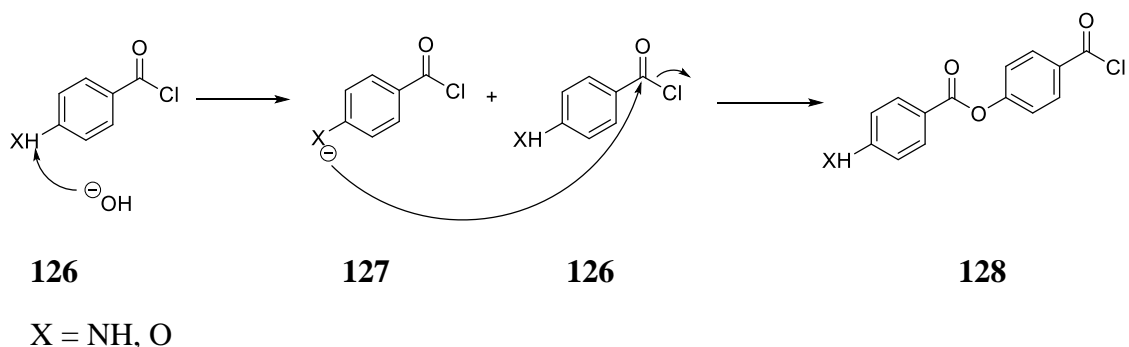
Phenyl boronic acid (**40**) was coupled with either 4-hydroxybenzoyl chloride (**104**) or 4-aminobenzoyl chloride (**105**) in the presence of a base (NaOH or K<sub>2</sub>CO<sub>3</sub>), producing desired

ketones in trace amounts and a number of unidentified side-products as evidenced on the TLC plate (Table 3, entries 1-4) (**Scheme 3.16**).



**Scheme 3.16**

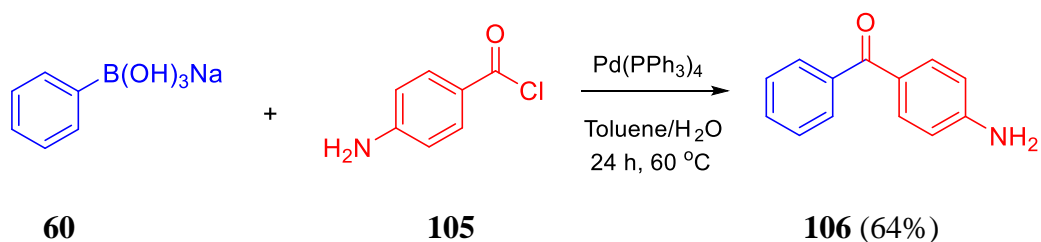
Low yields were observed when a base was used probably due to side reactions and between amino or hydroxyl group with the acyl chloride functional group to form side products (**128**) (**Scheme 3.17**).



**Scheme 3.17**

### 3.2.12 Synthesis of 4-aminobenzophenone (106)

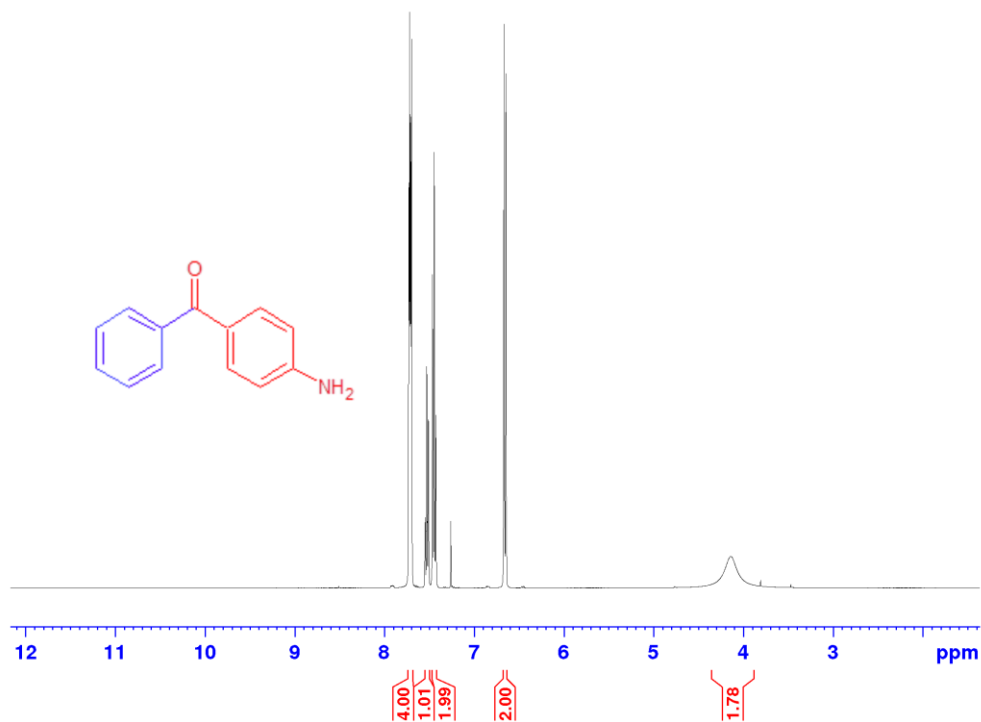
On the other hand, the application of a base-free acylation reaction coupling sodium (phenyltrihydroxyborate) (**60**) with 4-aminobenzoyl chloride (**105**) afforded the desired product 4-aminobenzophenone (**106**) in moderate (64%) yield as yellow crystals (**Scheme 3.18**). The TLC plate showed fewer spots when compared to the TLC when a base was used.



**Scheme 3.18**



The  $^1\text{H}$  NMR spectrum confirmed the successful synthesis of 4-aminobenzophenone (**106**) by showing the expected signals corresponding with the structure (**Figure 3.16**). A distinct broad signal resonating at 4.16 ppm was assigned to  $\text{N-H}_2$  and the other four signals resonating in the aromatic region are for the benzene protons.



**Figure 3.16:**  $^1\text{H}$  NMR spectrum for compound 106

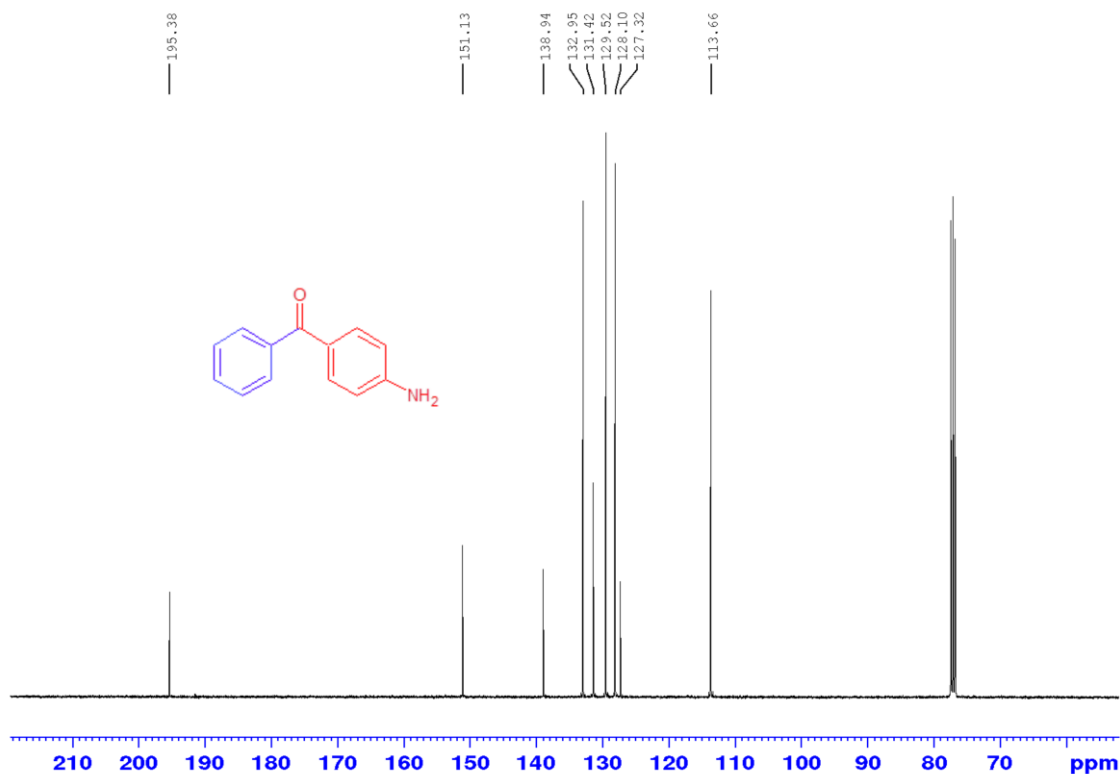
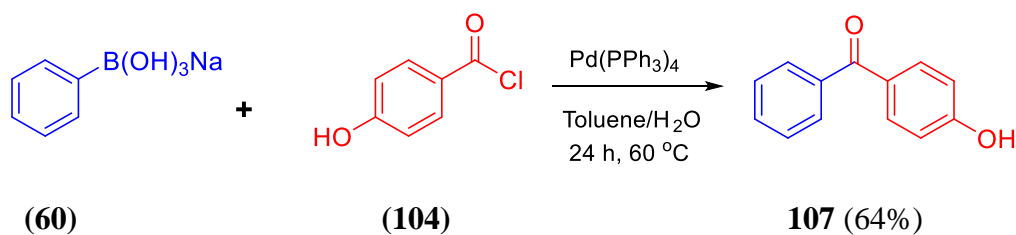


Figure 3.17:  $^{13}\text{C}$  NMR spectrum for compound **106**

### 3.2.13 Synthesis of 4-hydroxybenzophenone (**107**)

4-Hydroxybenzophenone (**107**) was synthesised from the reaction of sodium (phenyltrihydroxyborate) (**60**) with 4-hydroxybenzoyl chloride (**104**) in aqueous toluene (**Scheme 3.19**). The desired product (**107**) was obtained in moderate (64%) yield at 60 °C after 24 hours.



Scheme 3.19

4-Hydroxybenzophenone (**107**) was obtained as white powder. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were consistent with the anticipated structure revealing all the expected protons with their respective integrals (**Figure 3.18 and 3.19**).

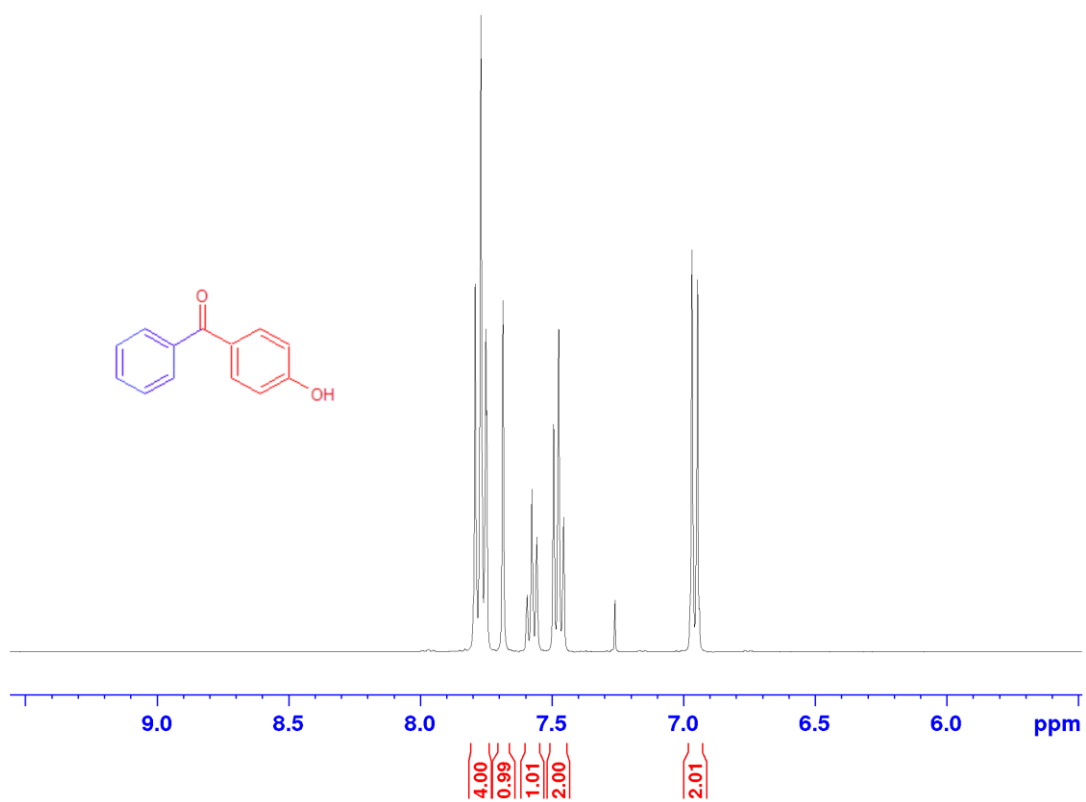


Figure 3.18: <sup>1</sup>H NMR spectrum for compound 107

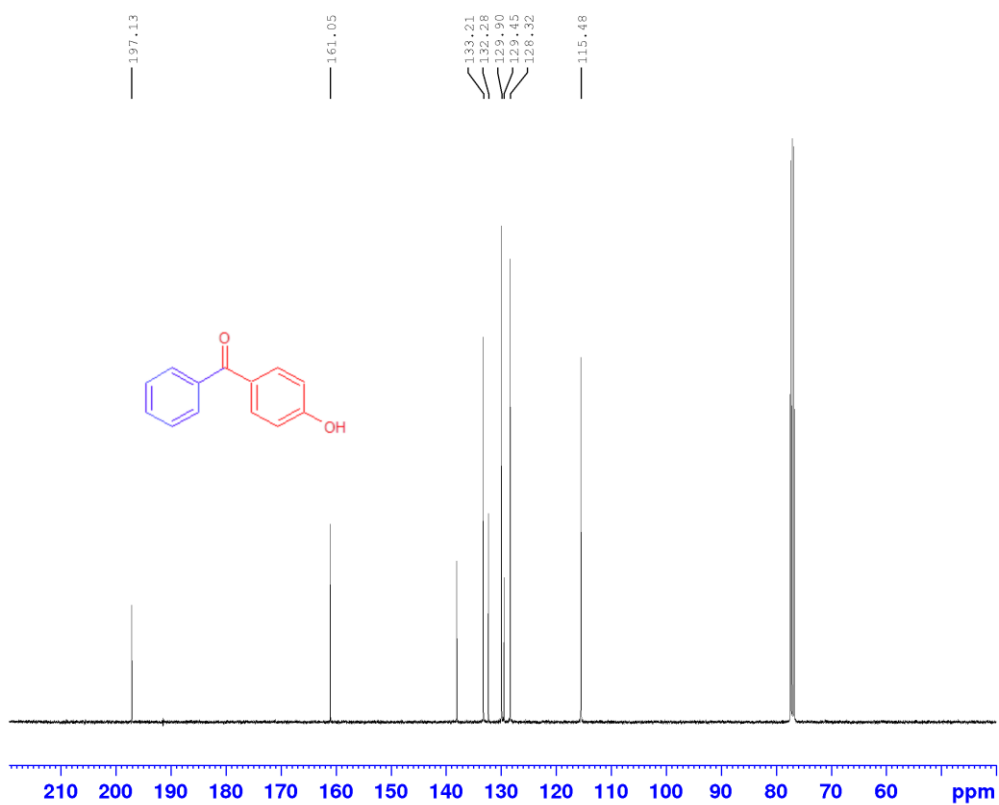


Figure 3.19: <sup>13</sup>C NMR spectrum for compound 107

The table below summarises the synthesis of base sensitive functionalities in the presence of a base as well as in base-free conditions.

**Table 3:** Synthesis of base sensitive diaryl ketones <sup>a</sup>

Entry	R <sup>1</sup>	Nucleophile	Base	Yield (%)
1	OH	PhB(OH) <sub>2</sub>	NaOH	Trace
2	NH <sub>2</sub>	PhB(OH) <sub>2</sub>	NaOH	Trace
3	OH	PhB(OH) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	8
4	NH <sub>2</sub>	PhB(OH) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	Trace
5	OH	PhB(OH) <sub>3</sub>		64
6	NH <sub>2</sub>	PhB(OH) <sub>3</sub>		57

<sup>a</sup> Reaction conditions: Acyl chloride (1.1 mmol), nucleophile (1.0 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 mmol), toluene (2.0 mL) and water (0.5 mL). All reactions were conducted under an argon atmosphere at 60 °C, 24 h. All yields were isolated using column and/or radial chromatography.

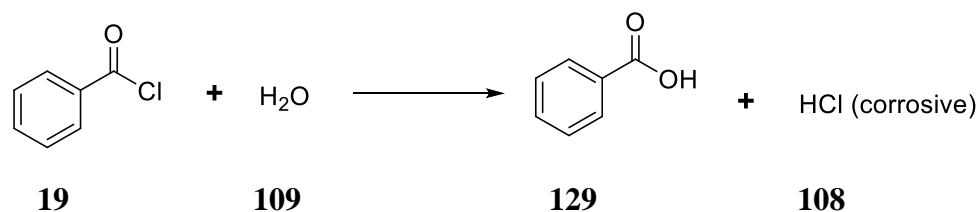
The true benefits of using the sodium (aryl trihydroxyborate) salts as nucleophilic coupling partners have been demonstrated (**Table 3**).

In summary, we have developed the first base-free Suzuki-Miyaura acylation reaction of acyl chlorides with sodium (aryl trihydroxyborate) salts to produce functionalised asymmetrical ketones in excellent yields. The catalytic system appeared versatile, mild and general tolerating a large range of functional groups such as NO<sub>2</sub>, OCH<sub>3</sub>, SCH<sub>3</sub> as well as base sensitive amino and hydroxyl functional groups, while furnishing the desired ketones with isolated yields of up to 94% in less than 24 hours at 60 °C. The results obtained from this study have successfully been published in the Journal of Organometallic Chemistry (Appendix).

### 3.3 Palladium-catalysed acylation of sodium (aryl trihydroxyborate) salts with carboxylic anhydrides

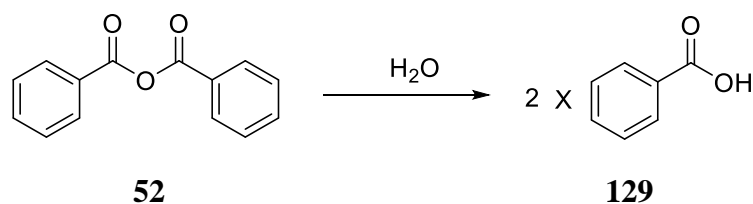
Carboxylic acid derivatives such as acid chloride [31] and thioesters [32] have been considered as significant acylating reagents in organic synthesis mostly because of their higher reactivity compared to their analogues such as acyl fluorides [33], carboxylic anhydrides [34] and carboxamides [15]. Among these carboxylic acid derivatives, acyl chlorides have received a lot of research attention because they are easily prepared from corresponding carboxylic acid and are generally commercially available. Despite their popularity as acylating agents, acyl chlorides are unstable towards nucleophiles such as water and amines making it difficult to handle and work with them in the laboratory and also their preparation requires a toxic chlorinating agent (SOCl<sub>2</sub>) [35]. For example, acyl chlorides (**19**)

are easily hydrolysed to the corresponding carboxylic acid (**129**) and have a high potential of producing the corrosive HCl (**108**) by-product which is disadvantageous in an industrial setting (**Scheme 3.20**).



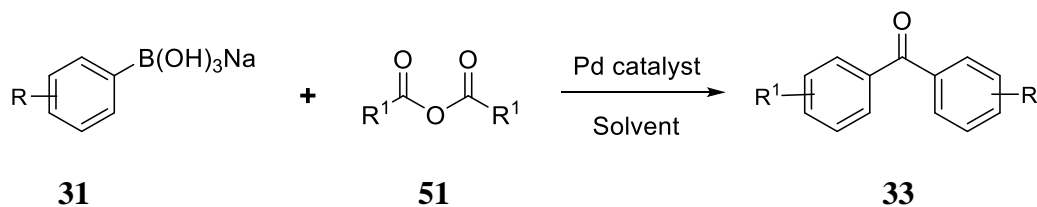
**Scheme 3.20**

On the other hand, carboxylic anhydrides are generally regarded as less reactive and easily handled electrophiles compared to acyl chlorides. In addition, the hydrolysis of carboxylic anhydrides (**52**) produces carboxylic acids (**129**) which do not pose a threat to the environment and could easily be recycled (**Scheme 3.21**).



**Scheme 3.21**

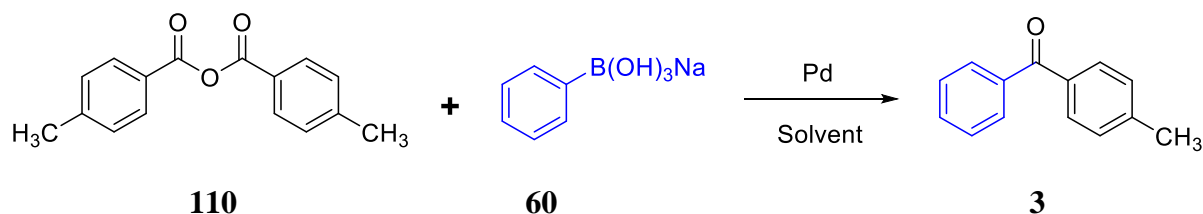
Based on the advantages associated with carboxylic anhydrides, we thought it would be logical to extend the scope of the developed reaction condition to carboxylic anhydrides as versatile acyl electrophiles in the cross-coupling reaction, therefore providing an alternative and attractive methodology for the preparation of functionalised ketones (**Scheme 3.22**).



**Scheme 3.22**

To the best of our knowledge, there are no published reports on the synthesis of ketones from sodium (aryl trihydroxyborate) salts and carboxylic anhydrides. Herein, we describe the first palladium-catalysed Suzuki-Miyaura cross-coupling reaction of sodium (aryl trihydroxyborate) salts and carboxylic anhydrides to synthesise ketones.

To commence the study, we firstly synthesised 4-methylbenzoic anhydride (**110**) following a previously published procedure [36] then coupled with sodium (phenyltrihydroxyborate) (**60**) in the presence of different palladium precursors during the optimisation of the reaction conditions (**Scheme 3.23**) (**Table 4**).



**Scheme 3.23**

**Table 4:** Parameter screening for the cross-coupling of 4-methylbenzoic anhydride with sodium (phenyltrihydroxyborate) (**60**)<sup>a</sup>

Entry	Catalyst	Solvent	Time	Yield (%) <sup>b</sup>
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Toluene (50 °C)	24 h	N.D
2	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub>	THF/H <sub>2</sub> O (60 °C)	24 h	N.D
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Toluene/H <sub>2</sub> O (80 °C)	24 h	N.D
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	THF (80 °C)	24 h	N.D
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Acetone (rt)	24 h	N.D
6	PdCl <sub>2</sub> /PPh <sub>3</sub>	THF/H <sub>2</sub> O (60 °C)	24 h	N.D
7	-	THF (rt)	24 h	N.R
8	PdCl <sub>2</sub>	Acetone/H <sub>2</sub> O (rt)	24 h	N.D
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	1,4-Dioxane (rt)	48 h	N.D
10	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Dioxane/H <sub>2</sub> O (100 °C)	24 h	N.R
<b>11</b>	<b>PdCl<sub>2</sub></b>	<b>Acetone/H<sub>2</sub>O (50 °C)</b>	<b>3 h</b>	<b>82</b>
12	PdCl <sub>2</sub>	Acetone (50 °C)	24 h	79
13	PdCl <sub>2</sub>	Acetone (rt)	24 h	39
14	Pd/C	Acetone/H <sub>2</sub> O	24 h	0

<sup>a</sup> Reaction conditions: 4-methylbenzoic anhydride (1 mmol), sodium (phenyltrihydroxyborate) (1.2 mmol), PdCl<sub>2</sub> (5 mol %). <sup>b</sup> Isolated yield, N.D-not determined, N.R-no reaction

The application of our previously published procedure on the current cross-coupling reaction did not give the desired product even after 24 hours (Table 4, entry 1). Changing solvents and the addition of Pd(II) precursor did not have any positive effect (Table 4, entry 2). The addition of zerovalent Pd catalyst did not promote the cross-coupling reaction (Table 4, entries 3-5, 9 and 10). The removal of Pd catalyst resulted in no product formation, as the starting material was recovered (Table 4, entry 7). Doubling the reaction time to 48 hours did not change the outcome of the reaction (Table 4, entry 9). No reaction occurred when the temperature was increased to 100 °C (Table 4, entry 10). A dramatic change was observed when PdCl<sub>2</sub> was used as a catalyst on aqueous acetone at 50 °C giving the desired coupled product in 82% yield (Table 4, entry 11). Using only acetone as a solvent reduced the yield

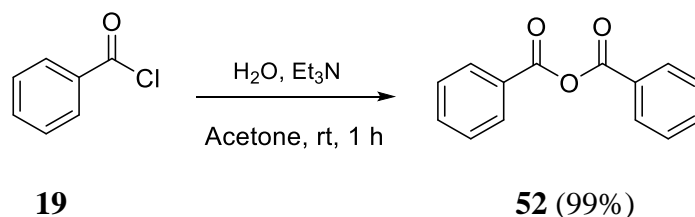
(Table 4, entry 12). The catalytic activity of PdCl<sub>2</sub> at room temperature was less effective as it produced the desired ketones in 39% yield (Table 4, entry 13). Pd/C did not initiate the desired cross-coupling reaction, instead it promoted the homocoupling reaction (Table 4, entry 14).

With the optimisation screening condition in hand (Table 4, entry 11), we next turned to the synthesis of different benzoic anhydrides in order to investigate the scope and the limitation of the newly developed cross-coupling conditions.

### 3.4 The synthesis of carboxylic anhydride compounds

#### 3.4.1 The synthesis of benzoic anhydride (52)

Dhimitruka and SantaLucia [36] previously reported the synthesis of benzoic anhydride (**52**) from the reaction of benzoyl chloride (**19**) with H<sub>2</sub>O and Et<sub>3</sub>N in acetone affording 97% of the desired product (**52**) (Scheme 3.19). Following the documented protocol [36], compound (**52**) was successfully synthesised and was obtained as yellow liquid in 99% (Scheme 3.24).



**Scheme 3.24**

The confirmation of the desired product was done using <sup>1</sup>H and <sup>13</sup>C NMR spectra corresponding to the expected results (Figure 3.20 and 3.21).

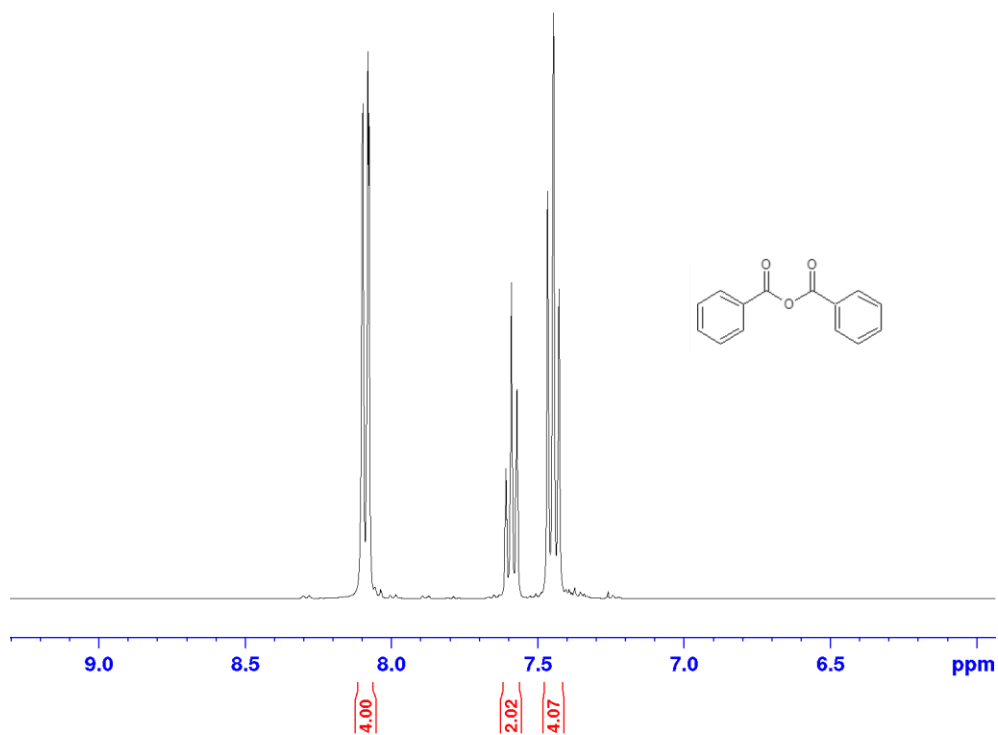


Figure 3.20:  $^1\text{H}$  NMR spectrum for benzoic anhydride (52)

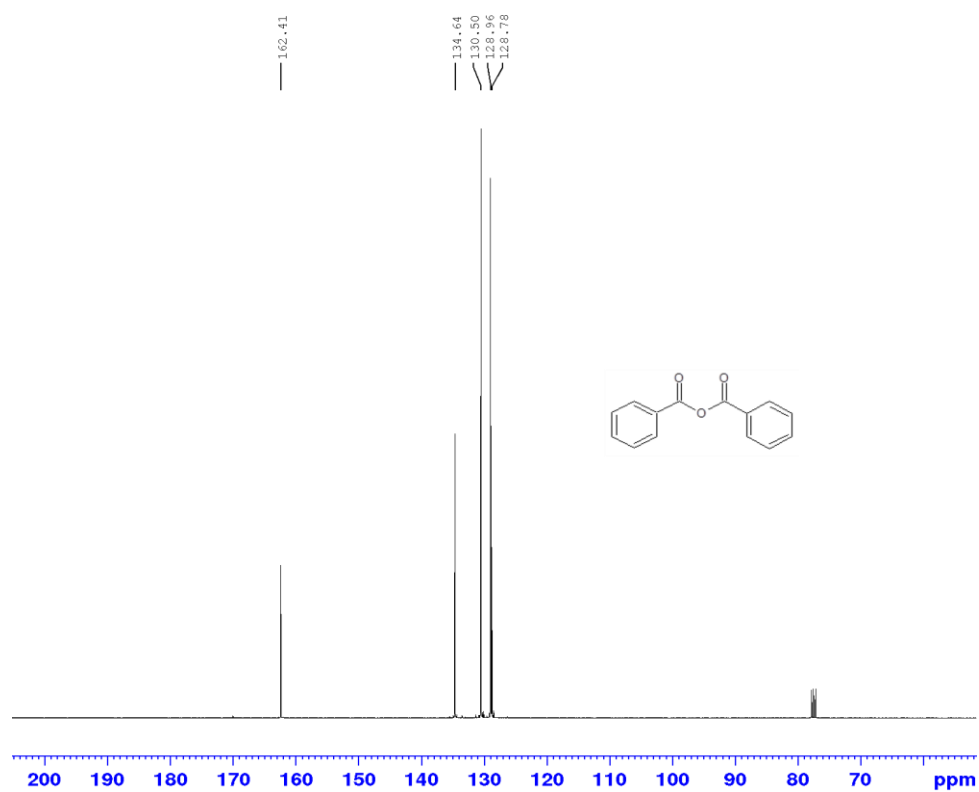
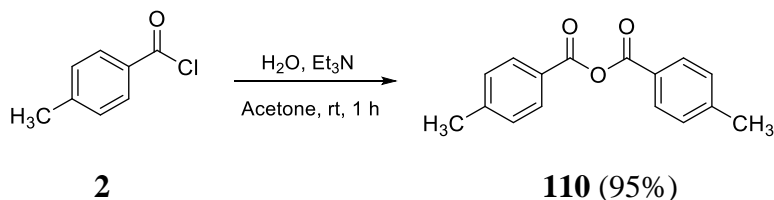


Figure 3.21:  $^{13}\text{C}$  NMR spectrum for benzoic anhydride (52)



### 3.4.2 The synthesis of 4-methylbenzoic anhydride (110)

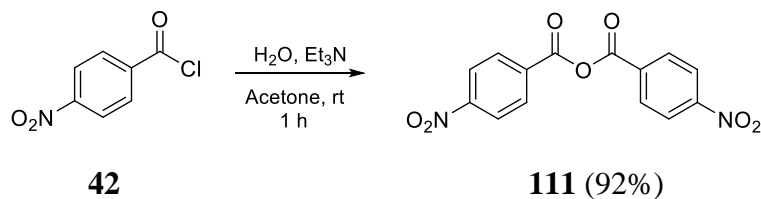
Following the same protocol, 4-methyl benzoic anhydride (**110**) was successfully synthesised as white crystals in 95% isolated yield (**Scheme 3.25**). The obtained product (**110**) was confirmed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra (See appendix).



**Scheme 3.25**

### 3.4.3 The synthesis of 4-nitrobenzoic anhydride (111)

The titled compound was prepared in 92% yield as yellowish crystals from 4-nitrobenzoyl chloride (**42**) and water following the representative procedure (**Scheme 3.26**).



**Scheme 3.26**

The structure of the product was confirmed using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic techniques which showed the expected number of peaks and the integration ratios consistent with the assigned structure (**Figure 3.22** and **3.23**).

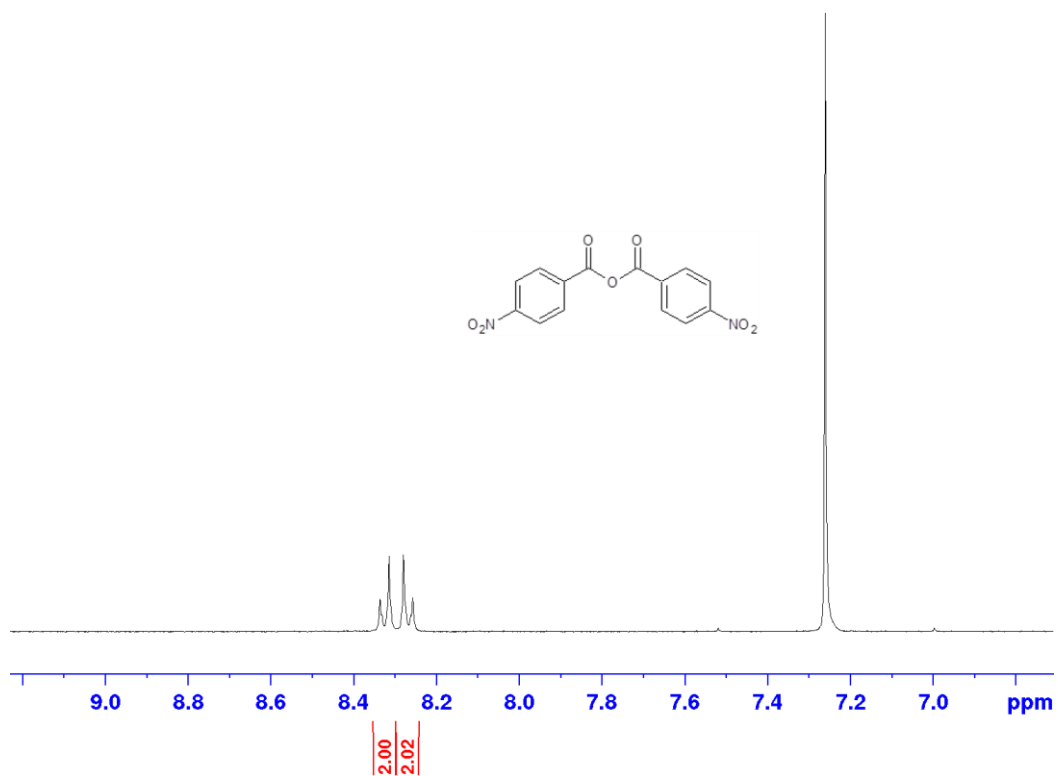


Figure 3.22: <sup>1</sup>H NMR spectrum of compound 111

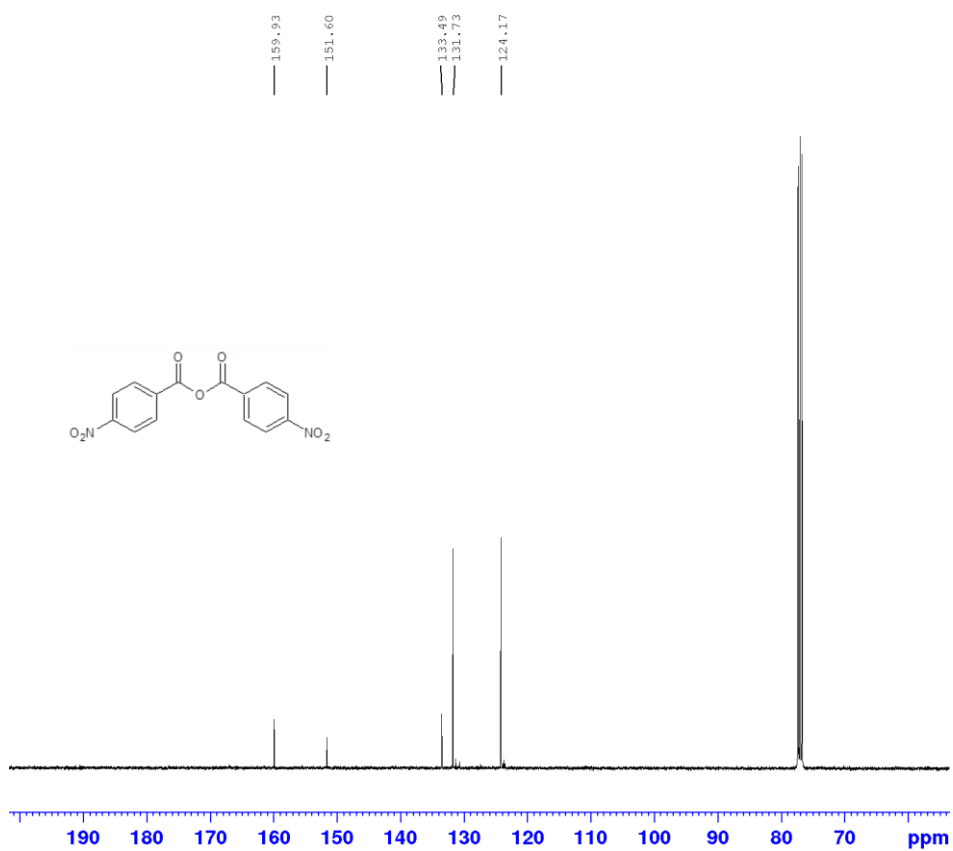
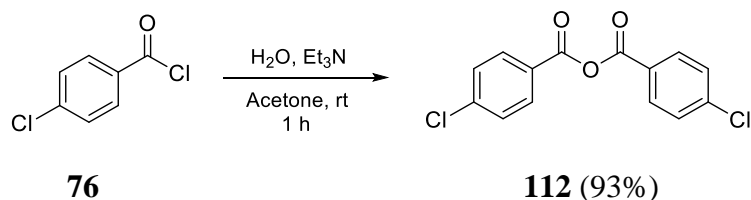


Figure 3.23: <sup>13</sup>C NMR spectrum for compound 111

### 3.4.4 The synthesis of 4-chlorobenzoic anhydride (**112**)

The reaction of 4-chloro benzoyl chloride with water was successfully achieved under the above-mentioned procedure. The desired product was obtained in 93% yield as reddish powder (**Scheme 3.27**).

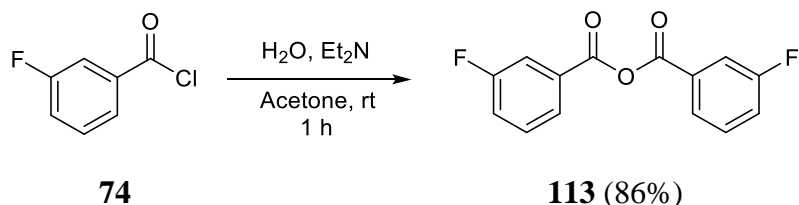


**Scheme 3.27**

The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of the white powder were acquired in order to confirm the structure of the product. The  $^{13}\text{C}$  NMR spectrum showed the number of carbon signals expected of the desired product.

### 3.4.5 The synthesis of 3-fluorobenzoic anhydride (**113**)

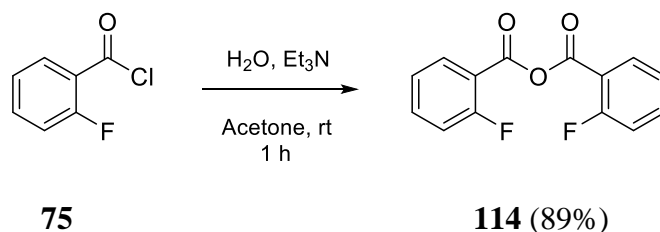
3-Fluorobenzoic anhydride (**113**) was synthesised in 86% yield from the reaction of 3-fluorobenzoyl chloride (**74**) with water (**Scheme 3.28**). The desired product was obtained as white crystals. The successful synthesis of compound (**113**) was confirmed with  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy.



**Scheme 3.28**

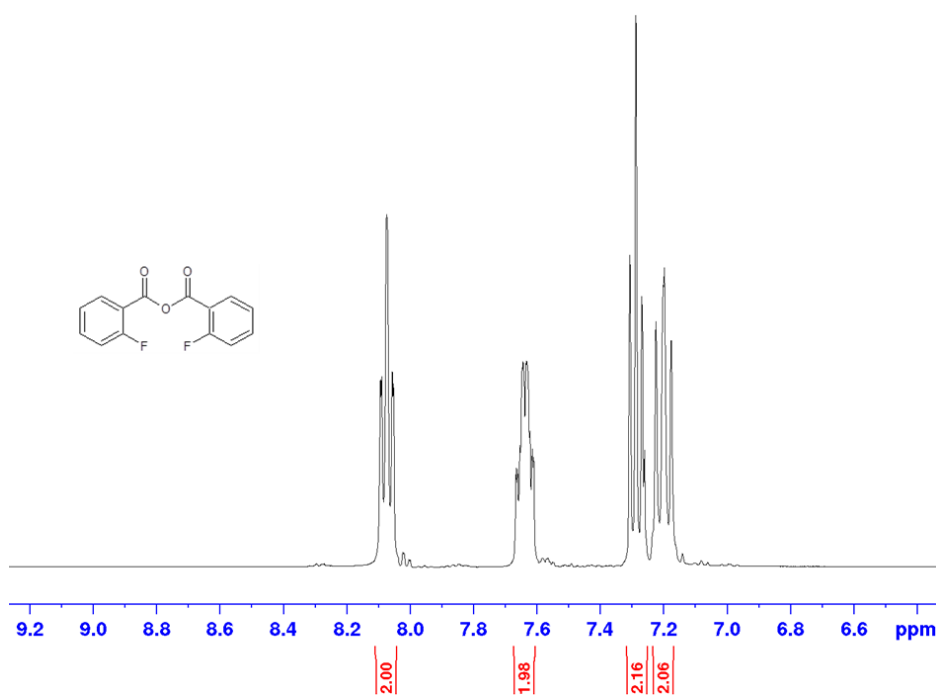
### 3.4.6 The synthesis of 2-fluorobenzoic anhydride (**114**)

Following the same protocol, 2-fluorobenzoic anhydride (**114**) was obtained from the reaction of 2-fluorobenzoyl chloride (**75**) and water (**Scheme 3.29**). This reaction furnished the desired product (**114**) as white powder in 89% yield.



**Scheme 3.29**

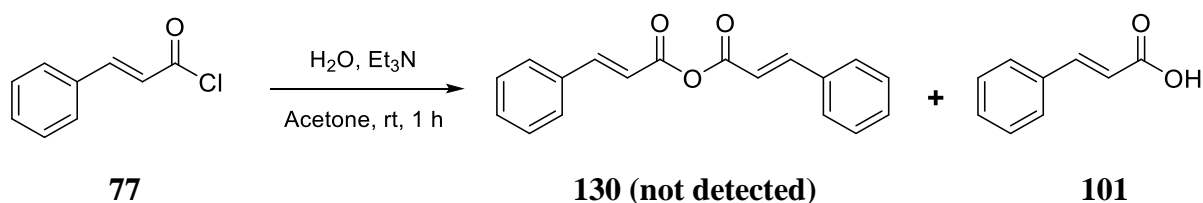
The  $^1\text{H}$  NMR spectrum showed the corresponding peaks with the structure as well as integral ratio corresponding with the number of protons in the structure (**Figure 3.24**).



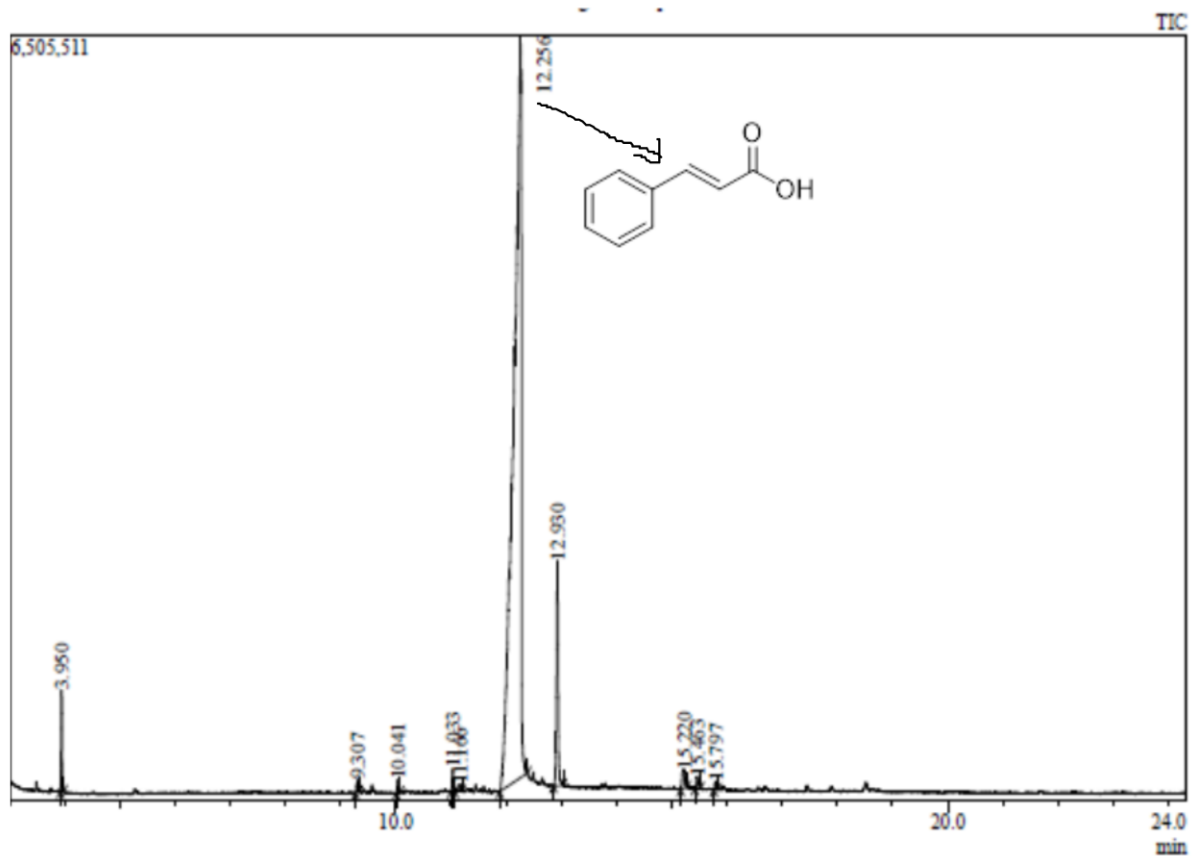
**Figure 3.24:  $^1\text{H}$  NMR spectrum for compound 114**

### 3.4.7 Attempted synthesis of cinnamic anhydride (130)

Cinnamoyl chloride (**77**) was reacted with water and triethylamine following the same procedure reported by Dhimitruka and SantaLucia [36]. However, to our surprise the desired cinnamic anhydride (**130**) did not form. Instead, a hydrolysis cinnamic acid (**101**) was detected on the TLC and was also confirmed by GC-MS (**Scheme 3.30**) (**Figure 3.25**).



**Scheme 3.30**



Hit#1 Entry:14478 Library:NIST11.lib  
 SI:97 Formula:C9H8O2 CAS:621-82-9 MolWeight:148 RetIndex:1357  
 CompName:2-Propenoic acid, 3-phenyl- \$\$ Cinnamic acid \$\$ Phenylacrylic acid \$\$ 3-Phenyl-2-propenoic acid \$\$ 3-Phenylacrylic acid \$\$ Zimtsaeure \$\$ 3-

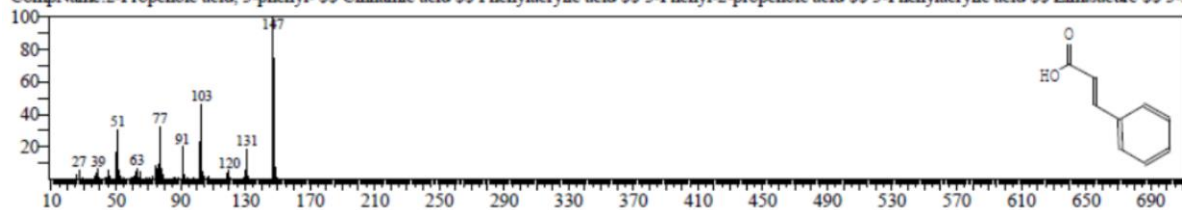


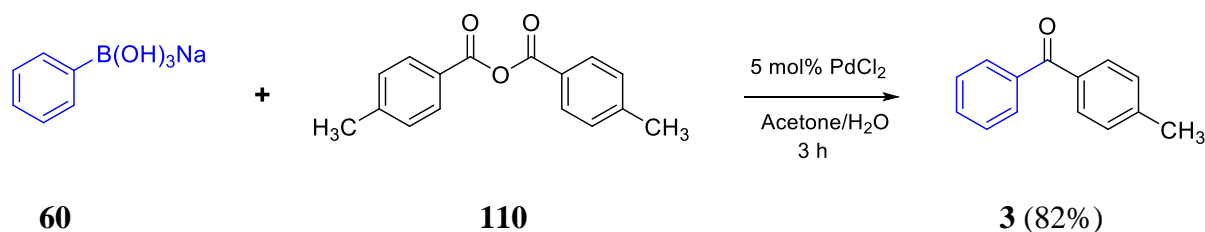
Figure 3.25: GC-MS spectrum for compound 101 and impurities

### 3.5 The synthesis of ketones from sodium (aryl trihydroxyborate) salts and carboxylic anhydride

The following section describes the scope and the limitation of palladium-catalysed Suzuki-Miyaura acylation of sodium (aryl trihydroxyborate) salts with different benzoic anhydrides under the optimised reaction condition to synthesise functionalised unsymmetrical ketones.

### 3.5.1 The synthesis of phenyl(*p*-tolyl)methanone (**3**)

Sodium (phenyltrihydroxyborate) (**60**) was smoothly coupled with 4-methylbenzoic anhydride (**110**) affording phenyl(*p*-tolyl)methanone (**3**) in excellent yields of 82% (**Scheme 3.31**). The yield is comparable with 87% yield obtained by Xin after 6 hours [18].

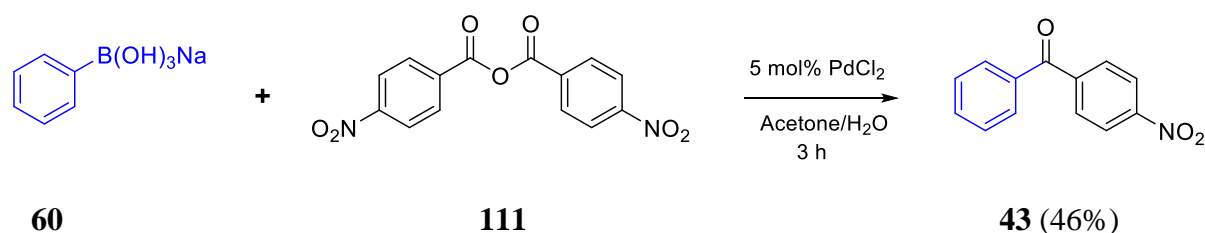


**Scheme 3.31**

The titled compound was obtained as white crystals and spectroscopic techniques (<sup>1</sup>H and <sup>13</sup>C NMR) confirmed the structure of the desired product.

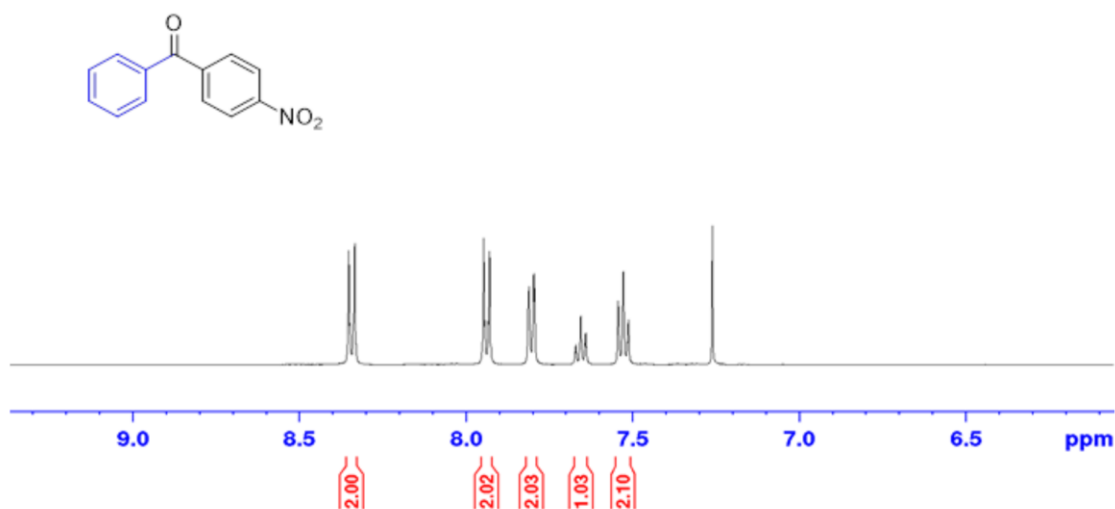
### 3.5.2 The synthesis of (4-nitrophenyl)(phenyl)methanone (**43**)

(4-Nitrophenyl)(phenyl)methanone (**43**) was produced from coupling sodium (phenyltrihydroxyborate) (**60**) with 4-nitrobenzoic anhydride (**111**) (**Scheme 3.32**). Since the benzoic acid anhydride used was bearing an electron-withdrawing substrate (NO<sub>2</sub>) an unsatisfactory yield of 46% was afforded (Table 5, entry 3), which was higher than the 37% yield reported by Gooben and Ghosh [39]. Low yield was probably due to unfavourable oxidative addition of the anhydride to the metal centre therefore promoting homocoupling and hydrolysis [39].



**Scheme 3.32**

The <sup>1</sup>H NMR spectrum was clean and only showing expected peaks of the desired product. The integration of all signals added up to nine which corresponds with the structure (**Figure 3.26**). Five signals resonating from 7.51 to 8.35 ppm in the aromatic region proves to be consistency with the structure of the product.

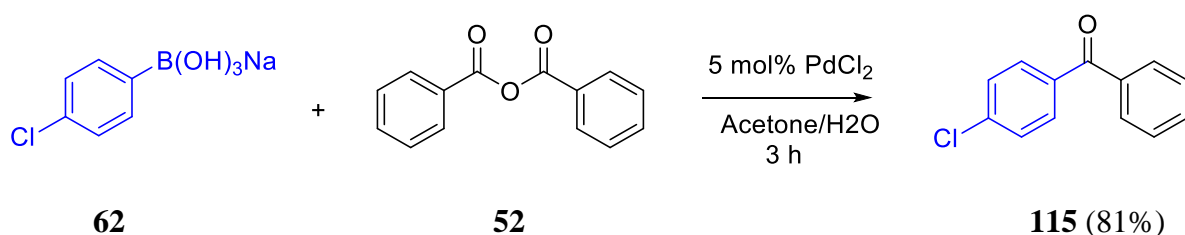


**Figure 3.26:**  $^1\text{H}$  NMR spectrum for (4-nitrophenyl)(phenyl)methanone (**43**)

### 3.5.3 The synthesis of (4-chlorophenyl)(phenyl)methanone (**115**)

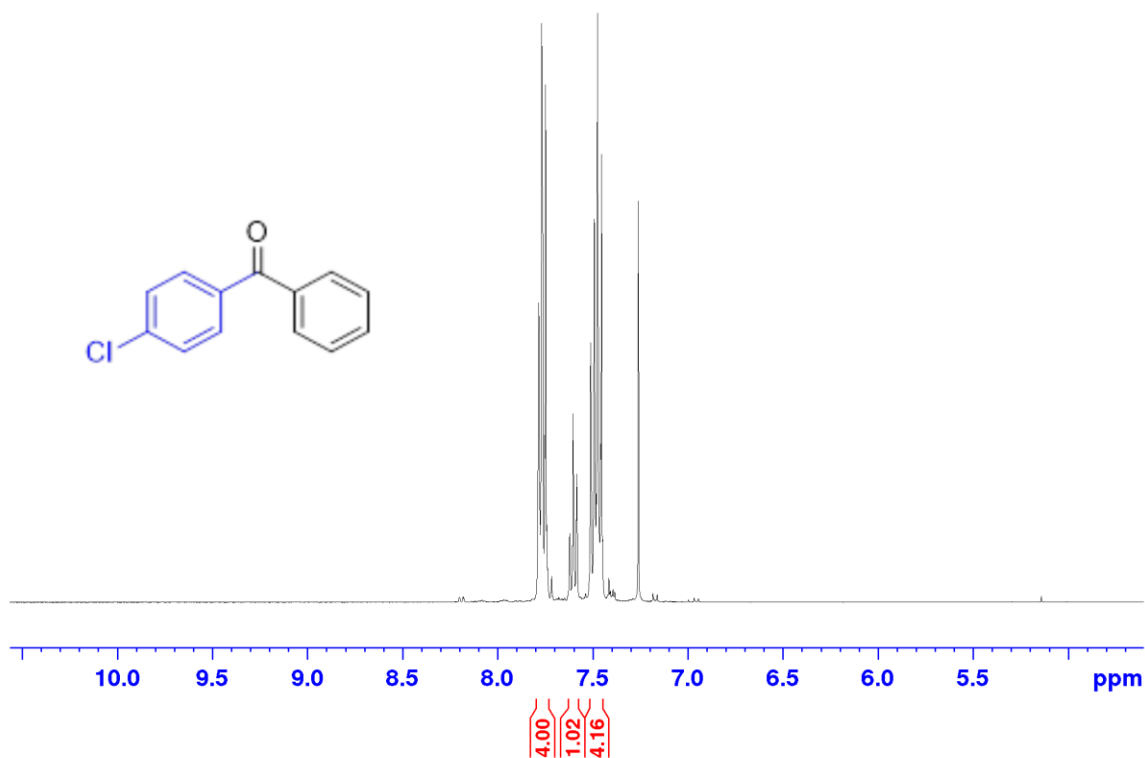
Smooth cross-coupling reaction was observed when sodium (aryl trihydroxyborate) bearing electron-withdrawing substrates (Cl and  $\text{CF}_3$ ) were reacted with benzoic acid anhydride bearing electron rich and neutral groups with yields of 64-88% (Table 5, entries 13, 14, 15, 18 and 22).

The preparation of (4-chlorophenyl)(phenyl)methanone (**115**) was successfully achieved through the coupling of sodium (4-chlorophenyltrihydroxyborate) (**62**) with benzoic anhydride (**52**) following the optimised condition (**Scheme 3.33**).



**Scheme 3.33**

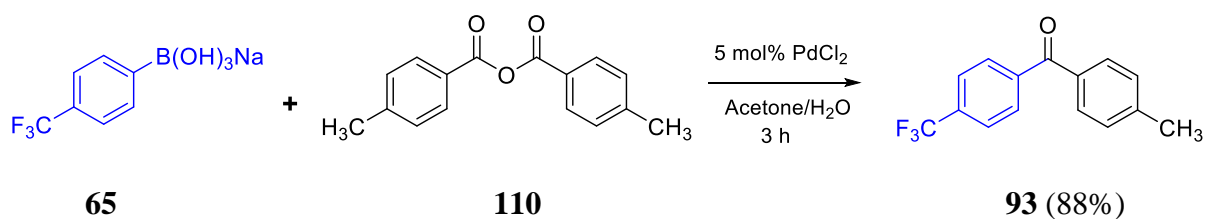
The titled compound (**115**) was obtained in 81% isolated yield as white solid. Spectroscopic elucidation was consistent with the structure. The yield obtained was higher than the 73% yield reported by Wu's *et al* [1].



**Figure 3.27:**  $^1\text{H}$  NMR spectrum for (4-chlorophenyl)(phenyl)methanone (**115**)

### 3.5.4 The synthesis of (4-methylphenyl)(4-trifluorophenyl)methanone (**93**)

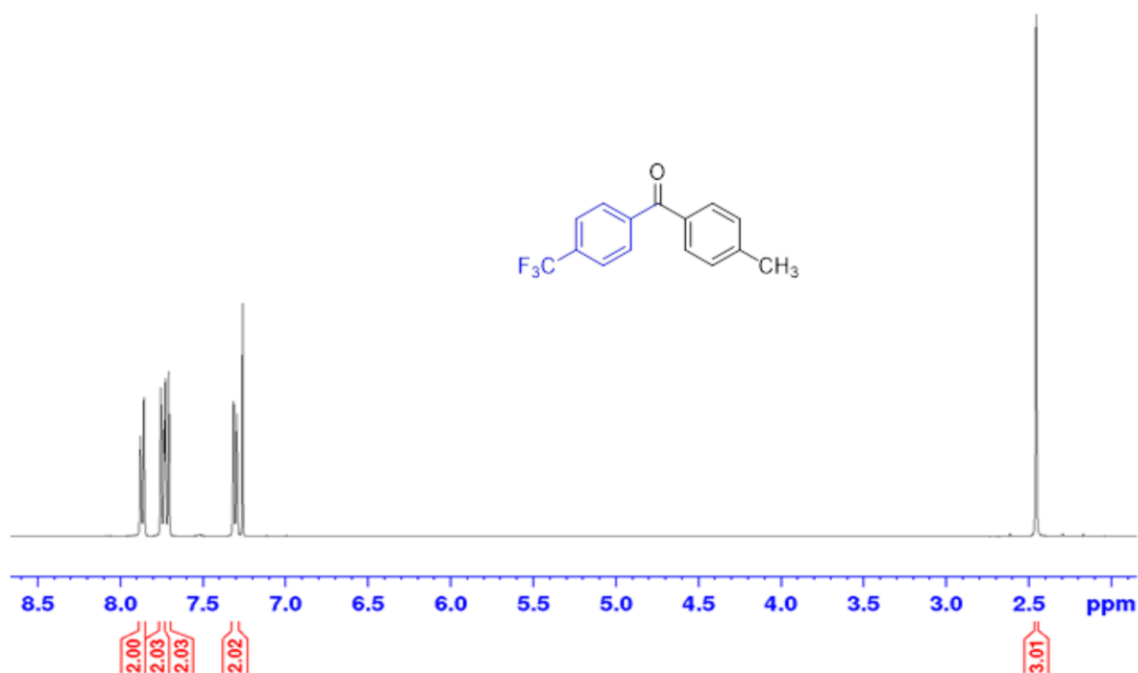
Following the optimised reaction conditions, (4-methylphenyl)(4-trifluorophenyl)methanone (**93**) was successfully synthesised in 88% yield from sodium (4-trifluorophenyl)trihydroxyborate (**65**) and 4-methylbenzoic anhydride (**110**) (Scheme 3.34). The yield obtained was slightly higher than the 79% yield reported by Xin [18].



**Scheme 3.34**

The  $^1\text{H}$  NMR spectrum showed all the expected signals with the corresponding integration. The signal resonating at 2.46 ppm integrated to methyl group and the four doublets in the aromatic region integrated to the protons in the benzene rings confirming the desired product (Figure 3.28).



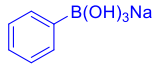
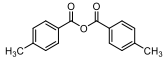
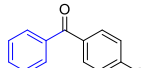
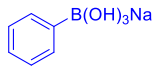
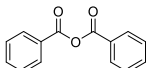
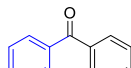
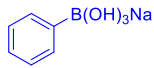
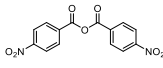
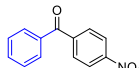
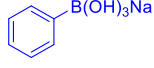
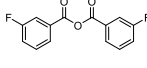
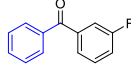
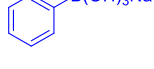
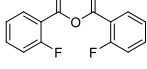
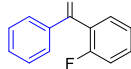
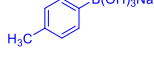
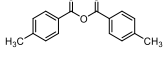
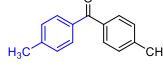
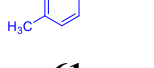
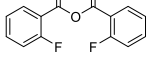
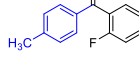
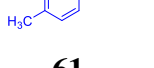
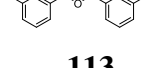
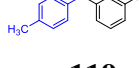
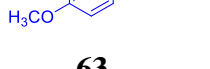
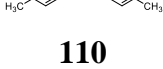
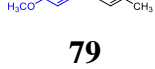
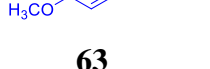
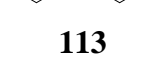
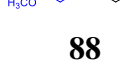


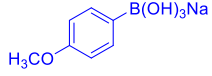
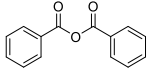
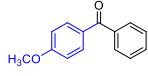
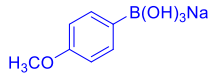
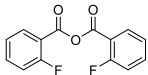
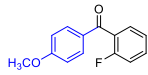
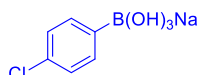
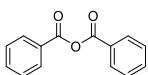
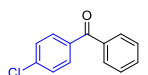
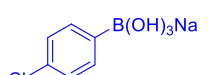
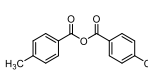
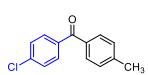
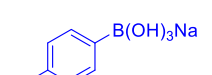
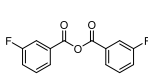
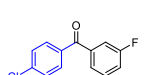
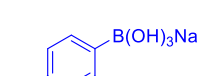
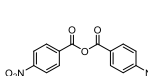
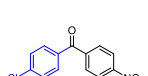
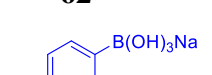
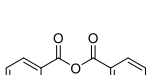
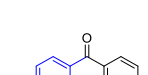
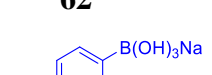
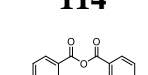
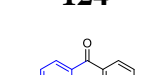
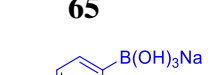
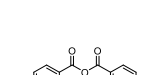
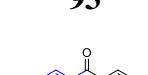
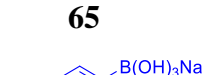

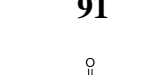
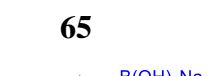
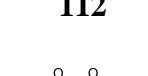
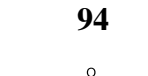
**Figure 3.28:** <sup>1</sup>H NMR spectrum for (4-methylphenyl)(4-trifluorophenyl)methanone (93)

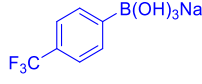
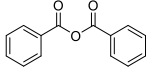
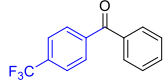
Generally, the cross-coupling reaction of benzoic anhydride bearing electron-withdrawing groups with different sodium (aryl trihydroxyborate) salts bearing electron-withdrawing and donating functionalities proceeded smoothly affording the desired ketones in good to excellent yields (Table 5). However, the reaction conditions seemed very sensitive to benzoic anhydride bearing electron-withdrawing groups. For example, the cross-coupling reaction of 4-nitrobenzoic anhydride with different boronate salts afforded the desired ketones in poor yield or no reaction occurred at all (Table 5, entries 3, 16 and 19). This observation was consistent with other benzoic anhydrides bearing moderate electron-withdrawing groups.

The cross-coupling reactions of 2-fluorobenzoic anhydride with different nucleophiles produced the desired ketones in only trace amounts (Table 5, entries 5, 7, 17 and 21). The cross-coupling reaction of benzoic anhydrides bearing the chloro group was also not successful (Table 5, entry 20). The optimised reaction condition also seemed sensitive to electron-withdrawing group on carboxylic anhydrides (Table 5, entries 17, 19, 20 and 21). Further screening to find optimised reaction conditions to accommodate electron-withdrawing groups are underway.

**Table 5:** Summary of Palladium-Catalysed Suzuki-Miyaura Cross-Coupling Reaction

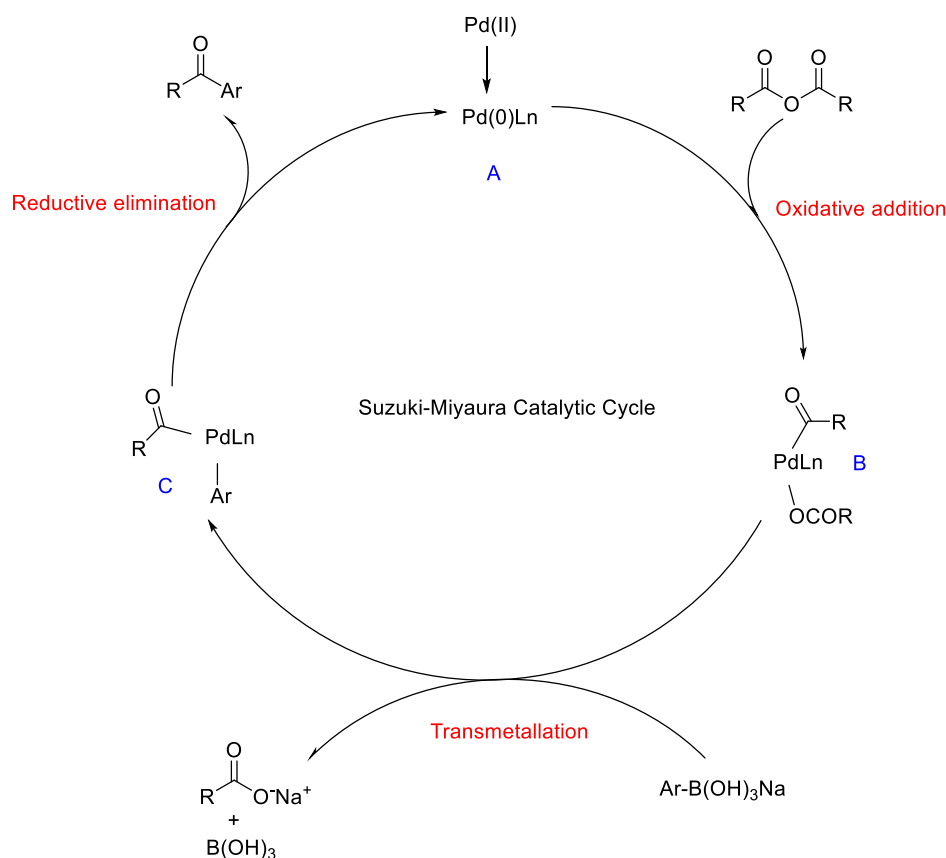
Entry	Sodium (aryl trihydroxyborate)	Carboxylic anhydride	Product	Yield (%)
1	 <b>60</b>	 <b>110</b>	 <b>3</b>	82
2	 <b>60</b>	 <b>52</b>	 <b>41</b>	86
3	 <b>60</b>	 <b>111</b>	 <b>43</b>	46
4	 <b>60</b>	 <b>113</b>	 <b>116</b>	69
5	 <b>60</b>	 <b>114</b>	 <b>117</b>	Trace
6	 <b>61</b>	 <b>110</b>	 <b>69</b>	75
7	 <b>61</b>	 <b>114</b>	 <b>118</b>	Trace
8	 <b>61</b>	 <b>113</b>	 <b>119</b>	Trace
9	 <b>63</b>	 <b>110</b>	 <b>79</b>	N.R
10	 <b>63</b>	 <b>113</b>	 <b>88</b>	N.R

Entry	Sodium (aryl trihydroxyborate)	Carboxylic anhydride	Product	Yield (%)
11	 <b>63</b>	 <b>52</b>	 <b>78</b>	N.R
12	 <b>63</b>	 <b>114</b>	 <b>120</b>	N.R
13	 <b>62</b>	 <b>52</b>	 <b>115</b>	81
14	 <b>62</b>	 <b>110</b>	 <b>121</b>	75
15	 <b>62</b>	 <b>113</b>	 <b>122</b>	64
16	 <b>62</b>	 <b>111</b>	 <b>123</b>	N.R
17	 <b>62</b>	 <b>114</b>	 <b>124</b>	Trace
18	 <b>65</b>	 <b>110</b>	 <b>93</b>	88
19	 <b>65</b>	 <b>111</b>	 <b>91</b>	N.R
20	 <b>65</b>	 <b>112</b>	 <b>94</b>	Trace
21	 <b>65</b>	 <b>114</b>	 <b>125</b>	N.R

Entry	Sodium (aryl trihydroxyborate)	Carboxylic anhydride	Product	Yield (%)
22	 <b>65</b>	 <b>52</b>	 <b>92</b>	83

<sup>a</sup> Reaction conditions: benzoic anhydride (1 mmol), sodium (aryl trihydroxyborate) (1.2 mmol), PdCl<sub>2</sub> (5 mol%), acetone (3 mL), H<sub>2</sub>O (3 mL), 50 °C, 3 hours. <sup>b</sup> Isolated yield

With a successful coupling of carboxylic anhydrides with activated sodium (aryl trihydroxyborate) salts as nucleophilic partners, we proposed that the mechanism of this study is similar to the general Suzuki cross-coupling mechanism but without a base. Oxidative addition of carboxylic anhydride to palladium(0) species **A** form an acyl(carboxylato)palladium species **B** from the C-O cleavage. Since we used activated nucleophiles, sodium (aryl trihydroxyborate) salts transmetallate via the boronate pathway to give acyl(alkyl)palladium species **C**. Reductive addition of acyl and alky moieties produce ketones, and zerovalent palladium species **A** is regenerated which allow the continuation of the cycle (**Figure 3.29**).



**Figure 3.29: Proposed Suzuki Catalytic Cycle**

The application of sodium (aryl trihydroxyborate) salts as nucleophilic partners have brought a great chance to use water as a solvent and eliminate the use of a base which is advantageous in case of base sensitive molecules. This methodology has proven to be cost effective because it is base-free, ligandless and uses water as a co-solvent.

In summary, a novel base-free palladium-catalysed Suzuki-Miyaura cross-coupling between less reactive benzoic acid anhydrides and sodium (aryl trihydroxyborate) salts have been investigated. The outcomes reveal that electron-withdrawing substrates on benzoic acid anhydrides decrease their reactivity furnishing the desired produce in trace amount or in poor yields. Further investigation on how to improve the reactivity on the substrates that were not accommodated under the reported reaction conditions are underway.

### **3.6 Conclusion**

In conclusion, we have successfully developed a base-free Suzuki-Miyaura acylation reaction for the synthesis of biaryl ketones from easily isolated free flowing sodium (aryl trihydroxyborate) salts with excellent yields of 94-98%. With trihydroxyborate reagents in hand, they coupled efficiently with a variety of acyl chlorides furnishing biaryl ketones with yields of up to 96% in 24 h. A wide range of functional groups were tolerated e.g OCH<sub>3</sub>, SCH<sub>3</sub>, CF<sub>3</sub>, F, Cl, Br and including base sensitive functionalities such as OH and NH<sub>2</sub>.

Encouraged by the reactivity of sodium (aryl trihydroxyborate) salts with acyl chlorides in base-free cross-coupling, another study was conducted using more environmentally benign carboxylic acids anhydrides as electrophiles in base-free Suzuki-Miyaura acylation. Carboxylic anhydrides were synthesised following a documented method with excellent yields ranging from 87-99% at room temperature in 1 h. Thereafter, the synthesised carboxylic anhydrides were successfully coupled with isolated yields of up to 88% in 3 hours.

The significance of the study is that it reports on a novel methodology for the preparation of biaryl ketones in mild reaction conditions using base-free palladium-catalysed Suzuki-Miyaura cross-coupling reactions using sodium (aryl trihydroxyborate) salts instead of boronic acids as nucleophiles allowing base sensitive functionalities to be accommodated. In addition, the great application of sodium (aryl trihydroxyborate) salts comes with no addition of a base and they are also pure salts unlike boronic acids which are difficult to isolate with their anhydrides thus complicating the stoichiometric calculation.

### 3.7 References

1. Zhang, J., et al., *Pd-tetraethyl tetra-t-butylcalixarene-tetra (oxyacetate) complex catalyzed acylodeboronation of arylboronic acids with benzoyl chloride or acetic anhydride*. ARKIVOC: Online Journal of Organic Chemistry, 2013.
2. Cho, C.S., K. Itotani, and S. Uemura, *Sodium tetraphenylborate as a phenylating reagent in the palladium-catalyzed phenylation of alkenes and acid chlorides*. Journal of Organometallic Chemistry, 1993. **443**(2): p. 253-259.
3. Medio-Simón, M., et al., *First synthesis of  $\beta$ -Keto sulfoxides by a palladium-catalyzed carbonylative Suzuki reaction*. Organic Letters, 2005. **7**(21): p. 4669-4672.
4. Cammidge, A.N., et al., *Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions*. Organic Letters, 2006. **8**(18): p. 4071-4074.
5. Basu, B., et al., *Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki–Miyaura coupling reaction*. Green Chemistry, 2010. **12**(10): p. 1734-1738.
6. Bjerglund, K.M., T. Skrydstrup, and G.A. Molander, *carbonylative Suzuki couplings of aryl bromides with boronic acid derivatives under base-free conditions*. Organic Letters, 2014. **16**(7): p. 1888-1891.
7. Haddach, M. and J.R. McCarthy, *A new method for the synthesis of ketones: The palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids*. Tetrahedron Letters, 1999. **40**(16): p. 3109-3112.
8. Kakino, R., I. Shimizu, and A. Yamamoto, *Synthesis of trifluoromethyl ketones by palladium-catalyzed cross-coupling reaction of phenyl trifluoroacetate with organoboron compounds*. Bulletin of the Chemical Society of Japan, 2001. **74**(2): p. 371-376.
9. Chen, Q., et al., *Nickel-catalyzed cross-coupling of carboxylic anhydrides with arylboronic acids*. RSC Advances, 2014. **4**(96): p. 53885-53890.
10. Korolev, D. and N. Bumagin, *Palladium-catalyzed reactions of arylboron compounds with carboxylic acid chlorides*. Russian Chemical Bulletin, 2004. **53**(2): p. 364-369.
11. Nagai, D. and H. Goto, *Effective heterogeneous catalyst for Suzuki–Miyaura cross-coupling in aqueous media: Melamine Cyanurate Complex Containing Pd Species*. Bulletin of the Chemical Society of Japan, 2017. **91**(2): p. 147-152.
12. Wang, X., et al., *Palladium-catalyzed denitrogenative synthesis of aryl ketones from arylhydrazines and nitriles using  $O_2$  as sole oxidant*. The Journal of Organic Chemistry, 2017. **82**(4): p. 2211-2218.
13. Zarei, A., A.R. Hajipour, and L. Khazdooz, *Friedel–Crafts acylation of aromatic compounds with carboxylic acids in the presence of  $P_2O_5/SiO_2$  under heterogeneous conditions*. Tetrahedron Letters, 2008. **49**(47): p. 6715-6719.
14. Charvátová, H., I. Císařová, and P. Štěpnička, *Synthesis of phosphanylferrocenecarboxamides bearing guanidinium substituents and their application in the palladium-catalyzed cross coupling of boronic acids with acyl chlorides*. European Journal of Inorganic Chemistry, 2017. **(2)**: p. 288-296.
15. Li, X. and G. Zou, *Acylative Suzuki coupling of amides: acyl-nitrogen activation via synergy of independently modifiable activating groups*. Chemical Communications, 2015. **51**(24): p. 5089-5092.
16. Parella, R., A. Kumar, and S.A. Babu, *Catalytic Friedel–Crafts acylation: magnetic nanopowder  $CuFe_2O_4$  as an efficient and magnetically separable catalyst*. Tetrahedron Letters, 2013. **54**(13): p. 1738-1742.
17. Tran, P.H., et al., *Erbium trifluoromethanesulfonate catalyzed Friedel–Crafts acylation using aromatic carboxylic acids as acylating agents under monomode-microwave irradiation*. Tetrahedron Letters, 2015. **56**(4): p. 612-618.

18. Xin, B., Y. Zhang, and K. Cheng, *The surfactant-promoted cross-coupling reactions of arylboronic acids with carboxylic anhydrides or acyl chlorides in water*. *Synthesis*, 2007. **13**: p. 1970-1978.
19. Poláčková, V., Š. Toma, and I. Augustínová, *Microwave-promoted cross-coupling of acid chlorides with arylboronic acids: a convenient method for preparing aromatic ketones*. *Tetrahedron*, 2006. **62**(50): p. 11675-11678.
20. Gujral, S.S., et al., *Suzuki cross coupling reaction-a review*. *Indo Global Journal of Pharmaceutical Sciences*, 2012. **2**: p. 351-367.
21. Miyaura, N., K. Yamada, and A. Suzuki, *A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides*. *Tetrahedron Letters*, 1979. **20**(36): p. 3437-3440.
22. Miyaura, N. and A. Suzuki, *Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst*. *Journal of the Chemical Society, Chemical Communications*, 1979(19): p. 866-867.
23. Miyaura, N., et al., *Novel and convenient method for the stereo- and regio-specific synthesis of conjugated alkenes and alkenynes via the palladium-catalyzed cross-coupling reaction of 1-alkenylboranes with bromoalkenes and bromoalkynes*. *Journal of the American Chemical Society*, 1985. **107**(4): p. 972-980.
24. Lennox, A.J. and G.C. Lloyd-Jones, *Transmetalation in the Suzuki–Miyaura coupling: The fork in the trail*. *Angewandte Chemie International Edition*, 2013. **52**(29): p. 7362-7370.
25. Braga, A.A., et al., *Computational characterization of the role of the base in the Suzuki–Miyaura cross-coupling reaction*. *Journal of the American Chemical Society*, 2005. **127**(25): p. 9298-9307.
26. Braga, A.A., et al., *Computational study of the transmetalation process in the Suzuki–Miyaura cross-coupling of aryls*. *Journal of Organometallic Chemistry*, 2006. **691**(21): p. 4459-4466.
27. Sicre, C., et al., *Mechanistic insights into the transmetalation step of a Suzuki–Miyaura reaction of 2 (4)-bromopyridines: characterization of an intermediate*. *Tetrahedron*, 2008. **64**(30): p. 7437-7443.
28. Xue, L. and Z. Lin, *Theoretical aspects of palladium-catalysed carbon–carbon cross-coupling reactions*. *Chemical Society Reviews*, 2010. **39**(5): p. 1692-1705.
29. Matos, K. and J.A. Soderquist, *Alkylboranes in the Suzuki–Miyaura coupling: Stereochemical and mechanistic studies*. *The Journal of Organic Chemistry*, 1998. **63**(3): p. 461-470.
30. Nunes, C.M. and A.L. Monteiro, *Pd-catalyzed Suzuki cross-coupling reaction of bromostilbene: insights on the nature of the boron species*. *Journal of the Brazilian Chemical Society*, 2007. **18**(7): p. 1443-1447.
31. Sithebe, S. and P. Molefe, *Base free Suzuki acylation reactions of sodium (aryl trihydroxyborate) salts: A novel synthesis of substituted aryl ketones*. *Journal of Organometallic Chemistry*, 2017. **846**: p. 305-311.
32. Liebeskind, L.S. and J. Srogl, *Thiol ester–boronic acid coupling. A mechanistically unprecedented and general ketone synthesis*. *Journal of the American Chemical Society*, 2000. **122**(45): p. 11260-11261.
33. Ogiwara, Y., et al., *Acid Fluorides as Acyl Electrophiles in Suzuki–Miyaura Coupling*. *European Journal of Organic Chemistry*, 2017.
34. Gooßen, L.J. and K. Ghosh, *Palladium-catalyzed synthesis of aryl ketones from boronic acids and carboxylic acids or anhydrides*. *Angewandte Chemie*, 2001. **113**(18): p. 3566-3568.
35. Goossen, L. and K. Ghosh, *Method for producing ketones from carboxylic acid anhydrides*. 2005, Google Patents.
36. Dhimitruka, I. and J. SantaLucia, *Investigation of the Yamaguchi esterification mechanism. Synthesis of a Lux-S enzyme inhibitor using an improved esterification method*. *Organic Letters*, 2006. **8**(1): p. 47-50.

37. Gooßen, L.J. and K. Ghosh, *Palladium-catalyzed synthesis of aryl ketones from boronic acids and carboxylic acids activated in situ by pivalic anhydride*. *European Journal of Organic Chemistry*, 2002. **19**: p. 3254-3267.
38. Xin, B.-W., *Synthesis of aryl ketones by cross-coupling reaction of arylboronic acids with carboxylic anhydrides in aqueous phase*. *Synthetic Communications*<sup>®</sup>, 2008. **38**(16): p. 2826-2837.
39. Gooßen, L.J. and K. Ghosh, *A new practical ketone synthesis directly from carboxylic acids: first application of coupling reagents in palladium catalysis*. *Chemical Communications*, 2001(20): p. 2084-2085.



# Chapter 4

## Experimental

### 4.1 Chemical and instrumental information

All reactions were carried out using oven-dried glassware containing a magnetic stirrer bar.  $^1\text{H}$  NMR (400 MHz),  $^{13}\text{C}$  NMR (100 MHz) and  $^{19}\text{F}$  (376.2 MHz) spectra were recorded on a Bruker Avance III NMR (9.4 T) spectrometer in normal glass NMR tubes. All the NMR spectra were recorded using solutions in specified deuterated solvents and are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard.  $^{11}\text{B}$  NMR (128 MHz) spectra were referenced to  $\text{BF}_3\cdot\text{OEt}_2$  (external, neat, with capillary tube of acetone- $d_6$  for the deuterium lock).

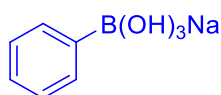
Low resolution (Electron Impact) mass spectra were obtained on a Thermo Finnigan trace GC, coupled with a Polaris Q mass spectrometer. Infrared spectra were recorded using the ID, Fourier Transform Infrared instrument; samples were placed on a diamond and compressed with infrared pressure steel. Purifications of the products were performed by flash-column chromatography and centrifugal preparative thin-layer chromatography (chromatotron) on Fluka silica gel 60 cat No. 70-230 mesh (0.063–0.2 mm) and Merk silica gel cat. No. 1.07749, respectively. Commercially available reagents were used without further purification.

### 4.2 Synthesis of sodium aryl trihydroxyborate salts

#### 4.2.1 General procedure A

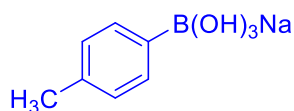
Aryl halide (8.20 mmol), Mg (398.0 mg, 16.40 mmol) and dry THF (50.0 mL) were placed in a 100 mL round-bottomed flask equipped with a Dean and Stark Apparatus, magnetic stirrer bar and reflux condenser. The mixture was stirred at room temperature until the Grignard reagent was formed completely (minimum 30 minutes) and eventually cooled to  $-78\text{ }^\circ\text{C}$ . Trimethyl borate solution (1.83 mL, 16.40 mmol) was added drop-wise at  $-78\text{ }^\circ\text{C}$  and the mixture was stirred overnight. THF was removed under reduced pressure leaving a white precipitate which was dissolved in refluxing toluene (30.0 mL) followed by the addition of concentrated NaOH solution until no further precipitation occurred. The precipitate was filtered under vacuum, dried in an oven and used without further purification [1].

#### 4.2.2 Synthesis of sodium (phenyltrihydroxyborate) (60)



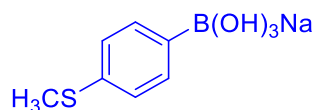
**Sodium (phenyltrihydroxyborate) (60):** Following the general procedure A, [1] compound **60** was obtained as cream white powder (95%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 7.16-7.21 (m, 1H), 7.25-7.30 (m, 2H), 7.53 (d,  $J = 6.79$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 125.7, 127.3, 131.3, 167.7.  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3.1 (s). Anal. calcd. for  $\text{C}_6\text{H}_5\text{NaBO}_3$ : C, 44.50, H, 4.98 Found C, 44.45, H, 4.92.

#### 4.2.3 Synthesis of sodium (4-methylphenyltrihydroxyborate) (61)



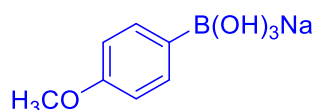
**Sodium (4-methylphenyltrihydroxyborate) (61):** Following the general procedure A, [1] compound **61** was obtained as cream white powder (98%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 2.28 (s, 3H), 7.14 (d,  $J = 7.44$  Hz, 2H), 7.45 (d,  $J = 7.73$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 20.2, 127.9, 131.5, 135.4, 168.0.  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3.2 (s). Anal. calcd. for  $\text{C}_7\text{H}_{10}\text{NaBO}_3$ : C, 47.78, H, 5.72 Found C, 44.71, H, 5.68.

#### 4.2.4 Synthesis of sodium (4-methylthiophenyltrihydroxyborate) (64)



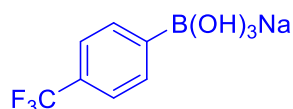
**Sodium (4-methylthiophenyltrihydroxyborate) (64):** Following the general procedure A, [1] compound **64** was obtained as white powder (94%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 2.47 (s, 3H), 7.25 (d,  $J = 8.20$  Hz, 2H), 7.52 (d,  $J = 8.27$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 15.1, 125.9, 132.2, 133.7, 165.0.  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3.8 (s). Anal. calcd. for  $\text{C}_7\text{H}_{10}\text{NaBO}_3\text{S}$ : C, 40.42, H, 4.84, S, 7.69 Found C, 40.39, H, 4.80, S, 7.79.

#### 4.2.5 Synthesis of sodium (4-methoxyphenyltrihydroxyborate) (63)



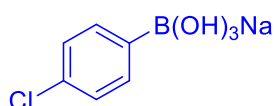
**Sodium (4-methoxyphenyltrihydroxyborate) (63):** Following the general procedure A, [1] compound **63** was obtained as white powder (97%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3.80 (s, 3H), 6.91 (d,  $J = 8.56$  Hz, 2H), 7.49 (d,  $J = 8.56$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 55.23, 112.8, 132.6, 157.0, 167.6.  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3.4 (s). Anal. calcd. for  $\text{C}_7\text{H}_{10}\text{NaBO}_4$ : C, 43.79, H, 5.25 Found C, 43.71, H, 5.22.

#### 4.3.6 Synthesis of sodium (4-trifluoromethylphenyltrihydroxyborate) (65)



**Sodium (4-trifluoromethylphenyltrihydroxyborate) (65):** Following the general procedure A, [1] compound **65** was obtained as white powder (98%):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 7.56 (d,  $J = 7.99$  Hz, 2H), 7.68 (d,  $J = 7.67$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 126.3, 126.4, 126.9 (q,  $1\text{JCF} = 33$  Hz), 168.0.  $^{19}\text{F}$  NMR (376.2 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 63.6 (s).  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 2.5 (s). Anal. calcd. for  $\text{C}_7\text{H}_7\text{NaBO}_3$ : C, 36.53, H, 3.07 Found C, 36.46, H, 3.03.

#### 4.3.7 Synthesis of sodium (4-chlorophenyltrihydroxyborate) (62)



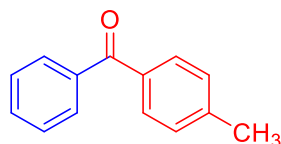
**Sodium (4-chlorophenyltrihydroxyborate) (62):** Following the general procedure A, [1] compound **62** was obtained as white powder (96 %):  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 7.32 (d,  $J = 8.54$ , 2H), 7.53 (d,  $J = 8.84$ , 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm (C-B is not observed) 126.97, 130.86, 132.96, 162.75.  $^{11}\text{B}$  NMR (128 MHz,  $\text{D}_2\text{O}$ ):  $\delta$ ppm 3 (s).

## 4.4 Synthesis of ketones

### 4.4.1 General procedure B

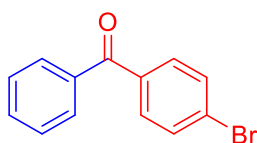
The corresponding borate salt (1 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.01 mmol, 11.56 mg), degassed toluene (2 mL), degassed water (0.50 mL) were placed in a 50 mL round-bottomed flask with a magnetic stirrer bar and a rubber septum. The contents of the flask were kept under argon while acyl chloride (1.1 mmol), dissolved in degassed toluene (1.0 mL), was added drop-wise via a syringe and the flask was heated to 60 °C on the oil bath. After 24 hours, the reaction mixture was filtered and solvent removed under *vacuo*. The resulting residue was dissolved in DCM and was purified using flash-column chromatography or centrifugal preparative thin-layer chromatography (chromatotron) using hexane: ethyl acetate (9:1) as an eluent.

### 4.4.2 Synthesis of phenyl(*p*-tolyl)methanone (**3**)



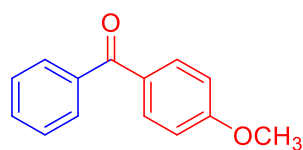
**Phenyl(*p*-tolyl)methanone (**3**):** Following the general procedure B, [2] compound **3** was obtained as white crystalline solid (88%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 7.45–7.51 (m, 2H), 7.56–7.61 (m, 1H), 7.78–7.82 (m, 2H). <sup>13</sup>C NMR (100. MHz, CDCl<sub>3</sub>): δppm 128.3, 130.1, 132.4, 137.6, and 196.75. MS (EI), *m/z* (%): 39 (5), 51 (10), 65 (11), 77 (22), 91 (30), 105 (30), 119 (100), 196 [M<sup>+</sup>] (60).

### 4.4.3 Synthesis of (4-bromophenyl)(phenyl)methanone (**68**)



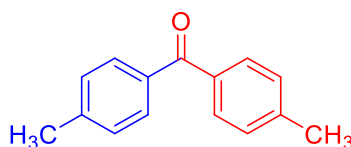
**(4-Bromophenyl)(phenyl)methanone (**68**):** Following the general procedure B, [3] compound **68** was obtained as crystalline solid (74%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 7.48-754 (m, 2 H), 7.60-7.73 (m, 5H), 7.78-7.82 (m, 2 H). <sup>13</sup>C NMR (100. MHz, CDCl<sub>3</sub>): δppm 127.5, 128.4, 129.9, 131.5, 131.6, 132.6, 136.3, 137.2 and 195.6. MS (EI), *m/z* (%): 51 (12), 77 (42), 105 (100), 152 (10), 183 (25), 260 [M<sup>+</sup>] (50).

#### 4.4.4 Synthesis of (4-methoxyphenyl)(phenyl)methanone (78)



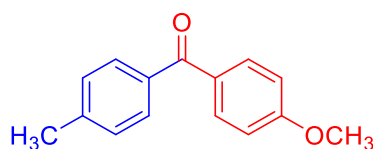
**(4-Methoxyphenyl)(phenyl)methanone (78):** Following the general procedure B, [4] compound **78** was obtained as white crystalline solid (79%):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 3.87 (s, 3H), 6.95–6.98 (m, 2H), 7.46 (t, 7.6 Hz, 2H), 7.56 (t,  $J = 7.2$  Hz, 1H), 7.74–7.76 (m, 2H), 7.81–7.84 (m, 2H).  $^{13}\text{C NMR}$  (100. MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  55.5, 113.5, 128.1, 129.7, 130.2, 131.8, 132.5, 138.3, 163.2 and 195.5 MS (EI),  $m/z$  (%): 50 (8), 77 (25), 105 (25), 151 (100), 228 [ $\text{M}^+$ ] (58).

#### 4.4.5 Synthesis of bis(p-tolyl)methanone (69)



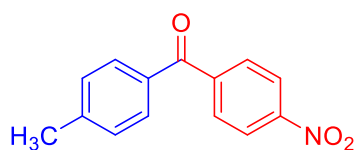
**Bis(p-tolyl)methanone (69):** Following the general procedure B, [5] compound **69** was obtained as white powder (94%) :  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  2.46 (s, 3H), 7.30 (d,  $J = 8.01$  Hz, 4H), 7.73 (d,  $J = 8.05$  Hz, 4H).  $^{13}\text{C NMR}$  (100. MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  21.6, 128.9, 130.1, 135.2, 142.9 and 196.2. MS (EI),  $m/z$  (%): 39 (4), 65 (15), 91 (31), 119 (100), 195 (10), 210 [ $\text{M}^+$ ] (31).

#### 4.4.6 Synthesis of (4-methoxyphenyl)(p-tolyl)methanone (79)



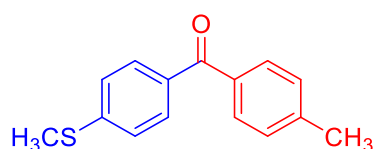
**(4-Methoxyphenyl)(p-tolyl)methanone (79):** Following the general procedure B, [6] compound **79** was obtained as white solid (86%):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  2.44 (s, 3H), 3.94 (s, 3H), 7.00 (d,  $J = 7.6$  Hz, 2H), 7.30 (d,  $J = 7.6$  Hz, 2H), 7.71 (d,  $J = 8.0$  Hz, 2H), 7.84 (d,  $J = 8.4$  Hz, 2H).  $^{13}\text{C NMR}$  (100. MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  21.6, 55.4, 113.5, 128.8, 130.0, 130.5, 132.4, 135.5, 142.6, 163.0 and 195.3. MS (EI),  $m/z$  (%): 65 (8), 77 (15), 91 (21), 107 (9), 119 (25), 135 (100), 211 (13), 226 [ $\text{M}^+$ ] (50).

#### 4.4.7 Synthesis of (4-nitrophenyl)(p-tolyl)methanone (12)



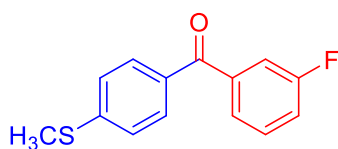
**(4-Nitrophenyl)(p-tolyl)methanone (12):** Following the general procedure B, [7] compound **12** was obtained as white solid (67%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.51 (s, 3H), 7.35 (d,  $J = 7.6$  Hz, 2H), 7.95 (d,  $J = 7.6$  Hz, 2H), 8.46 (d,  $J = 8.0$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 21.7, 123.4, 129.3, 130.3, 130.5, 133.6, 143.3, 144.5, 149.7 and 194.5. MS (EI),  $m/z$  (%): 39 (9), 50 (9), 65 (17), 76 (10), 91 (39), 104 (5), 119 (100), 241 [ $\text{M}^+$ ] (20).

#### 4.4.8 Synthesis of (4-methylthiophenyl)(p-tolyl)methanone (81)



**(4-Methylthiophenyl)(p-tolyl)methanone (81):** Following the general procedure B, [8] compound **81** was obtained as pale yellow product (74%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.46 (s, 3H), 2.55 (s, 3H), 7.29-7.35 (m, 4H), 7.71 (d,  $J = 8.13$  Hz, 2H), 7.75 (d,  $J = 8.18$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 14.9, 21.6, 124.8, 126.2, 128.9, 129.5, 130.0, 130.5, 130.6, 134.0, 135.1, 142.9, 144.9, 145.5, 162.5 and 195.5. MS (EI),  $m/z$  (%): 65 (18), 91 (33), 119 (63), 151 (100), 195 (12), 242 [ $\text{M}^+$ ] (80).

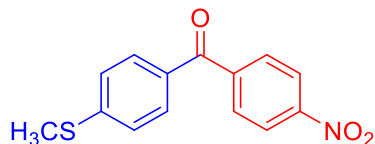
#### 4.4.9 Synthesis of (4-methylthiophenyl)(3-fluorophenyl)methanone (82)



**(4-Methylthiophenyl)(3-fluorophenyl)methanone (82):** Following the general procedure B, [9] compound **82** was obtained as white powder (86%) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.57 (s, 3H), 7.27-7.36 (m, 3H), 7.44-7.54 (m, 2H), 7.53-7.58 (m, 1H), 7.76 (d,  $J = 8.51$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 14.8, 116.5 (d,  $2\text{JCF} = 22$  Hz, 2C), 119.1 (d,  $2\text{JCF} = 22$  Hz, 2C), 124.9, 125.5, 127.1 (d,  $3\text{JCF} = 8$  Hz, 2C), 129.9 (d,  $3\text{JCF} = 8$  Hz, 2C), 130.5, 133.0, 139.9 (d,  $3\text{JCF} = 6.6$  Hz, 2C), 145.9, 161.1 (d,  $1\text{JCF} = 250$  Hz, 2C), and 194.2.  $^{19}\text{F}$

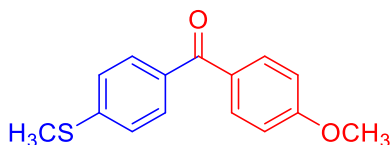
NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -111.4 (s).MS (EI), *m/z* (%): 95 (20), 123 (30), 151 (2), 151 (100), 246 [M<sup>+</sup>] (68).

#### 4.4.10 Synthesis of (4-methylthiophenyl)(4-nitrophenyl)methanone (71)



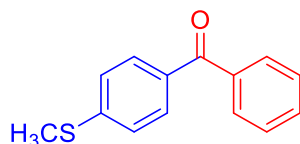
**(4-Methylthiophenyl)(4-nitrophenyl)methanone (71):** Following the general procedure B, [7] compound **71** was obtained as yellow crystals (69%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 2.58 (s, 3H), 7.34 (d, *J* = 8.50 Hz, 2H), 7.75 (d, *J* = 8.77Hz, 2H), 7.92 (d, *J* = 8.82 Hz, 2H), 8.36 (d, *J* = 8.80 Hz, 2H). <sup>13</sup>C NMR (100. MHz, CDCl<sub>3</sub>): δppm 14.7, 123.5, 125.0, 130.4, 132.2, 143.3, 147.0, 149.7 and 193.7. MS (EI), *m/z* (%): 77 (67), 122 (12), 123 (45), 151 (100), 150 (45), 227 (89), 273 [M<sup>+</sup>] (24).

#### 4.4.11 Synthesis of (4-methylthiophenyl)(4-methoxyphenyl)methanone (73)



**(4-Methylthiophenyl)(4-methoxyphenyl)methanone (73):** Following the general procedure B, [8] compound **73** was obtained as colourless crystals (94%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 2.56 (s, 3H), 3.91 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δppm 14.9, 55.4, 113.5, 124.9, 130.3, 132.3, 134.4, 144.4, 163.0, 194.6. MS (EI), *m/z* (%): MS (EI), *m/z* (%): 65 (18), 91 (33), 119 (63), 151 (100), 195 (12), 258 [M<sup>+</sup>] (80).

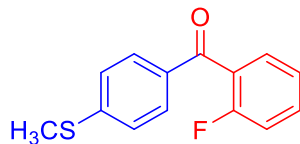
#### 4.4.12 Synthesis of (4-methylthiophenyl)(phenyl)methanone (83)



**(4-Methylthiophenyl)(phenyl)methanone (83):** Following the general procedure B, [8] compound **83** was obtained as yellow crystalline solid (89%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 2.56 (s, 3H), 7.28–7.36 (m, 2H), 7.47–7.54 (m, 2H), 7.57–7.63 (m, 1H), 7.75–7.82 (m,

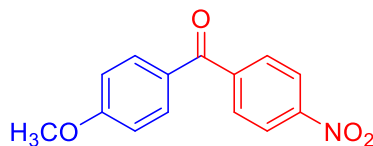
4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 14.8, 124.8, 127.1, 128.2, 129.8, 130.6, 132.1, 133.7, 137.9, 145.3 and 195.7. MS (EI),  $m/z$  (%): 50 (8), 77 (25), 105 (25), 151 (100), 228 [ $\text{M}^+$ ] (58).

#### 4.4.13 Synthesis of (4-methylthiophenyl)(2-fluorophenyl)methanone (84)



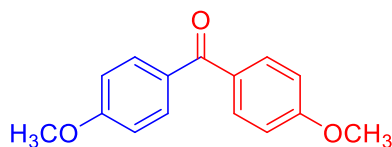
**(4-Methylthiophenyl)(2-fluorophenyl)methanone (84):** Following the general procedure B, [11] compound **84** was obtained as colourless crystals (51%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.54 (s, 3H), 7.14-7.21 (m, 1H), 7.25-7.34 (m, 3H), 7.50-7.58 (m, 2H), 7.74-7.81 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 14.7, 116.2 (d,  $2\text{JCF} = 22$  Hz, 2C), 124.2, 124.8, 127.2, 130.6 (d,  $3\text{JCF} = 3$  Hz, 2C), 132, 133.5, 146.6, 158.6, 161.1 (d,  $1\text{JCF} = 250$  Hz, 2C) and 192.3.  $^{19}\text{F}$  NMR (376.2 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm -63.6 (s). MS (EI),  $m/z$  (%): 95 (20), 123 (25), 151 (25), 151 (100), 246 [ $\text{M}^+$ ] (60).

#### 4.4.14 Synthesis of (4-methoxyphenyl)(4-nitrophenyl)methanone (85)



**(4-Methoxyphenyl)(4-nitrophenyl)methanone (85):** Following the general procedure B, [8] compound **85** was obtained as colourless solid (64%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 3.93 (s, 3H), 7.02 (d,  $J = 8.76$  Hz, 2H), 7.84 (d,  $J = 8.77$  Hz, 2H), 7.90 (d,  $J = 8.50$  Hz, 2H), 8.35 (d,  $J = 8.45$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 55.6, 114.0, 123.4, 128.9, 130.3, 132.6, 143.8, 149.5, 164.0, and 193.4. MS (EI),  $m/z$  (%): 77 (67), 122 (12), 92 (14), 123 (45), 151 (100), 150 (45), 227 (89), 257.2 [ $\text{M}^+$ ] (45).

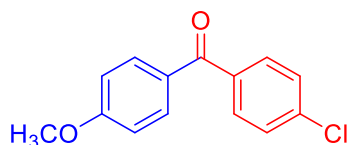
#### 4.4.15 Synthesis of bis(4-methoxyphenyl)methanone (86)





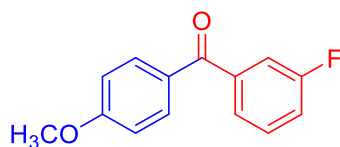
**Bis(4-methoxyphenyl)methanone (86):** Following the general procedure B, [8] compound **86** was obtained as colourless needles (93%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 3.91 (s, 6H), 6.99 (d,  $J = 8.77$  Hz, 4H), 7.81 (d,  $J = 8.75$  Hz, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 55.4, 113.4, 130.8, 132.2, 162.8, and 194.4. MS (EI),  $m/z$  (%): 77 (13), 122 (12), 92 (10), 107 (10), 135 (100), 211 (15), 242 [ $\text{M}^+$ ] (30).

#### 4.4.16 Synthesis of (4-methoxyphenyl)(4-chlorophenyl)methanone (87)



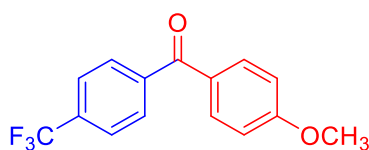
**(4-Methoxyphenyl)(4-chlorophenyl)methanone (87):** Following the general procedure B, [8] compound **87** was obtained as colourless solid (90%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 3.91 (s, 3H), 6.99 (d,  $J = 8.79$  Hz, 2H), 7.47 (d,  $J = 8.48$  Hz, 2H), 7.73 (d,  $J = 8.53$  Hz, 2H), 7.82 (d,  $J = 8.78$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 55.2, 113.7, 128.5, 129.8, 131.1, 132.4, 136.4, 138.2, 163.4, and 194.2. MS (EI),  $m/z$  (%): 77 (15), 92 (10), 111 (15), 135 (100), 246 [ $\text{M}^+$ ] (30).

#### 4.4.17 Synthesis of (4-methoxyphenyl)(3-fluorophenyl)methanone (88)



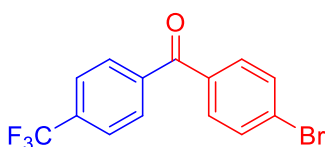
**(4-Methoxyphenyl)(3-fluorophenyl)methanone (88):** Following the general procedure B, [12] compound **88** was obtained as colourless solid (73%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 3.92 (s, 3H), 7.00 (d,  $J = 8.78$  Hz, 2H), 7.25-7.32 (m, 1H), 7.45-7.50 (m, 2H), 7.53-7.58 (m, 1H), 7.84 (d,  $J = 8.99$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 55.5, 113.7, 116.5 (d,  $2\text{JCF} = 22$  Hz, 2C), 118.8 (d,  $2\text{JCF} = 22$  Hz, 2C), 125.4 (d,  $4\text{JCF} = 3$  Hz, 2C), 129.9 (d,  $3\text{JCF} = 8$  Hz, 2C), 132.5, 140.4, 161.2, 163.5 (d,  $1\text{JCF} = 250$  Hz, 2C) and 194.0.  $^{19}\text{F}$  NMR (376.2 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm -111.9 (s). MS (EI),  $m/z$  (%): 64 (2), 77 (12), 95 (10), 107 (9), 123 (5), 135 (100), 230 [ $\text{M}^+$ ] (44).

#### 4.4.18 Synthesis of (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (89)



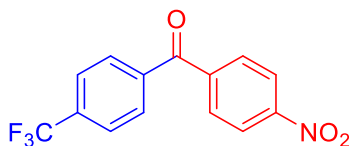
**(4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (89):** Following the general procedure B, [13] compound **89** was obtained as white needle-like crystals (82%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 3.93 (s, 3H), 7.01 (d, J = 8.78 Hz, 2H), 7.77 (d, J = 8.18 Hz, 2H), 7.82-7.90 (m, 4H). <sup>13</sup>C NMR (100. MHz, CDCl<sub>3</sub>): δppm 53.4, 55.5, 113.8, (q, 3JCF = 3.8 Hz), 123.8 (q, 1JCF = 217 Hz) 129.4, 129.7, 133.6 (q, 2JCF = 33 Hz), 141.5, 163.7 and 194.2. <sup>19</sup>F NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.6 (s). MS (EI), *m/z* (%): 77 (11), 92 (12), 107 (12), 135 (100), 145 (9), 280 [M<sup>+</sup>] (33).

#### 4.4.19 Synthesis of (4-bromophenyl)(4-(trifluoromethyl)phenyl)methanone (90)



**(4-Bromophenyl)(4-(trifluoromethyl)phenyl)methanone (90):** Following the general procedure B, [14] compound **90** was obtained as light brown powder (91%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 7.65-7.72 (m, 4H), 7.79 (d, J = 8.18 Hz, 2H), 7.89 (d, J = 8.21 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δppm 53.4, 125.4 (q, 2JCF = 3 Hz), 128.3, 130.0, 131.5, 131.9, 133.8, 134.1 (q, 1JCF = 33 Hz), 135.4, 140.3 and 194.4. <sup>19</sup>F NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.0 (s). MS (EI), *m/z* (%): 50 (40), 75 (49), 95 (13), 125 (15), 155 (29), 173 (62), 183 (100), 330 [M<sup>+</sup>] (15).

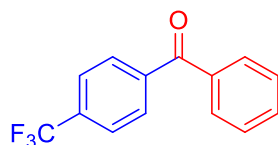
#### 4.4.20 Synthesis of (4-nitrophenyl)(4-(trifluoromethyl)phenyl)methanone (91)



**(4-Nitrophenyl)(4-(trifluoromethyl)phenyl)methanone (91):** Following the general procedure B, [15] compound **91** was obtained as light yellow solid (70%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 7.83 (d, J = 8.18 Hz, 2H), 7.93 (d, J = 8.16 Hz, 2H), 7.98 (d, J = 8.76 Hz, 2H), 8.39 (d, J = 8.77 Hz, 2H). <sup>13</sup>C NMR (100. MHz, CDCl<sub>3</sub>): δppm 123.7, 125.7 (q,

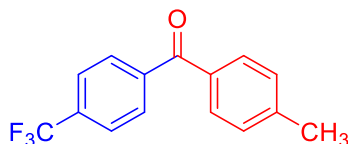
2JCF = 3 Hz), 130.2, 130.8, 134.7 (q, 1JCF = 33 Hz) 139.3, 141.8, 150.2, and 193.6. <sup>19</sup>F NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.1 (s). MS (EI), *m/z* (%): 50 (40), 76 (13), 95 (7), 120 (5), 173 (100), 295 [M<sup>+</sup>] (55).

#### 4.4.21 Synthesis of (4-(trifluoromethyl)phenyl)methanone (92)



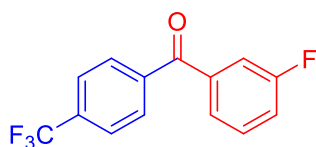
**(4-(Trifluoromethyl)phenyl)methanone (92):** Following the general procedure B, [4] compound **92** was obtained as white powder (86%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 7.50-7.57 (m, 2H), 7.63-7.69 (m, 1H), 7.78 (d, J = 8.20 Hz, 2H), 7.83 (d, J = 8.66 Hz, 2H), 7.92 (d, J = 7.91 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δppm 122.3, 125.3, 125.7 (q, 2JCF = 3 Hz), 128.5, 130.1, 133.2, 133.5, 133.9 (q, 1JCF = 33 Hz), 136.7, 140.7, and 195.5. <sup>19</sup>F NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.6 (s). MS (EI), *m/z* (%): 51 (10), 77 (38), 105 (100), 145 (29), 173 (31), 250 [M<sup>+</sup>] (38).

#### 4.4.22 Synthesis of (p-tolyl)(4-(trifluoromethyl)phenyl)methanone (93)



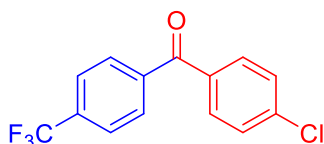
**(p-Tolyl)(4-(trifluoromethyl)phenyl)methanone (93):** Following the general procedure B, [16] compound **93** was obtained as colourless crystals (81%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 2.48 (s, 3H), 7.33 (d, J = 7.85 Hz, 2H), 7.72-7.80 (m, 4H), 7.90 (d, J = 8.21 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δppm 21.69, 125.3, 125.7 (q, 2JCF = 3 Hz), 129.2, 129.9, 130.3, 133.7 (q, 1JCF = 33 Hz), 134.1, 141.1, 144.0, and 195.2. <sup>19</sup>F NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.0 (s). MS (EI), *m/z* (%): 65 (10), 91 (38), 119 (100), 145 (19), 264 [M<sup>+</sup>] (38).

#### 4.4.23 Synthesis of (3-fluorophenyl)(4-(trifluoromethyl)phenyl)methanone (95)



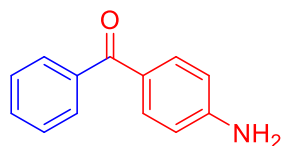
**(3-Fluorophenyl)(4-(trifluoromethyl)phenyl)methanone (95):** Following the general procedure B, [17] compound **95** was obtained as white needle-like crystals (89%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 7.31-7.39 (m, 1H), 7.44-7.50 (m, 1H), 7.71-7.77 (m, 1H), 7.79 (d,  $J = 8.19$  Hz, 2H), 7.92 (d,  $J = 8.19$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 53.4, 116.7 (d,  $2\text{JCF} = 22$  Hz, 2C), 120.1 (d,  $2\text{JCF} = 22$  Hz, 2C), 125.4 (q,  $2\text{JCF} = 3$  Hz), 125.8 (d,  $4\text{JCF} = 3$  Hz, 2C), 128.4, 128.5, 130.2 (d, d,  $3\text{JCF} = 8$  Hz, 2C), 132.3, 132.5, 134 (q,  $2\text{JCF} = 33$  Hz), 140.1, 162.7 (d,  $1\text{JCF} = 250$  Hz, 2C), and 194.1.  $^{19}\text{F}$  NMR (376.2 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm -62.9 (s) and -111.8 (s). MS (EI),  $m/z$  (%): 77 (11), 92 (12), 107 (12), 135 (100), 145 (9), 280 [ $\text{M}^+$ ] (33).

#### 4.4.24 Synthesis of (4-chlorophenyl)(4-(trifluoromethyl)phenyl)methanone (94)



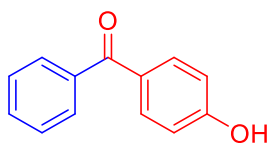
**(4-Chlorophenyl)(4-(trifluoromethyl)phenyl)methanone (94):** Following the general procedure B, [17] compound **94** was obtained as white needle-like crystals (94%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 7.51 (d,  $J = 8.5$  Hz, 2H), 7.76-7.81 (m, 4H), 7.89 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 125.4 (q,  $2\text{JCF} = 3$  Hz), 128.9, 130.0, 131.4, 134 (q,  $2\text{JCF} = 33$  Hz), 135.0, 139.7, 140.3 and 194.2. MS (EI),  $m/z$  (%): 43 (11), 75 (21), 95 (8), 111 (25), 113 (9), 139 (100), 141 (40), 173 (30), 284 [ $\text{M}^+$ ] (30).

#### 4.4.25 Synthesis of (4-Aminophenyl)phenyl-methanone (106)



**(4-Aminophenyl)phenyl-methanone (106):** Following the general procedure B, [18] compound **106** was obtained as yellow crystals (57%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 4.16 (br s,  $\text{NH}_2$ ), 6.68 (d,  $J = 8.7$  Hz, 2H), 7.44-7.51 (m, 2H), 7.52-7.58 (m, 1H), 7.70-7.78 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 113.6, 127.3, 128.1, 129.5, 131.4, 132.9, 138.9, 151.1 and 195.3. MS (EI),  $m/z$  (%): 39 (16), 50 (8), 51 (30), 63 (9), 65 (40), 79 (38), 92 (30), 105 (8), 120 (100), 197 [ $\text{M}^+$ ] (55).

#### 4.4.26 Synthesis of (4-Hydroxyphenyl)phenyl-methanone (107)



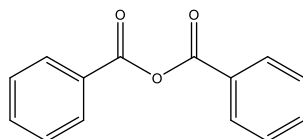
**(4-Hydroxyphenyl)phenyl-methanone (107):** Following the general procedure B, [19] compound **107** was obtained as yellow crystals (64%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 6.98 (d,  $J = 8.7$  Hz, 2H), 7.47-7.53 (m, 2H), 7.57-7.63 (m, 1H), 7.66 (s, 1H), 7.76-7.84 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 115.4, 128.3, 129.4, 129.8, 132.2, 133.2, 138.0, 161.0 and 197.1. MS (EI),  $m/z$  (%): 39(6), 41 (8), 63 (11), 77 (20), 85 (5), 93 (38), 92 (11), 105 (20), 121 (100), 198 [ $\text{M}^+$ ] (55).

### 4.5 Synthesis of anhydrides

#### 4.5.1 General Procedure C

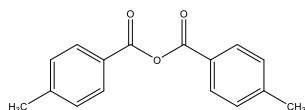
Acyl chloride (0.03 mol, 1eq) and water (0.015 mol, 0.5 eq) were dissolved in acetone (30 mL) in a 100 mL rounded-bottomed flask with magnetic stirrer bar. Triethylamine (0.03 mol, 1 eq) was added drop-wise at room temperature over 1-2 min and the mixture was stirred for 1 hour. Triethylammonium chloride was filtered and washed with acetone. Acetone was evaporated then the residue was separated between dichloromethane (3x5 mL) and water (3x1 mL). The organic layer was dried with magnesium sulfate then filtered and evaporated to afford the pure product [20].

#### 4.5.2 Synthesis of benzoic anhydride (52)



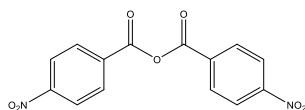
**Benzoic anhydride (52):** Following the general procedure C, [20] compound **52** was afforded as yellow liquid (99%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.14-7.47(m, 4H), 7.58-7.62 (m, 2H), 8.08-8.10 (m, 4H),  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 128.78, 128.96, 130.50, 134.64, 162.41. MS (EI),  $m/z$  (%): 51 (11), 77 (45), 105 (100), 198 (13), 226 [ $\text{M}^+$ ] (12).

#### 4.5.3 Synthesis of 4-methylbenzoic anhydride (110)



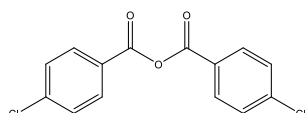
**4-Methylbenzoic anhydride (110):** Following the general procedure C, [20] compound **110** was afforded as a white solid (95%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.02-8.04 (d,  $J=8.22$  Hz, 4H), 7.30-7.32 (d,  $J=8.31$  Hz, 4H), 2.45 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 21.82, 126.26, 129.57, 130.63, 145.54, 162.56. MS (EI),  $m/z$  (%): 65 (9), 91 (21), 119 (100), 226 (8), 254 [ $\text{M}^+$ ] (24).

#### 4.5.4 Synthesis of 4-nitrobenzoic anhydride (111)



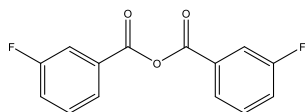
**4-Nitrobenzoic anhydride (111):** Following the general procedure C, [20] compound **111** was synthesised as yellowish solid (92%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.25-8.27 (d,  $J=8.98$  Hz, 4H), 8.31-8.33 (d,  $J=8.86$  Hz, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 124.17, 131.73, 133.49, 151.60, 159.93.

#### 4.5.5 Synthesis of 4-chlorobenzoic anhydride (112)



**4-Chlorobenzoic anhydride (112):** Following the general procedure C, [20] compound **112** was afforded as a reddish solid (93%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.50-7.52 (d,  $J=8.57$  Hz, 4H), 8.06-8.08 (d,  $J=8.61$  Hz, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 127.13, 129.39, 131.89, 141.44, 161.32. MS (EI),  $m/z$  (%): 75 (10), 111 (20), 113 (8), 139 (100), 141 (35), 294 [ $\text{M}^+$ ] (18).

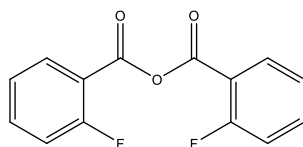
#### 4.5.6 Synthesis of 3-fluorobenzoic anhydride (113)



**3-Fluorobenzoic anhydride (113):** Following the general procedure C, [20] compound **113** was synthesised as a white solid (86%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.35-7.40 (m,

2H), 7.49-7.54 (m, 2H), 7.77-7.81 (m, 2H), 7.92-7.94 (d,  $J=7.78$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 117.10, 121.99, 126.31, 130.76, 160.85, 161.46, 163.93. MS (EI),  $m/z$  (%):50 (7), 69 (7), 75 (21), 95 (48), 123 (100), 262 [ $\text{M}^+$ ] (5).

#### 4.5.7 Synthesis of 2-fluorobenzoic anhydride (114)



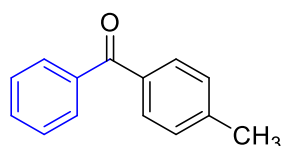
**2-Fluorobenzoic anhydride (114)** :Following the general procedure C, [20] compound **114** was synthesised as a white solid (89%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.17-7.22(m, 2H), 7.26-7.30(m, 2H), 7.61-7.66(m, 2H), 8.05-8.09(m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 117.48, 124.48, 132.93, 136.29, 159.35, 161.26, 163.87. MS (EI),  $m/z$  (%):50 (10), 69 (10), 75 (29), 95 (36), 123 (100), 262 [ $\text{M}^+$ ] (5).

## 4.6 Synthesis of biaryl ketones

### 4.6.1 General procedure D

**General procedure D:** A 100 mL round-bottomed flask with magnetic stirrer bar was charged with benzoic anhydride (1 mmol),  $\text{PdCl}_2$  (5 mol %), acetone (3 mL) and water (3 mL). The mixture was stirred at 50 °C then sodium (aryl trihydroxyborate) (1.2 mmol) was added to afford the desired product in 4 hours. The resulting suspension was filtered then concentrated, and the pure product was obtained by purification using flash-column chromatography or centrifugal preparative thin-layer chromatography (chromatotron) using Hexane: Ethyl acetate (9:1) as an eluent.

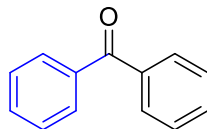
### 4.6.2 Synthesis of phenyl(*p*-toyl)methanone (3)



**Phenyl(*p*-toyl)methanone (3):** Following the general procedure D, [2] compound **3** was obtained as white crystals (82%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.44 (s, 3H), 7.27-7.29 (d,  $J=8.21$  Hz, 2H), 7.45–7.51 (m, 2H), 7.56–7.61 (m, 1H), 7.78–7.82 (m, 2H).  $^{13}\text{C}$  NMR

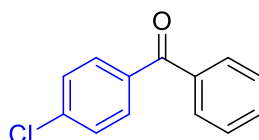
(100 MHz, CDCl<sub>3</sub>): δppm 128.3, 130.1, 132.4, 137.6, and 196.75. MS (EI), *m/z* (%): 39 (5), 51 (10), 65 (11), 77 (22), 91 (30), 105 (30), 119 (100), 196 [M<sup>+</sup>] (60).

#### 4.6.3 Synthesis of benzophenone (41)



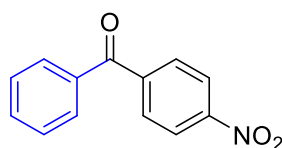
**Benzophenone (41):** Following the general procedure D, [21] compound **41** was obtained as white crystals (86%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δppm: 7.46-7.50 (m, 4H), 7.57-7.61 (m, 2H), 7.80-7.81 (m, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δppm: 127.25, 129.03, 131.37, 136.62, 195.71. MS (EI), *m/z* (%): 50 (22), 77 (61), 105 (100), 181 (8), 182 [M<sup>+</sup>] (41).

#### 4.6.4 Synthesis of (4-chlorophenyl)(phenyl)methanone (115)



**(4-Chlorophenyl)(phenyl)methanone (115):** Following general procedure D, [21] compound **115** was obtained as yellow crystals (81%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δppm: 7.45-7.51 (m, 4H), 7.58-7.62 (m, 1H), 7.74-7.78 (m, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δppm: 128.41, 128.64, 129.93, 131.46, 132.63, 135.92, 137.30, 138.91, 195.48. MS (EI), *m/z* (%): 51 (18), 77 (47), 105 (100), 139 (79), 141 (28), 181 (11), 216 [M<sup>+</sup>] (42).

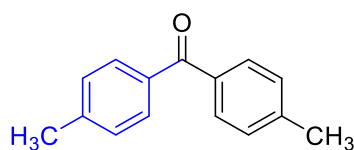
#### 4.6.5 Synthesis of phenyl(4-nitrophenyl)methanone (43)



**Phenyl(4-nitrophenyl)methanone (43)** Following general procedure D, [22] compound **43** was obtained as white crystals (46%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δppm: 7.51-7.54 (m, 2H), 7.64-7.67 (m, 1H), 7.79-7.81 (m, 2H), 7.93-7.95 (m, 2H), 8.33-8.35 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δppm: 123.55, 128.69, 130.10, 130.69, 133.46, 142.93, 149.89, 194.78. MS (EI), *m/z* (%): 51 (9), 77 (43), 105 (100), 150 (11), 227 [M<sup>+</sup>] (39).

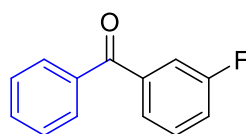


#### 4.6.6 Synthesis of Bis(*p*-tolyl)methanone (**69**)



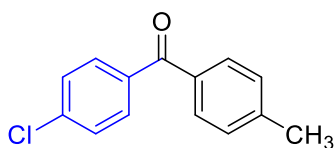
**Bis(*p*-tolyl)methanone (**69**):** Following general procedure D, [5] compound **69** was obtained as white crystals (75%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δppm 2.46 (s, 3H), 7.30 (d, J = 8.01 Hz, 4H), 7.73 (d, J = 8.05 Hz, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δppm 21.6, 128.9, 130.1, 135.2, 142.9 and 196.2. MS (EI), *m/z* (%): 39 (4), 65 (15), 91 (31), 119 (100), 195 (10), 210 [M<sup>+</sup>] (31).

#### 4.6.7 Synthesis of Phenyl(3-fluorophenyl)methanone (**116**)



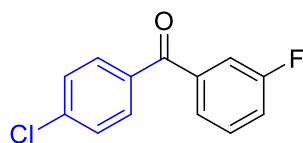
**Phenyl(3-fluorophenyl)methanone (**116**):** Following general procedure D, [23] compound **116** was obtained as white crystals (69%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δppm: 7.26-7.31 (m, 1H), 7.74-7.51 (m, 4H), 7.56-7.63 (m, 2H), 7.70-7.80 (d, J=8.62 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δppm: 116.86, 119.30, 125.82, 128.43, 130.01, 132.76, 139.75, 161.29, 163.75, 195.27. MS (EI), *m/z* (%): 51(19), 77 (60), 95 (29), 105 (100), 123 (77), 180 (5), 200 [M<sup>+</sup>] (50).

#### 4.6.8 Synthesis of (4-chlorophenyl)(4-methylphenyl)methanone (**121**)



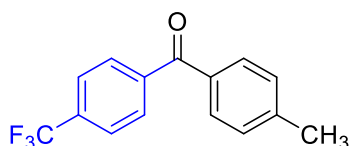
**(4-Chlorophenyl)(4-methylphenyl)methanone (**121**):** Following general procedure D, [24] compound **121** was obtained as white crystals (75%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δppm: 2.45 (s, 3H), 7.28-7.30 (d, J = 7.90 Hz, 2H), 7.44-7.46 (d, J = 8.62 Hz, 2H), 7.67-7.70 (d, J = 8.13 Hz, 2H), 7.72-7.74 (d, J = 7.46 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δppm: 21.66, 128.57, 129.90, 130.18, 131.34, 134.59, 143.53, 195.24.

#### 4.6.9 Synthesis of (4-chlorophenyl)(3-fluorophenyl)methanone (122)



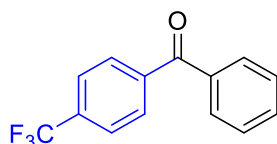
**(4-Chlorophenyl)(3-fluorophenyl)methanone (122):** Following general procedure D, [24] compound **122** was obtained as white crystals (64%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.28-7.32 (m, 1H), 7.46-7.48 (m, 4H), 7.53-7.55 (d,  $J = 7.63$  Hz, 1H), 7.74-7.76 (d,  $J = 8.49$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 116.53, 116.76, 119.55, 119.76, 125.68, 128.81, 130.15, 131.40, 135.34, 139.34, 161.32, 163.79.

#### 4.6.10 Synthesis of (4-(trifluoromethyl)phenyl)(4-methylphenyl)methanone (93)



**(4-(Trifluoromethyl)phenyl)(4-methylphenyl)methanone (93):** Following general procedure D, [16] compound **93** was obtained as white crystals (88%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 2.48 (s, 3H), 7.33 (d,  $J = 7.85$  Hz, 2H), 7.72-7.80 (m, 4H), 7.90 (d,  $J = 8.21$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 21.69, 125.3, 125.7 (q,  $2\text{JCF} = 3$  Hz), 129.2, 129.9, 130.3, 133.7 (q,  $1\text{JCF} = 33$  Hz), 134.1, 141.1, 144.0, and 195.2.  $^{19}\text{F}$  NMR (376.2 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm -63.0 (s). MS (EI),  $m/z$  (%): 65 (10), 91 (38), 119 (100), 145 (19), 264 [ $\text{M}^+$ ] (38).

#### 4.6.11 Synthesis of (4-(trifluoromethyl)phenyl)(phenyl)methanone (92)



**(4-(Trifluoromethyl)phenyl)(phenyl)methanone (92):** Following general procedure D, [4] compound **92** was obtained as white crystals (83%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 7.50-7.57 (m, 2H), 7.63-7.69 (m, 1H), 7.78 (d,  $J = 8.20$  Hz, 2H), 7.83 (d,  $J = 8.66$  Hz, 2H), 7.92 (d,  $J = 7.91$  Hz, 2H).  $^{13}\text{C}$  NMR (100. MHz,  $\text{CDCl}_3$ ):  $\delta$ ppm 122.3, 125.3, 125.7 (q,  $2\text{JCF} = 3$  Hz), 128.5, 130.1, 133.2, 133.5, 133.9 (q,  $1\text{JCF} = 33$  Hz), 136.7, 140.7, and 195.5.  $^{19}\text{F}$

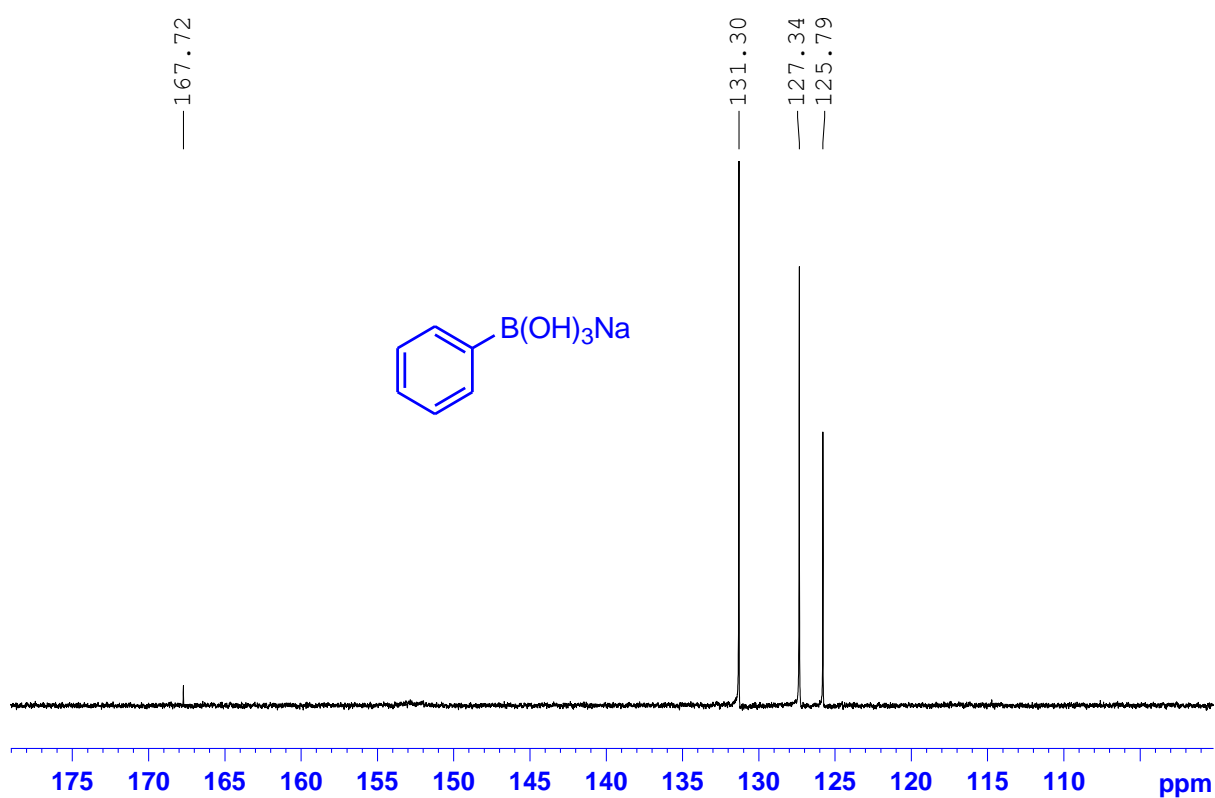
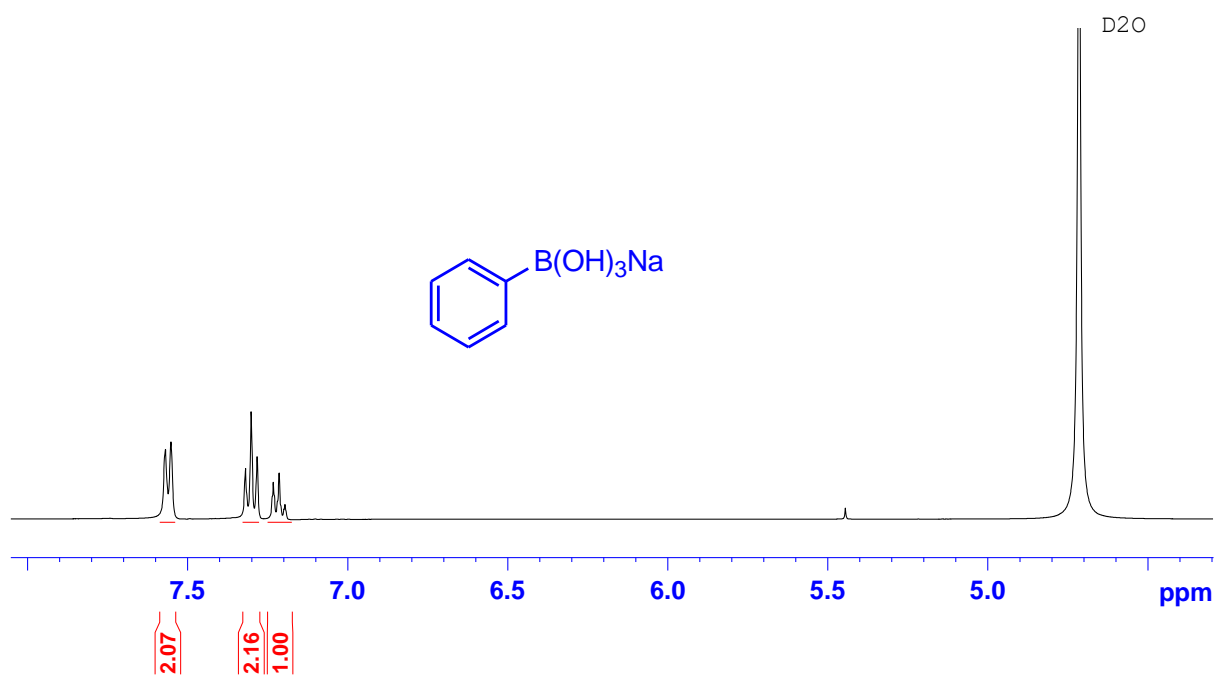
NMR (376.2 MHz, CDCl<sub>3</sub>): δppm -63.6 (s). MS (EI), *m/z* (%): 51 (10), 77 (38), 105 (100), 145 (29), 173 (31), 250 [M<sup>+</sup>] (38).

## 4.7 References

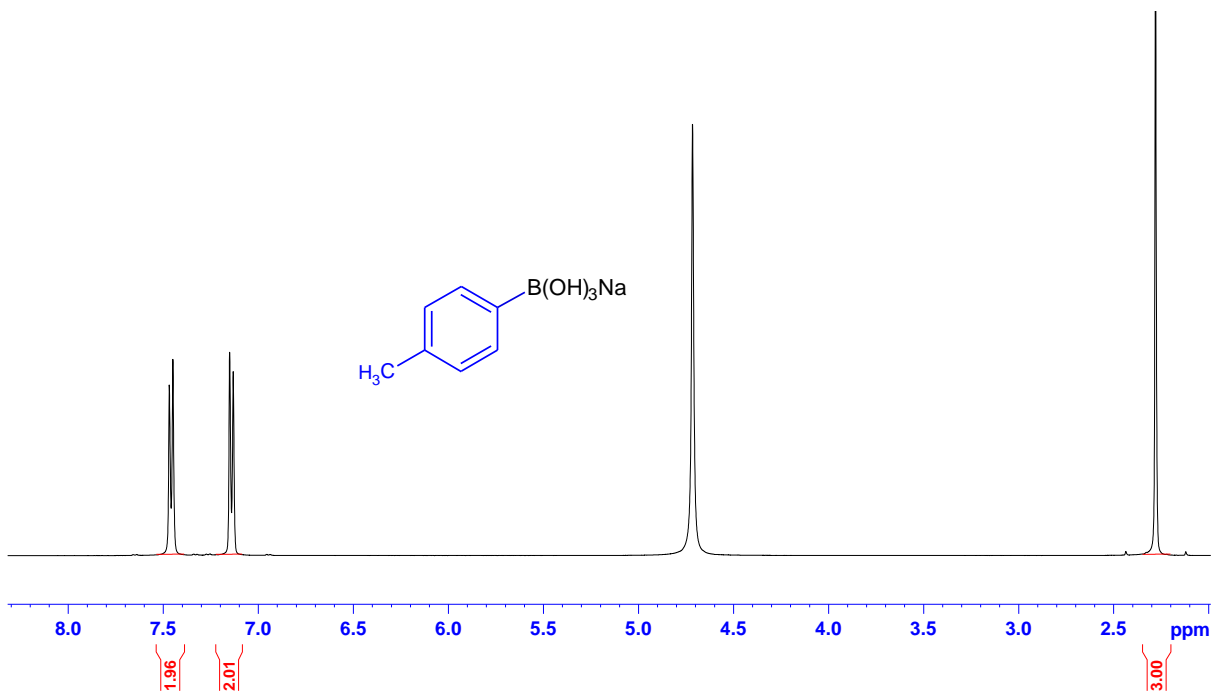
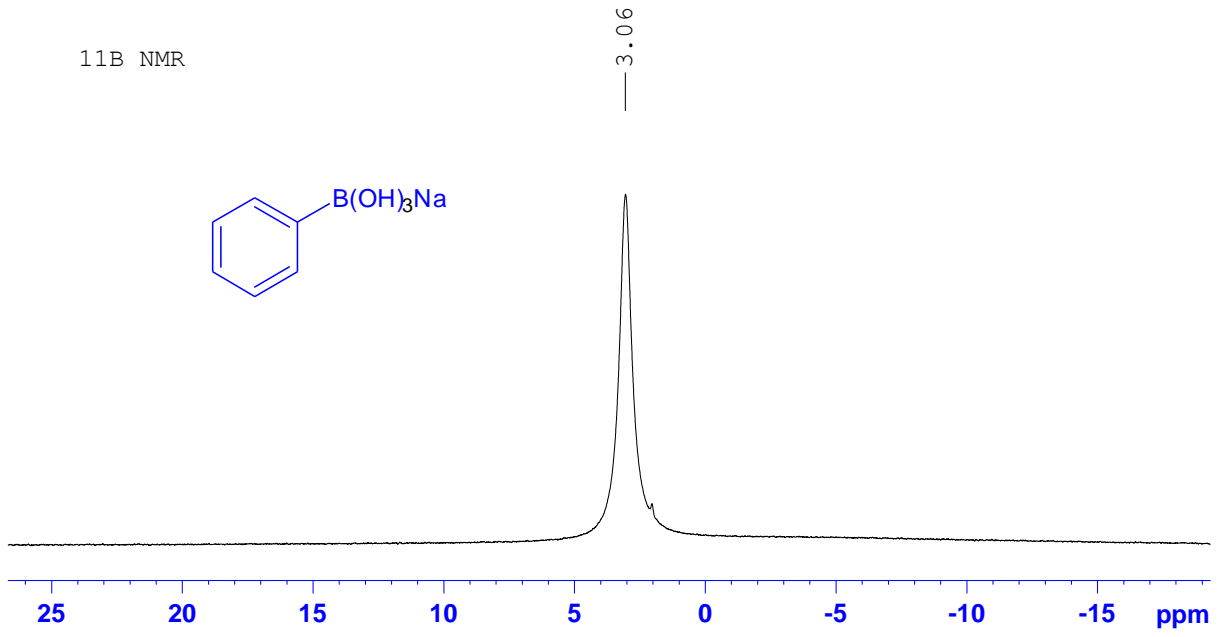
1. Cammidge, A.N., et al., *Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions*. *Organic Letters*, 2006. **8**(18): p. 4071-4074.
2. Haddach, M. and J.R. McCarthy, *A new method for the synthesis of ketones: the palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids*. *Tetrahedron Letters*, 1999. **40**(16): p. 3109-3112.
3. Bumagin, N.A. and D.N. Korolev, *Synthesis of unsymmetric ketones via ligandless Pd-catalyzed reaction of acyl chlorides with organoboranes*. *Tetrahedron Letters*, 1999. **40**(15): p. 3057-3060.
4. Li, X. and G. Zou, *Palladium-catalyzed acylative cross-coupling of amides with diarylboronic acids and sodium tetraarylborates*. *Journal of Organometallic Chemistry*, 2015. **794**: p. 136-145.
5. Wang, X., et al., *Palladium-catalyzed denitrogenative synthesis of aryl ketones from arylhydrazines and nitriles using O<sub>2</sub> as sole oxidant*. *The Journal of Organic Chemistry*, 2017. **82**(4): p. 2211-2218.
6. Lin, X.-F., et al., *NHC–Pd (II)–Im (NHC= N-heterocyclic carbene, Im= 1-methylimidazole) complex catalyzed coupling reaction of arylboronic acids with carboxylic acid anhydrides in water*. *Tetrahedron*, 2012. **68**(29): p. 5806-5809.
7. Zarei, A., A.R. Hajipour, and L. Khazdooz, *Friedel–Crafts acylation of aromatic compounds with carboxylic acids in the presence of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> under heterogeneous conditions*. *Tetrahedron Letters*, 2008. **49**(47): p. 6715-6719.
8. Parella, R., A. Kumar, and S.A. Babu, *Catalytic Friedel–Crafts acylation: magnetic nanopowder CuFe<sub>2</sub>O<sub>4</sub> as an efficient and magnetically separable catalyst*. *Tetrahedron Letters*, 2013. **54**(13): p. 1738-1742.
9. Kulp, S.S. and M.J. McGee, *Oxidative decyanation of benzyl and benzhydryl cyanides. A simplified procedure*. *The Journal of Organic Chemistry*, 1983. **48**(22): p. 4097-4098.
10. Nicolaou, K., P.G. Bulger, and D. Sarlah, *Palladium-catalyzed cross-coupling reactions in total synthesis*. *Angewandte Chemie International Edition*, 2005. **44**(29): p. 4442-4489.
11. Tran, P.H., et al., *Erbium trifluoromethanesulfonate catalyzed Friedel–Crafts acylation using aromatic carboxylic acids as acylating agents under monomode-microwave irradiation*. *Tetrahedron Letters*, 2015. **56**(4): p. 612-618.
12. Sharma, P., S. Rohilla, and N. Jain, *Palladium catalyzed carbonylative coupling for synthesis of arylketones and arylesters using chloroform as the carbon monoxide source*. *The Journal of Organic Chemistry*, 2017. **82**(2): p. 1105-1113.
13. Benischke, A.D., et al., *Iron-Catalyzed Acylation of Polyfunctionalized Aryl- and Benzylzinc Halides with Acid Chlorides*. *Organic Letters*, 2016. **18**(15): p. 3626-3629.
14. Kim, S.-H. and R.D. Rieke, *Direct preparation of arylmanganese bromides using active manganese*. *Synthetic Communications*, 1998. **28**(6): p. 1065-1072.
15. Zhong, Y., et al., *In situ generated nickel nanoparticle-catalyzed carbonylative Suzuki reactions of aryl iodides with arylboronic acids at ambient CO pressure in poly (ethylene glycol)*. *RSC Advances*, 2014. **4**(108): p. 63216-63220.
16. Si, S., et al., *Palladium-catalyzed room-temperature acylative Suzuki coupling of high-order aryl borons with carboxylic Acids*. *The Journal of Organic Chemistry*, 2016. **81**(10): p. 4364-4370.
17. Dohi, S., K. Moriyama, and H. Togo, *Practical one-pot preparation of ketones from aryl and alkyl bromides with aldehydes and DIH via Grignard reagents*. *Tetrahedron*, 2012. **68**(32): p. 6557-6564.
18. Porta, R., et al., *Continuous-flow synthesis of primary amines: Metal-free reduction of aliphatic and aromatic nitro derivatives with trichlorosilane*. *Beilstein Journal of Organic Chemistry*, 2016. **12**: p. 2614.

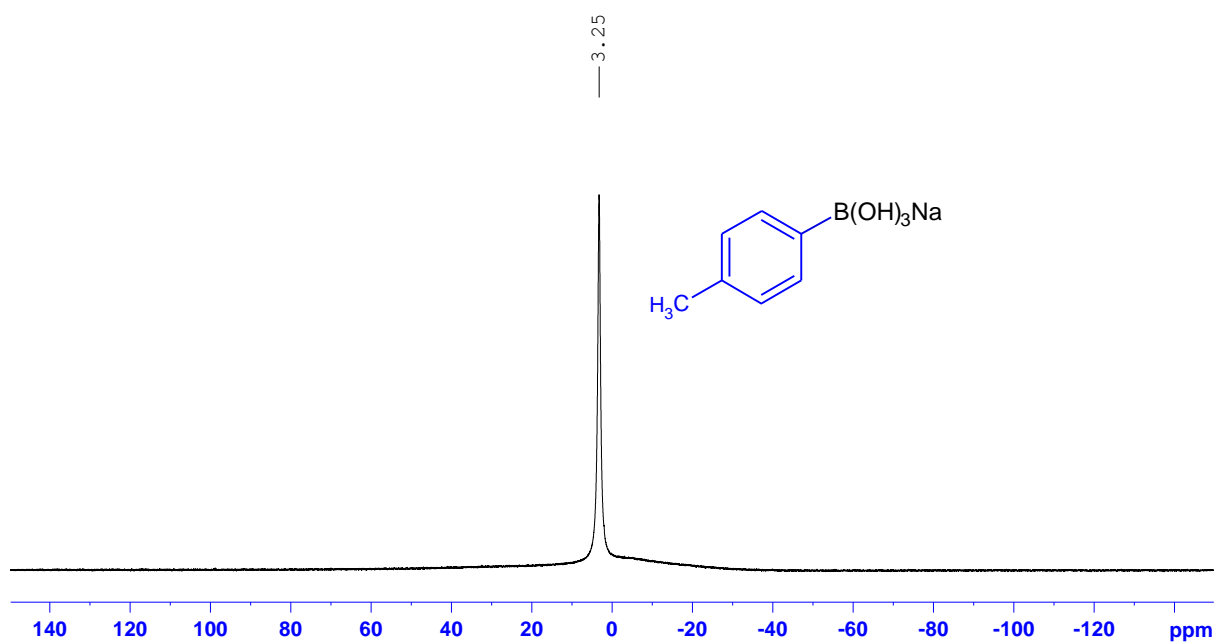
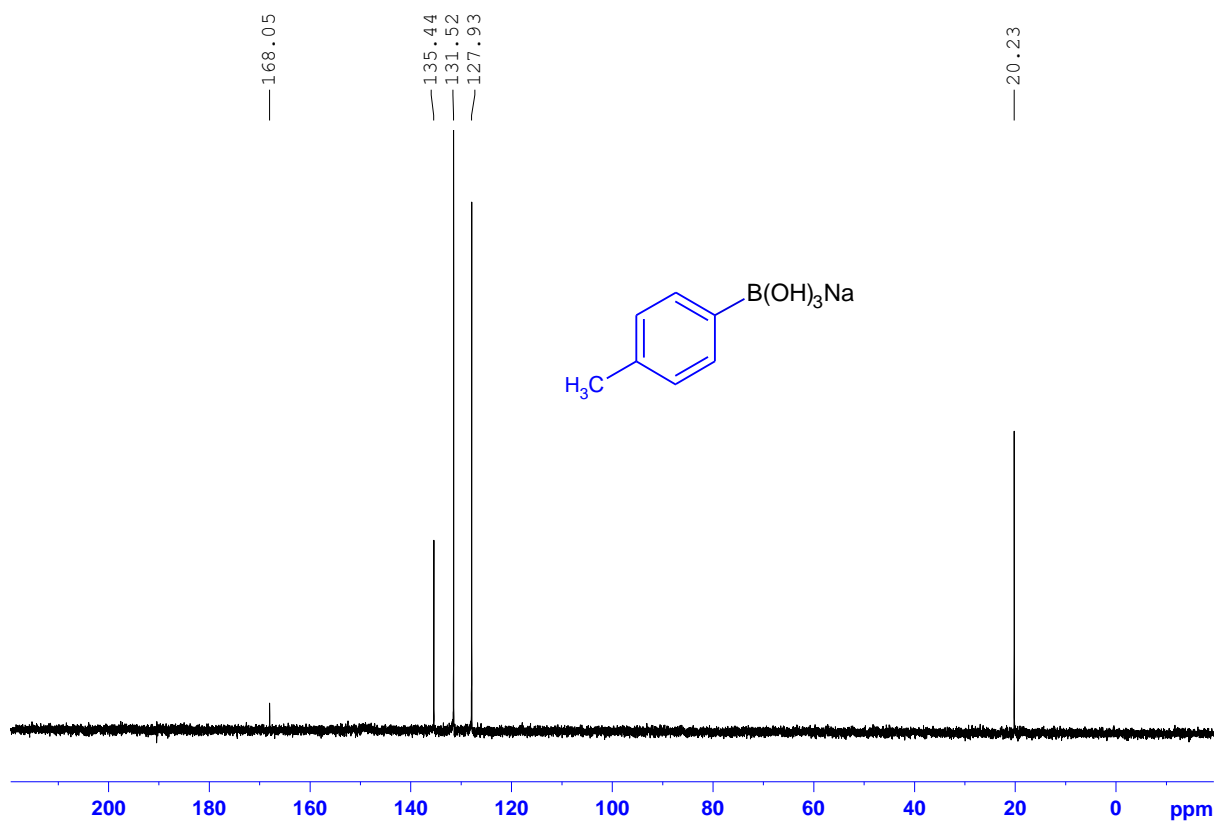
19. Hao, C.Y., et al., *Carbonylative coupling of aryl tosylates/triflates with arylboronic acids under CO atmosphere*. RSC Advances, 2016. **6**(89): p. 86502-86509.
20. Dhimitruka, I. and J. SantaLucia, *Investigation of the Yamaguchi esterification mechanism. Synthesis of a Lux-S enzyme inhibitor using an improved esterification method*. Organic Letters, 2006. **8**(1): p. 47-50.
21. Ekoue-Kovi, K., H. Xu, and C. Wolf, *Palladium-phosphinous acid-catalyzed cross-coupling of aliphatic and aromatic acyl chlorides with boronic acids*. Tetrahedron Letters, 2008. **49**(40): p. 5773-5776.
22. Goossen, L.J., et al., *Pd-catalyzed synthesis of functionalized arylketones from boronic acids and carboxylic acids activated in situ with dimethyl dicarbonate*. Synlett, 2002. 08: p. 1237-1240.
23. Ni, S., et al., *Ni-Catalyzed Reductive Cross-Coupling of Amides with Aryl Iodide Electrophiles via C–N Bond Activation*. Organic Letters, 2017. **19**(10): p. 2536-2539.
24. Jin, F. and W. Han, *Transition-metal-free, ambient-pressure carbonylative cross-coupling reactions of aryl halides with potassium aryltrifluoroborates*. Chemical Communications, 2015. **51**(44): p. 9133-9136.

# Appendix

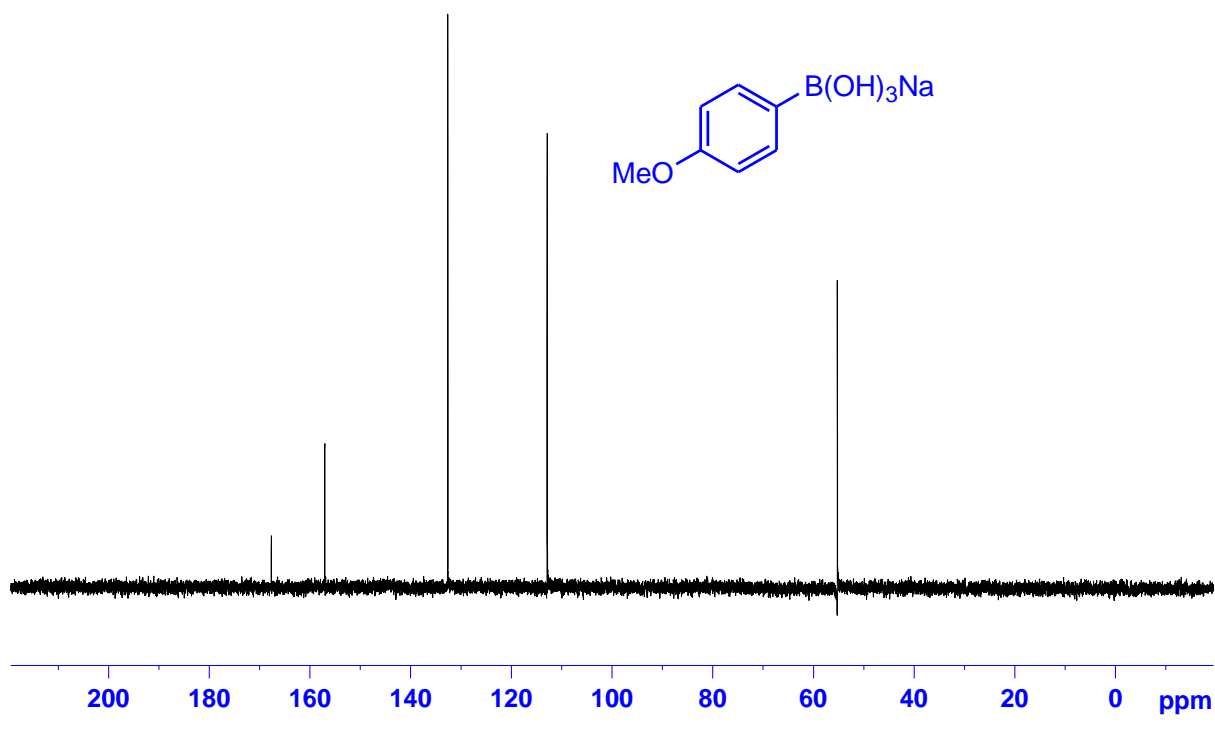
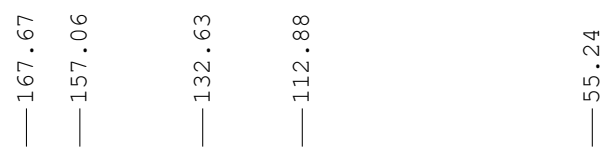
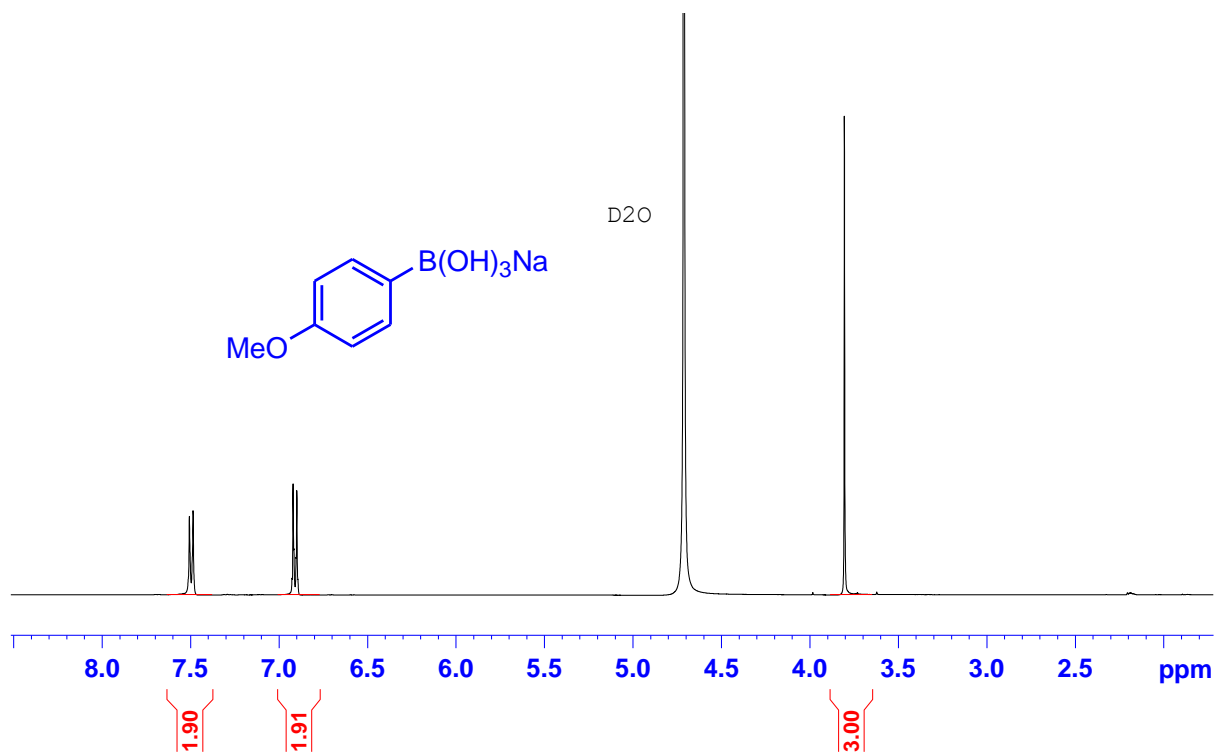


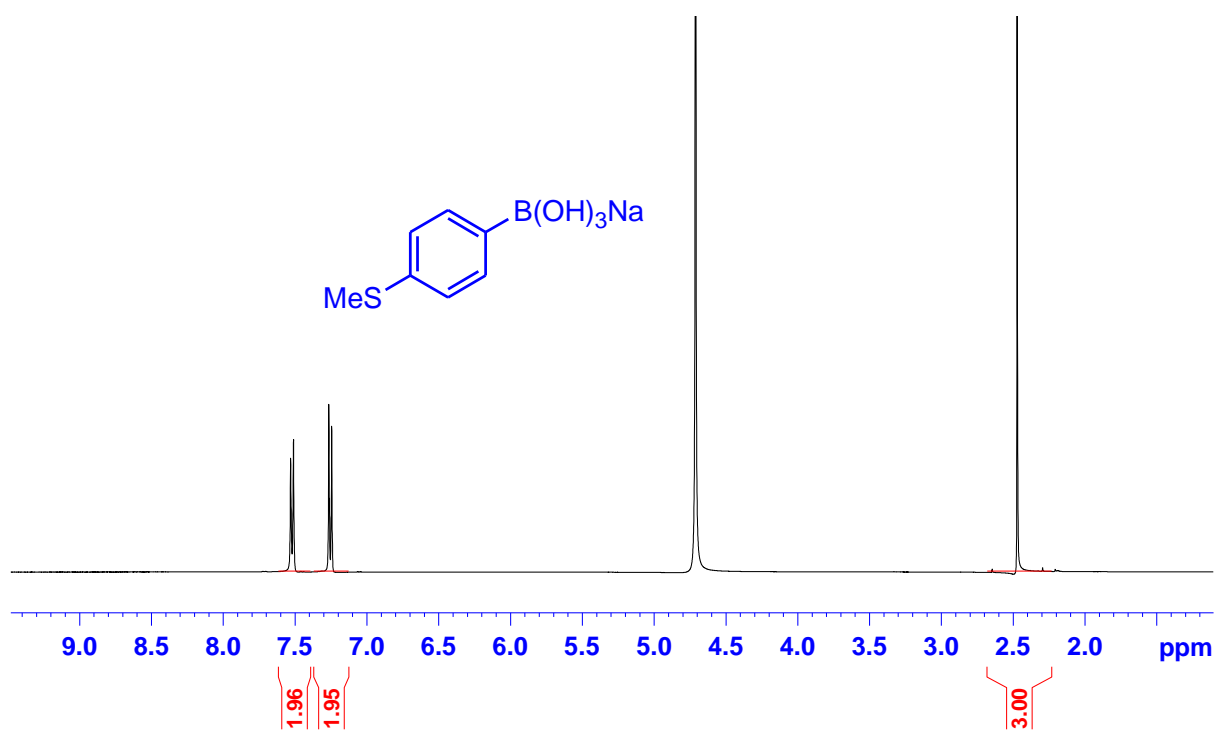
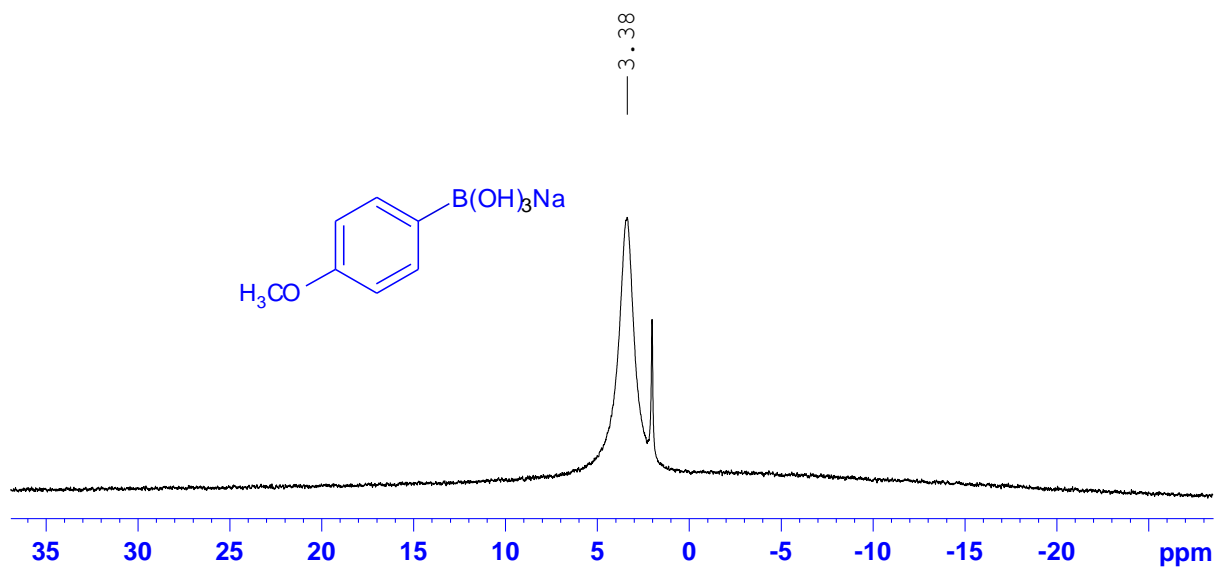
$^{11}\text{B}$  NMR

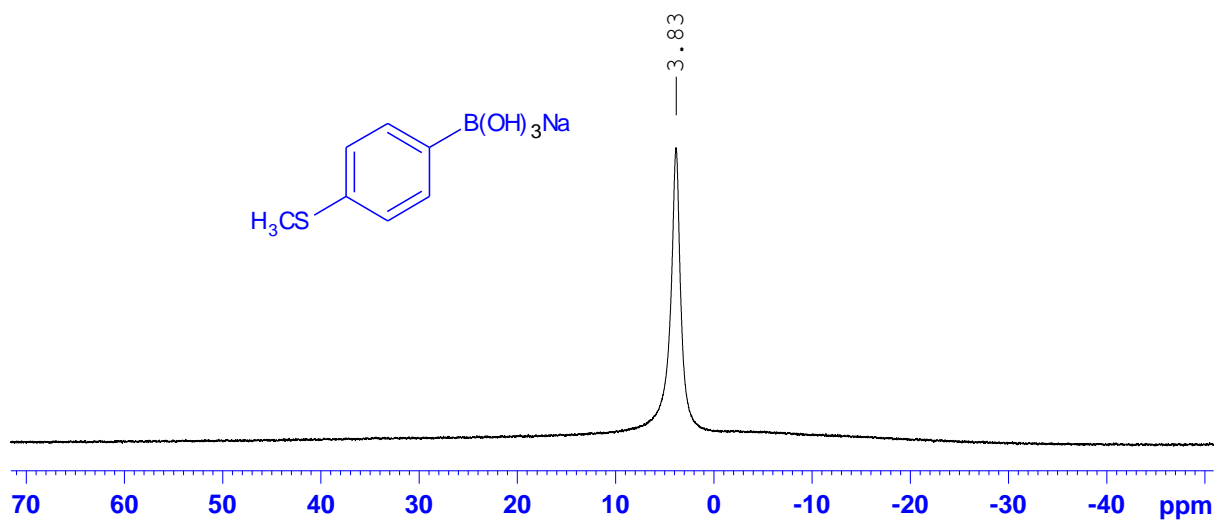
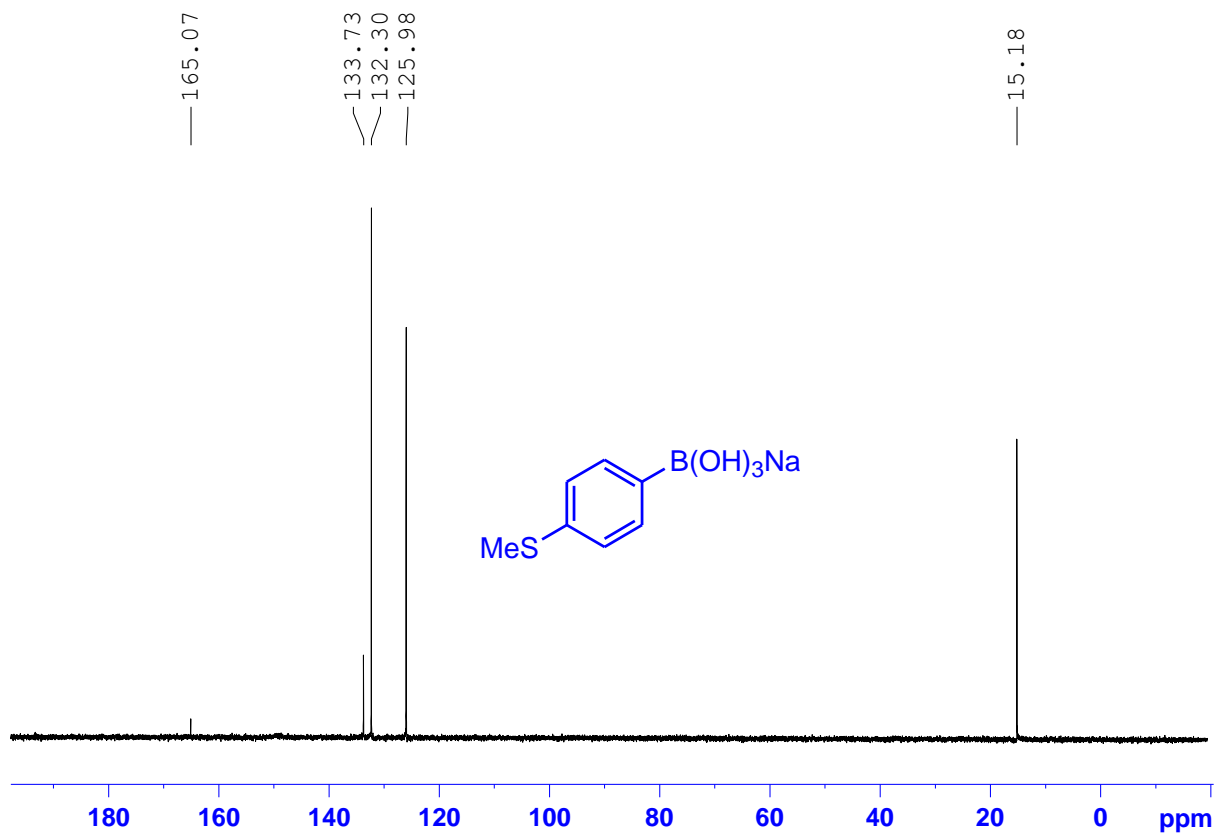


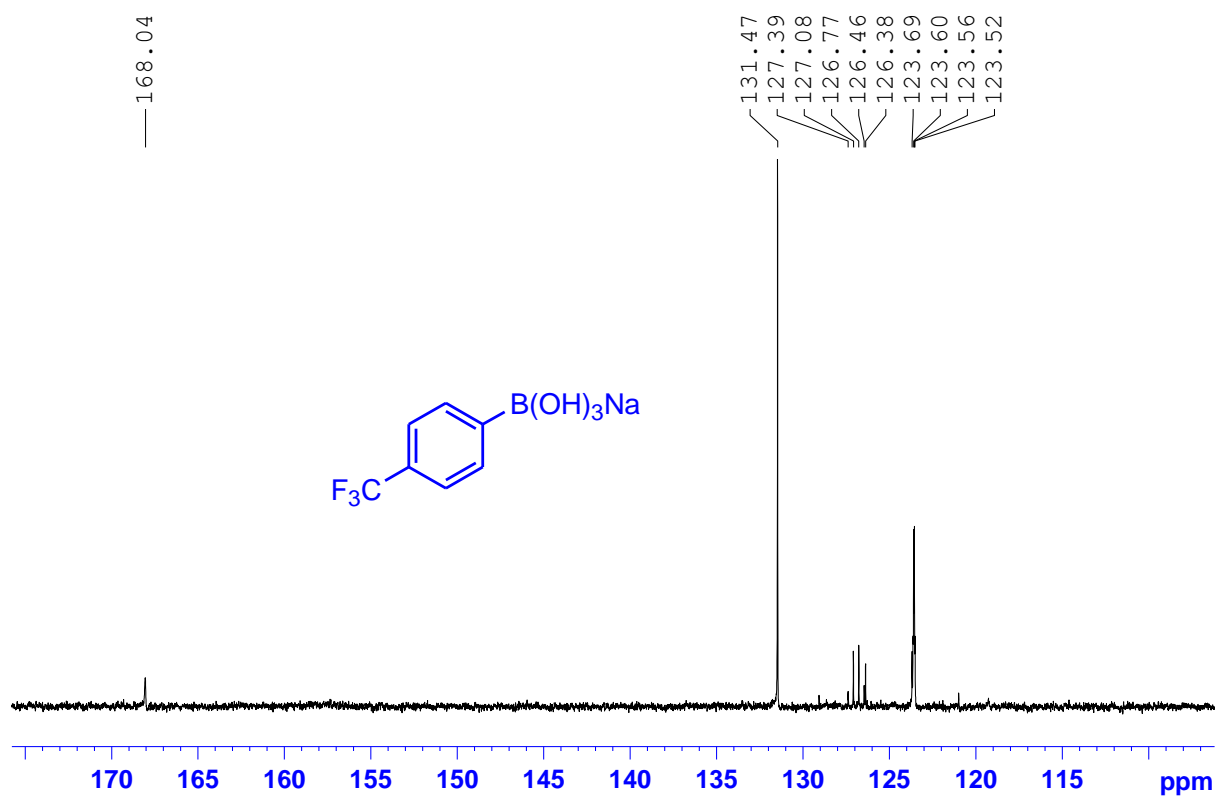
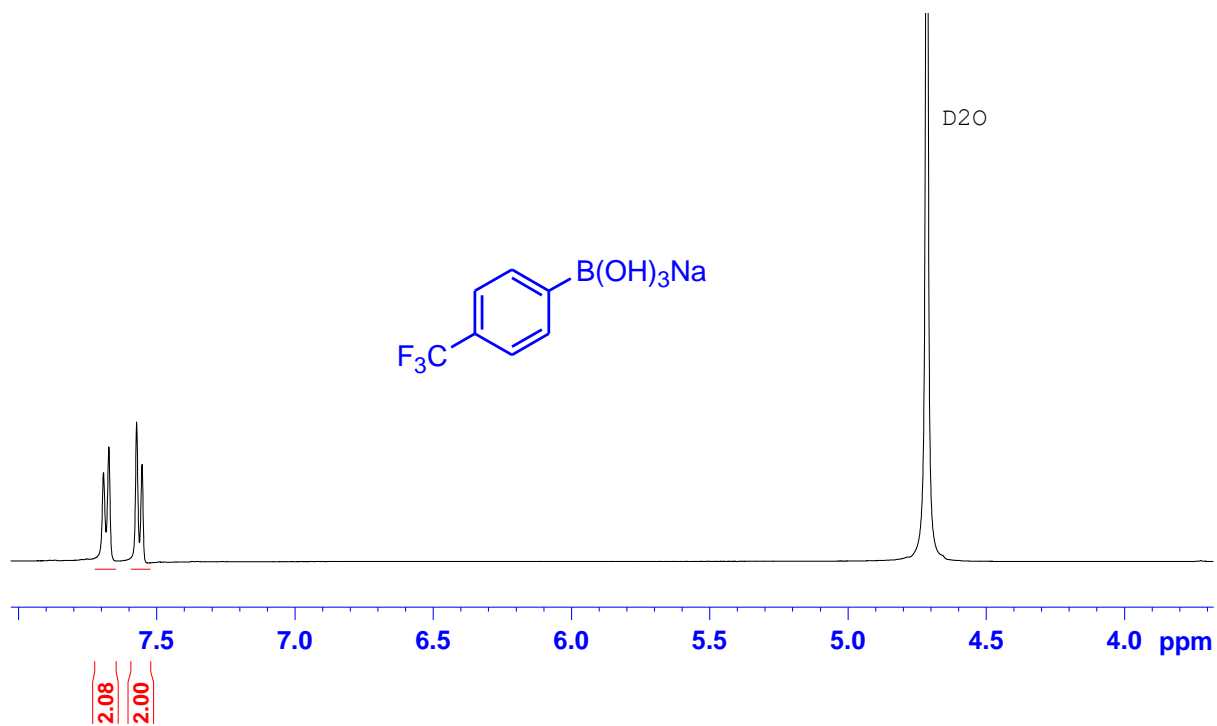




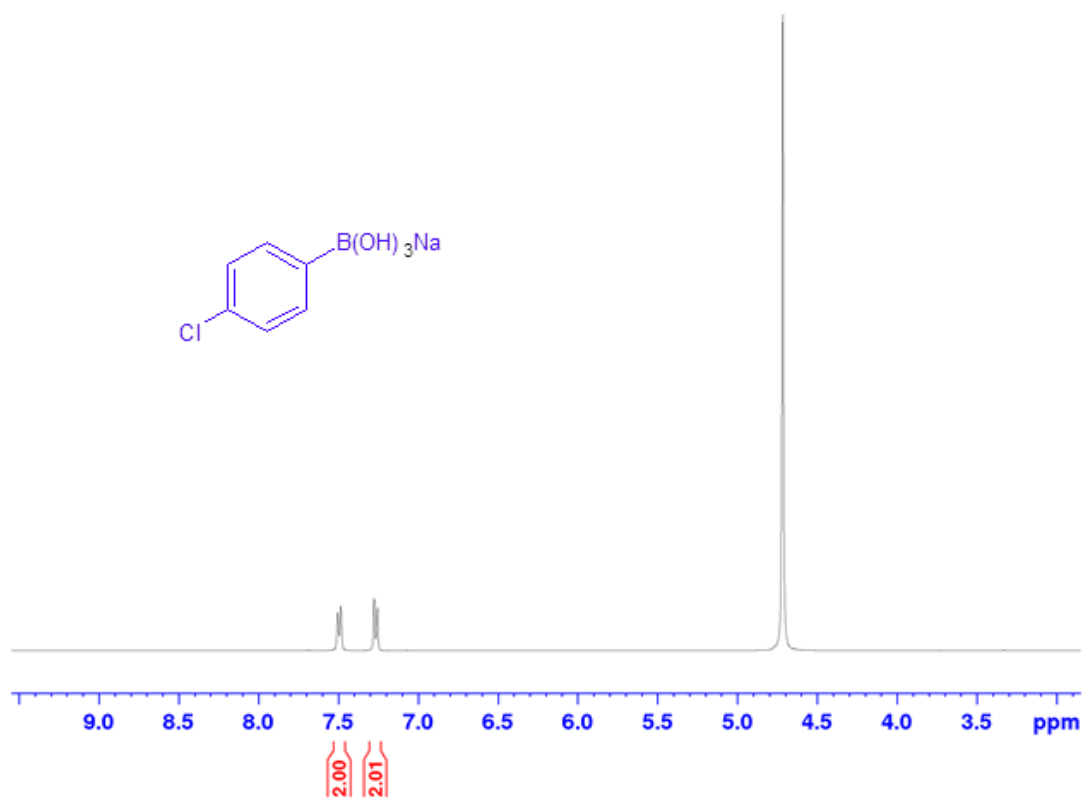
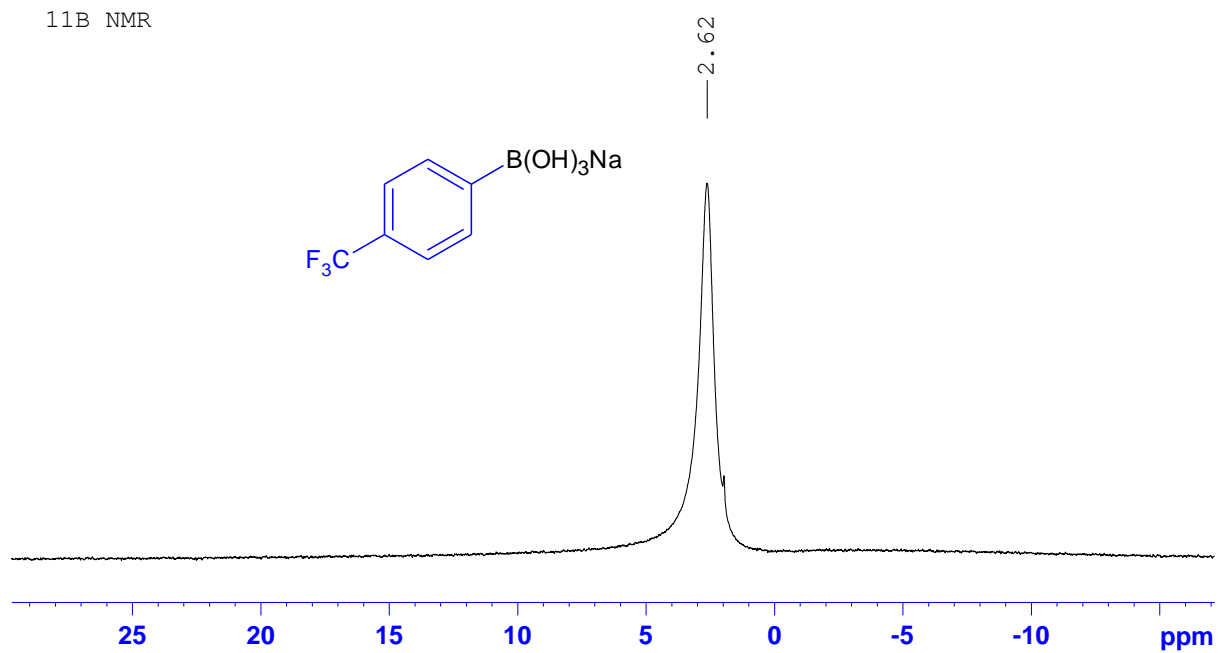


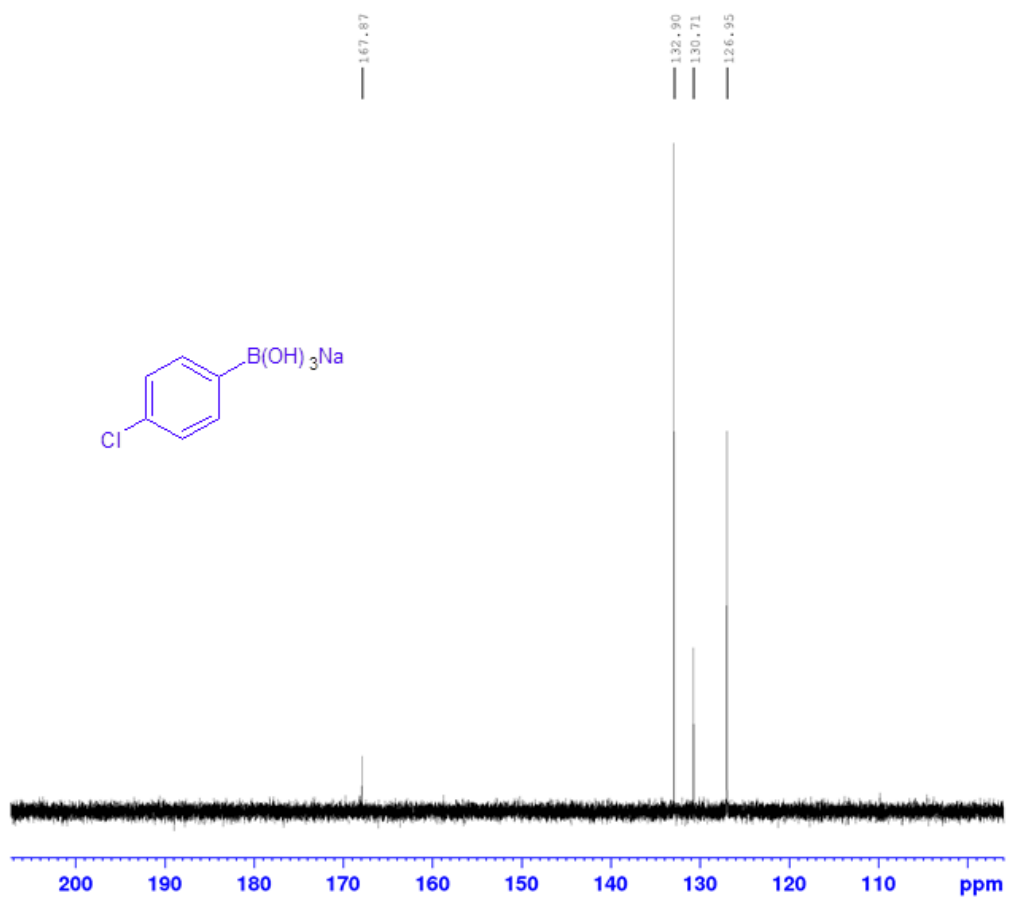
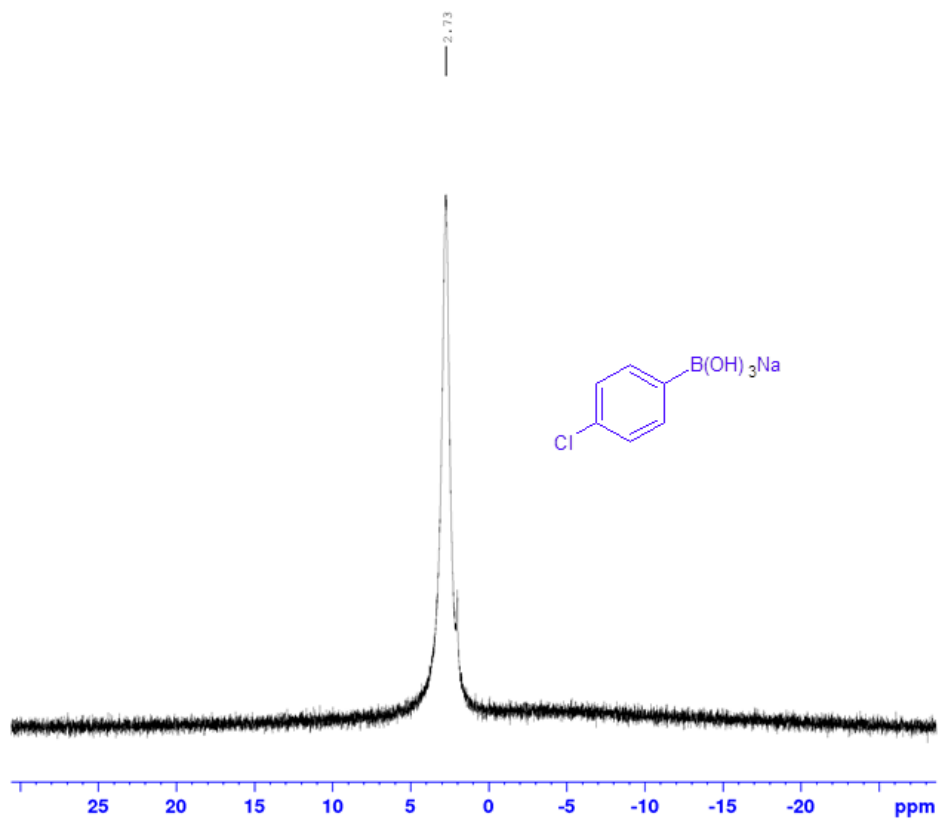


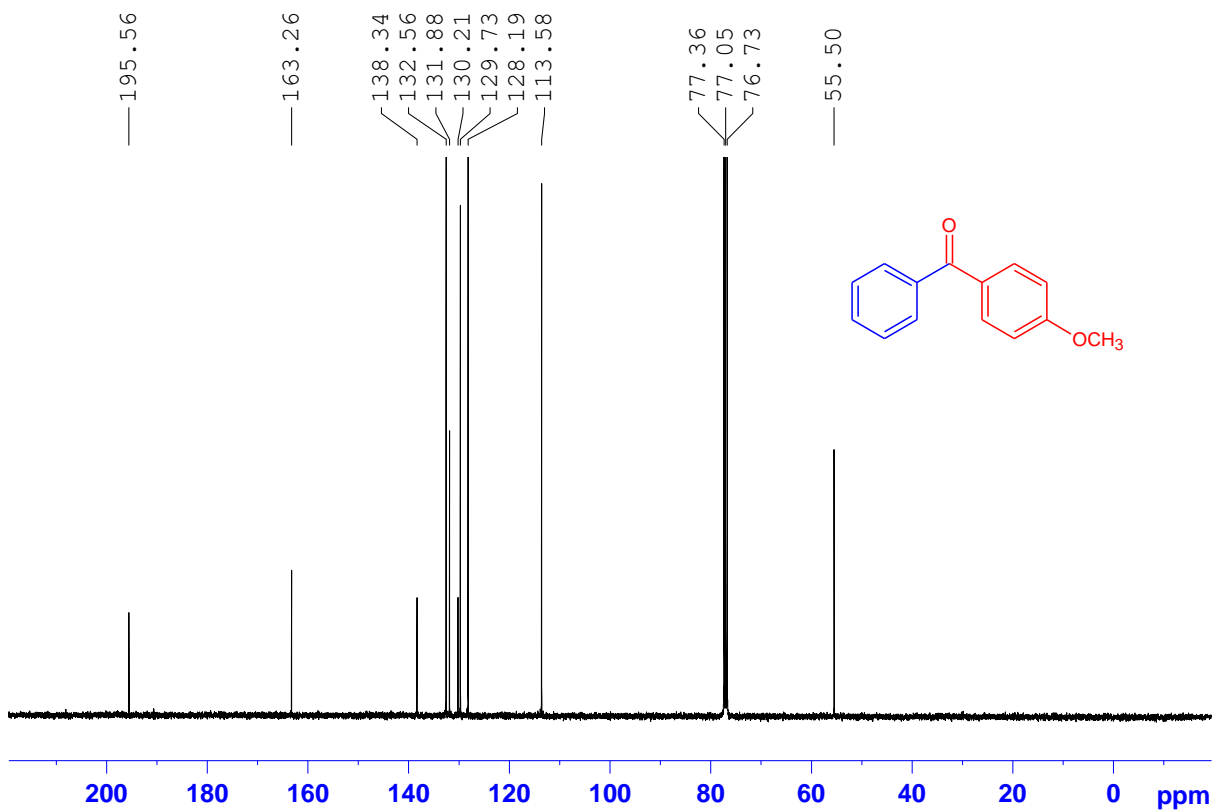
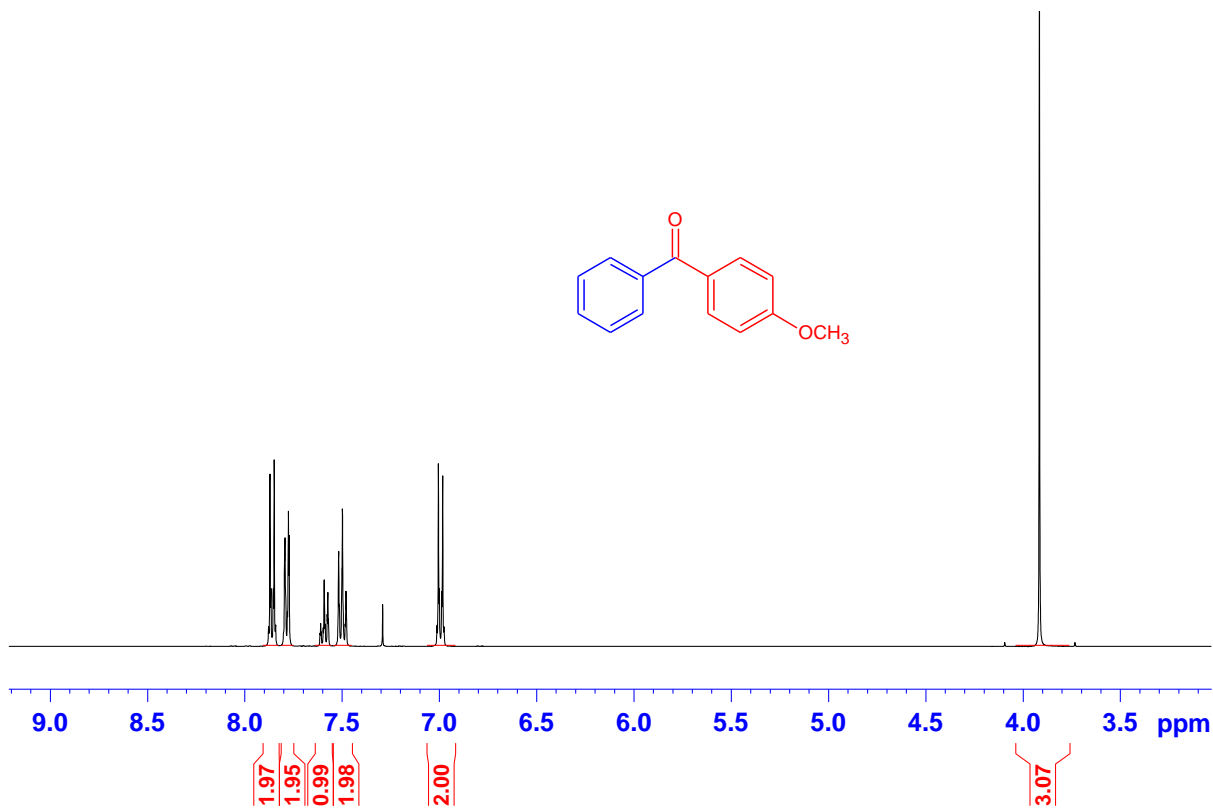


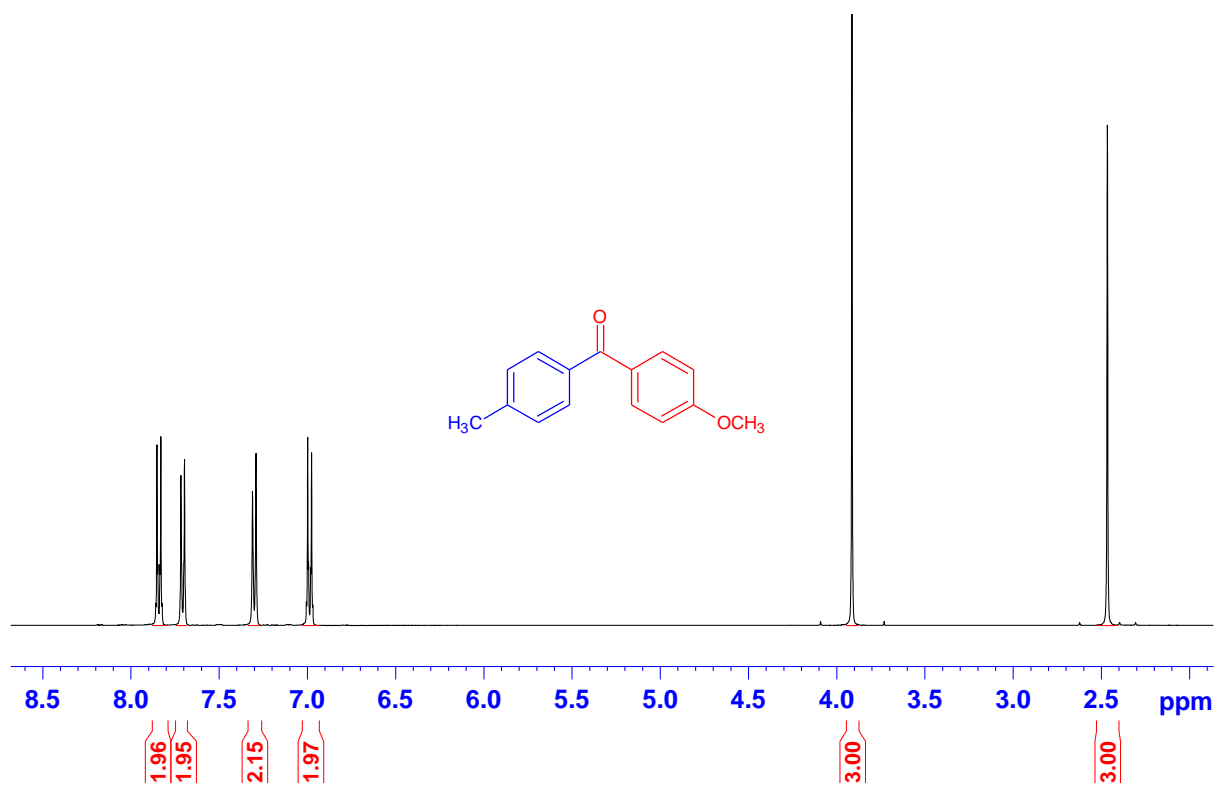
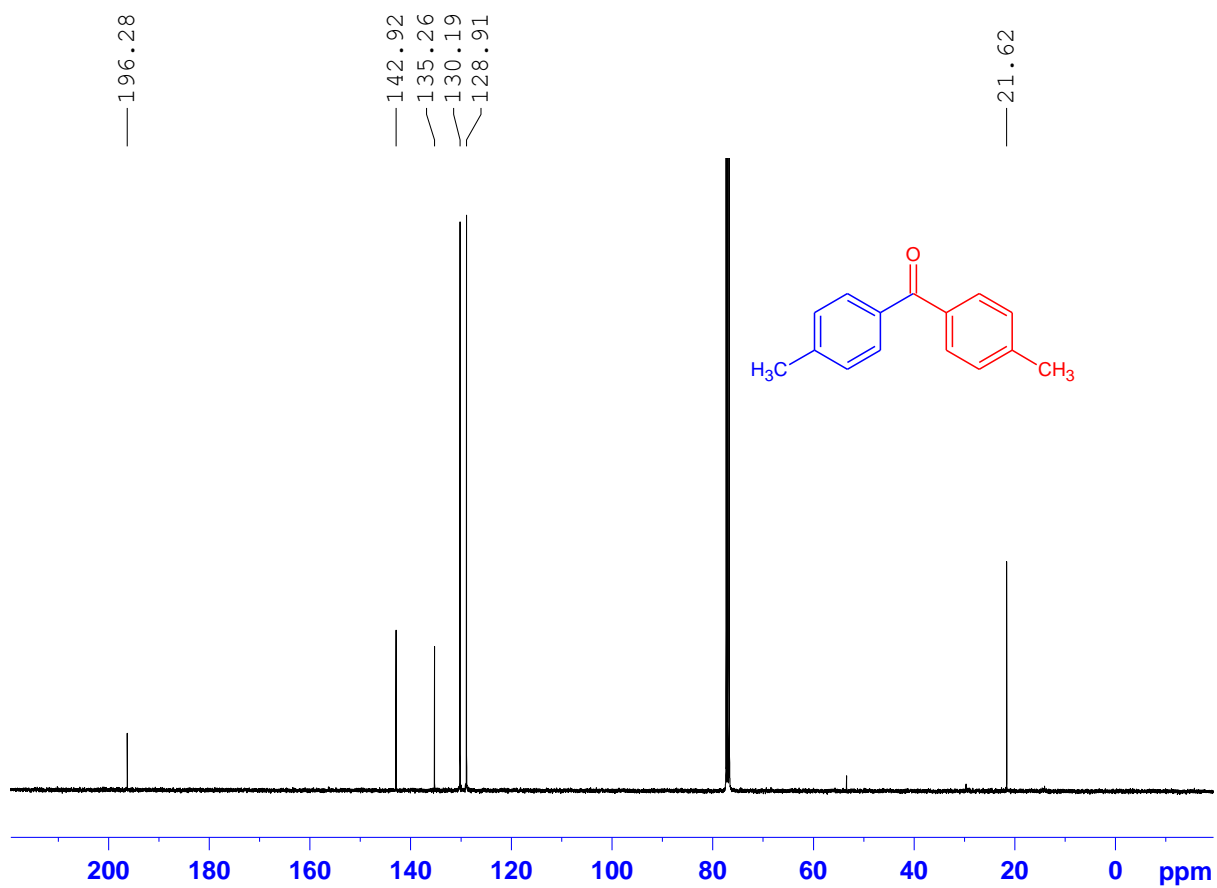


11B NMR

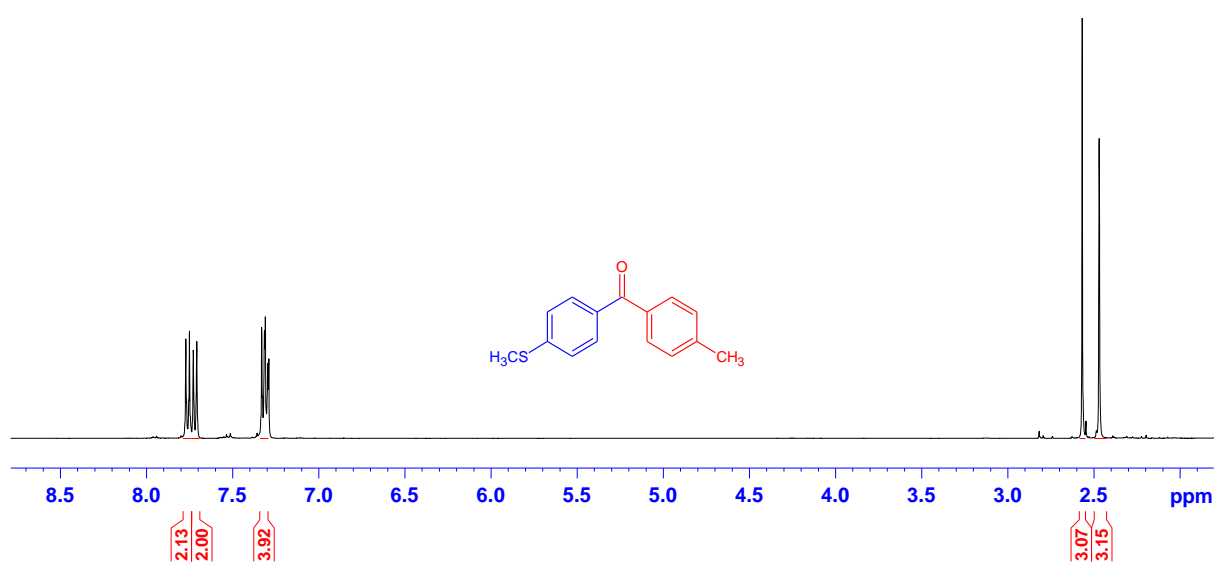
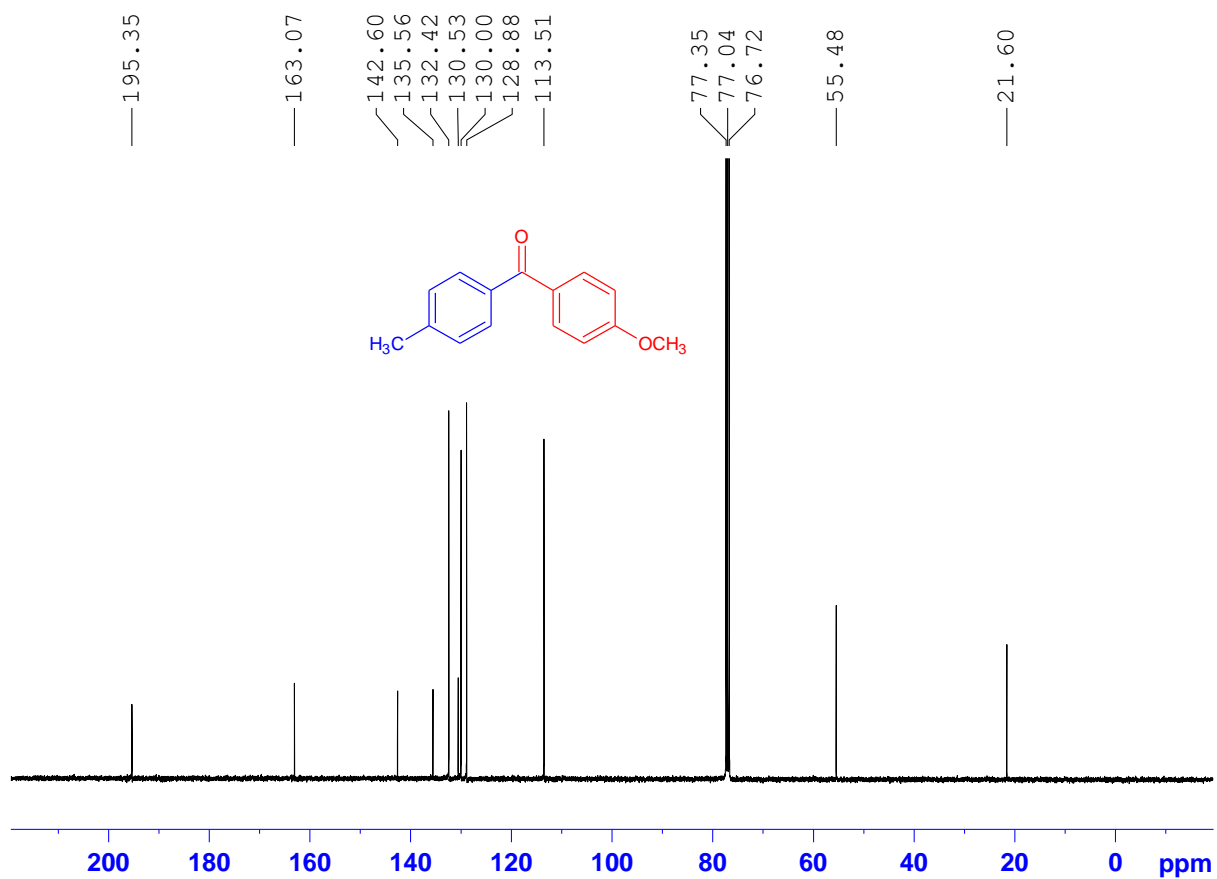


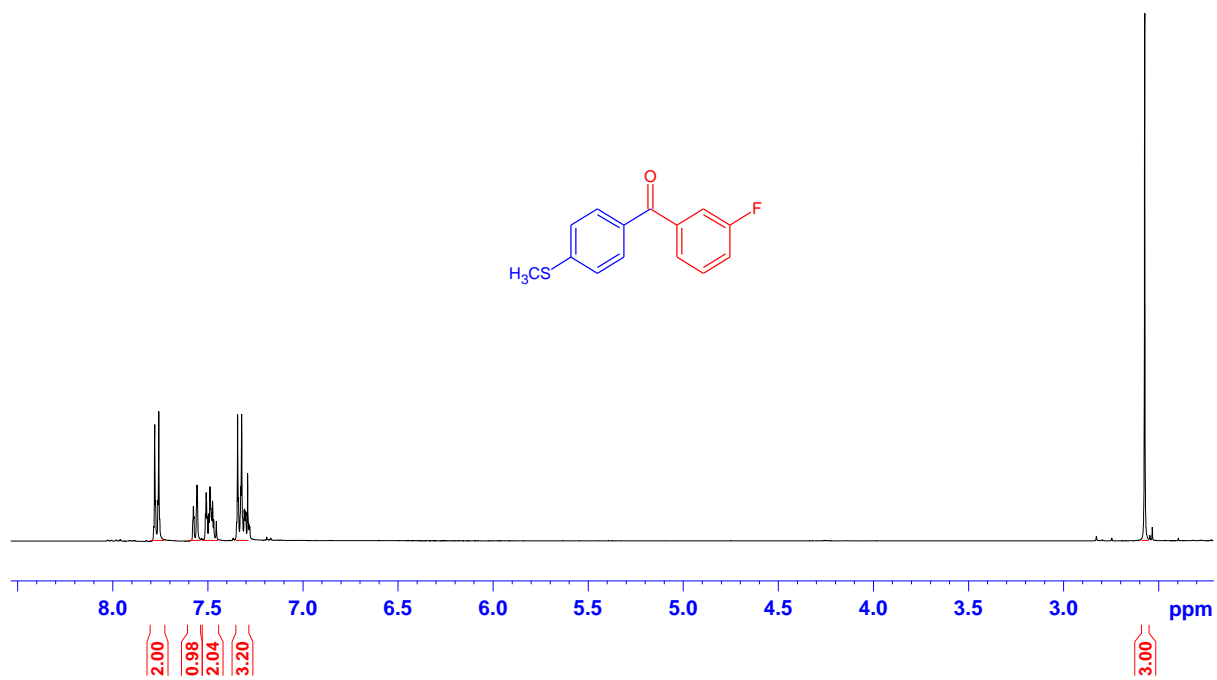
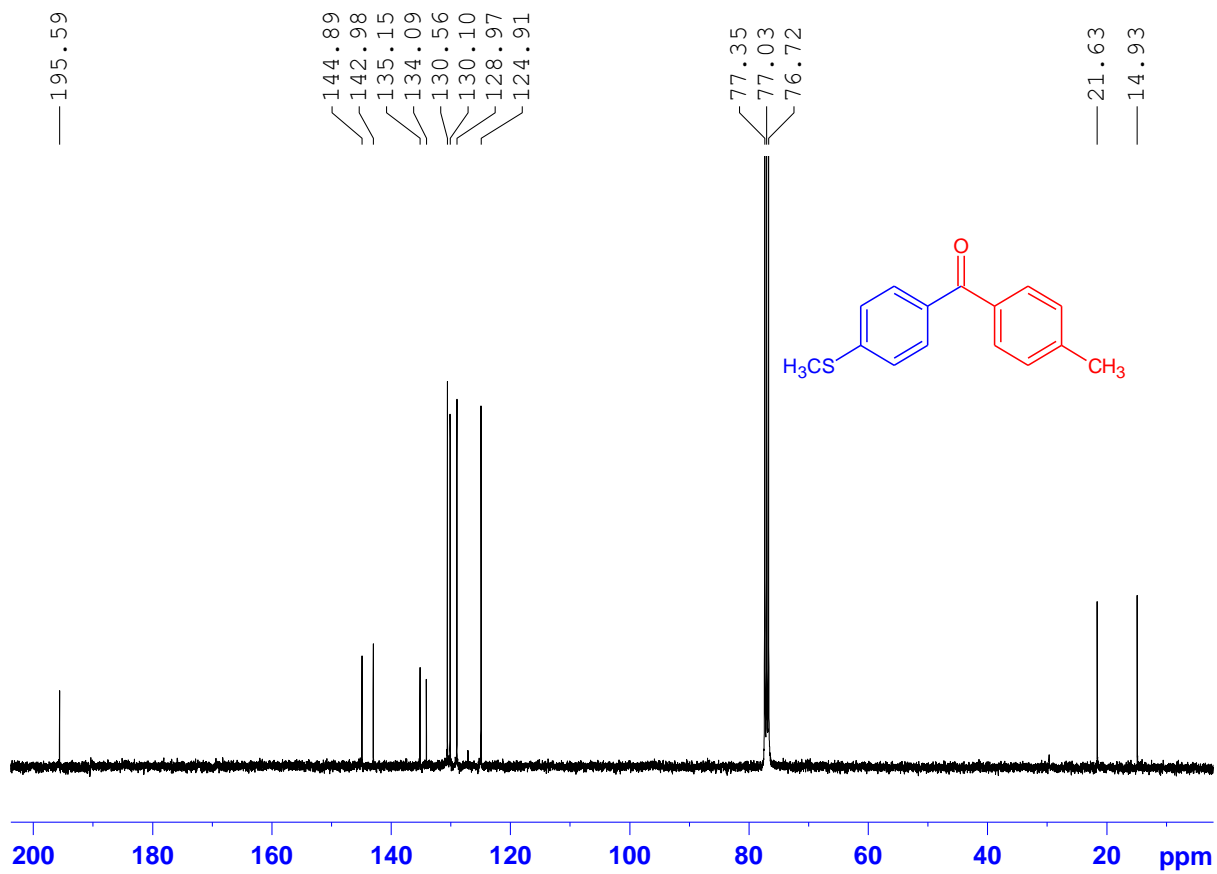


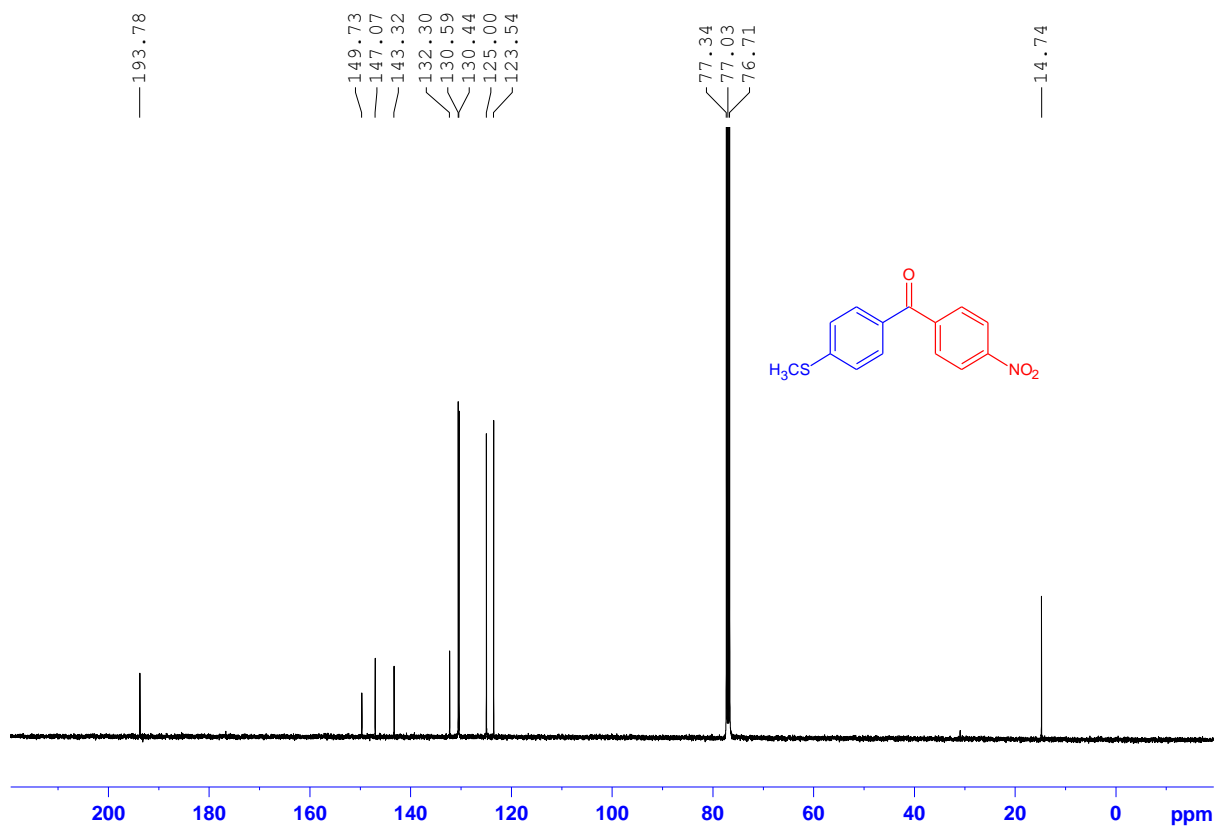
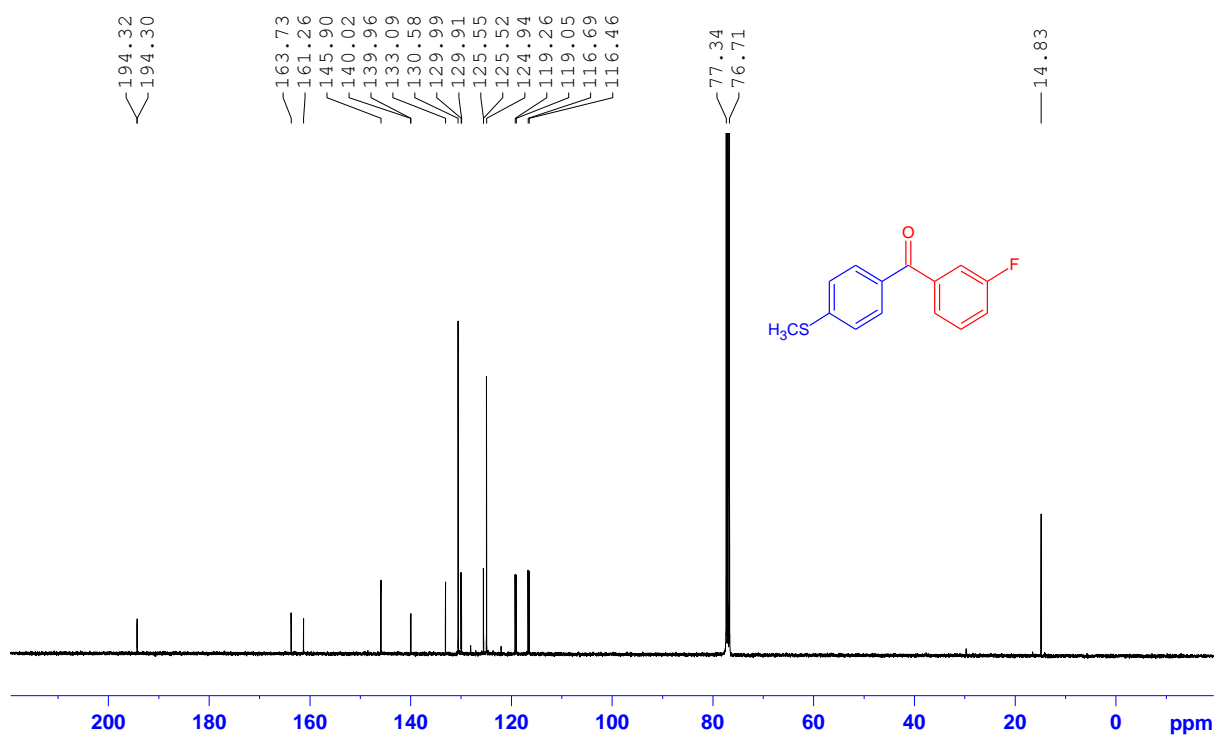


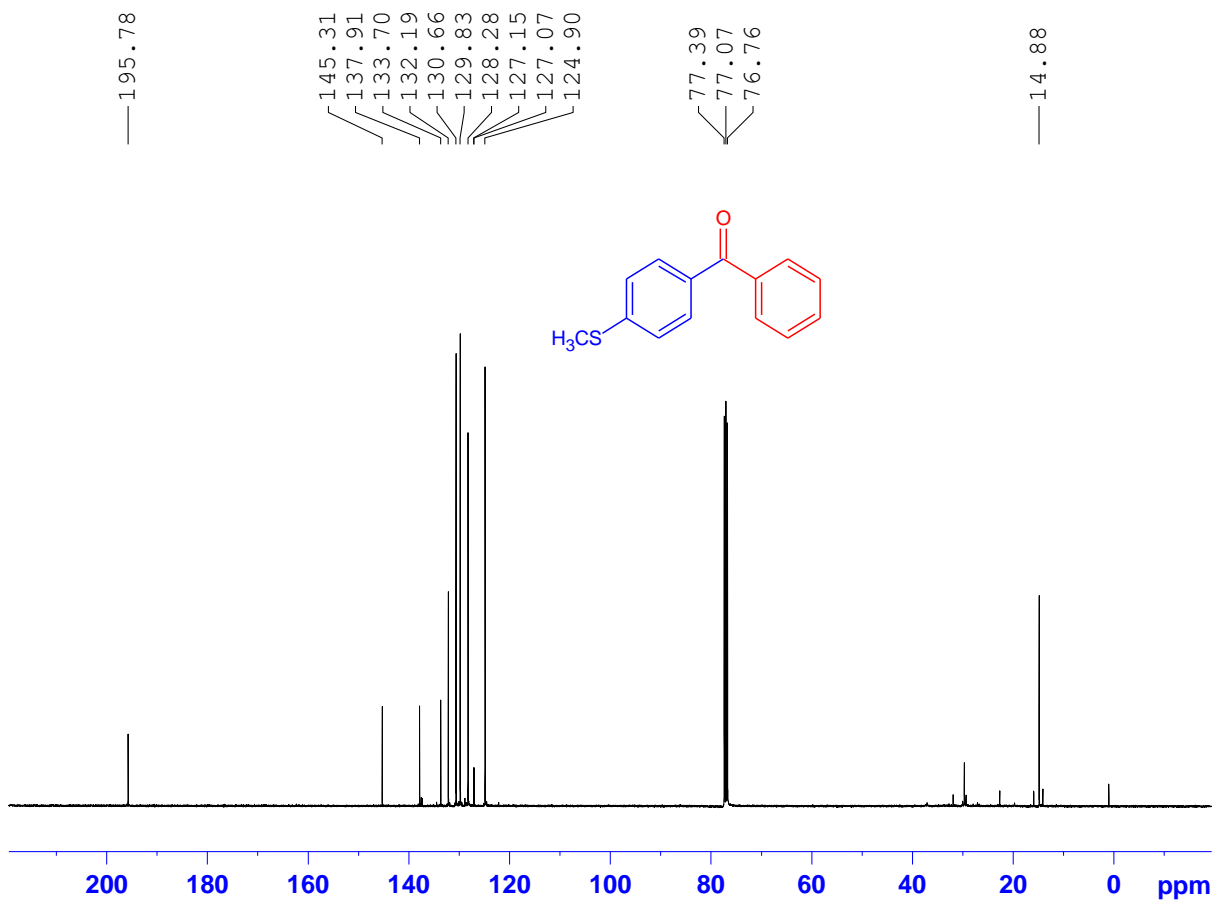
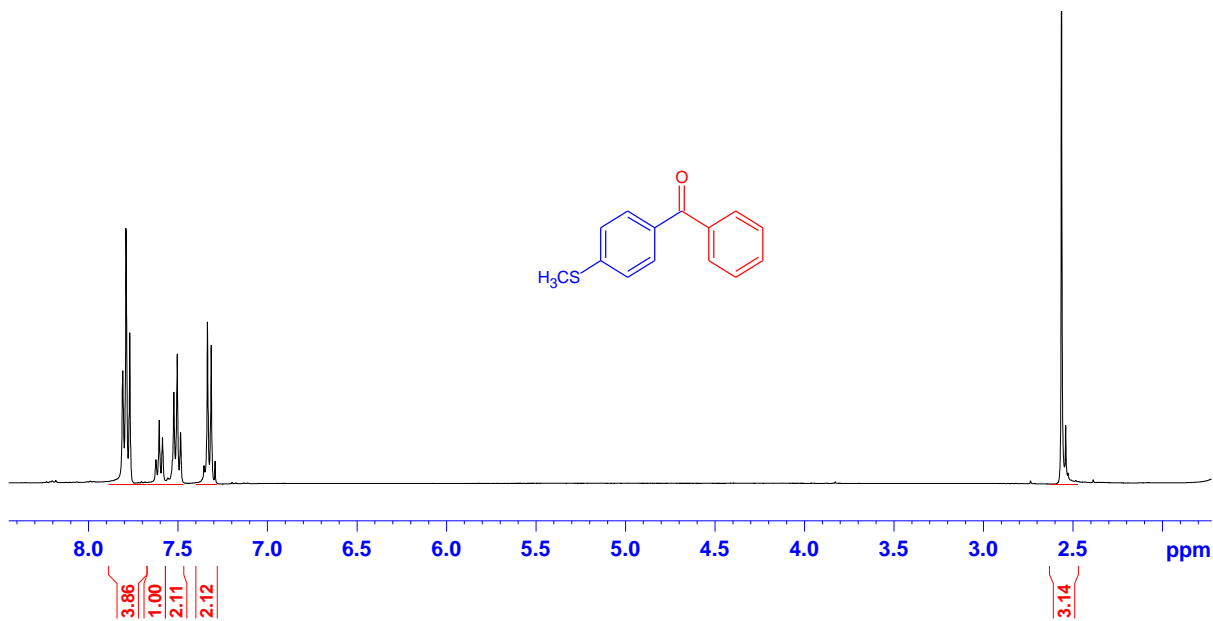


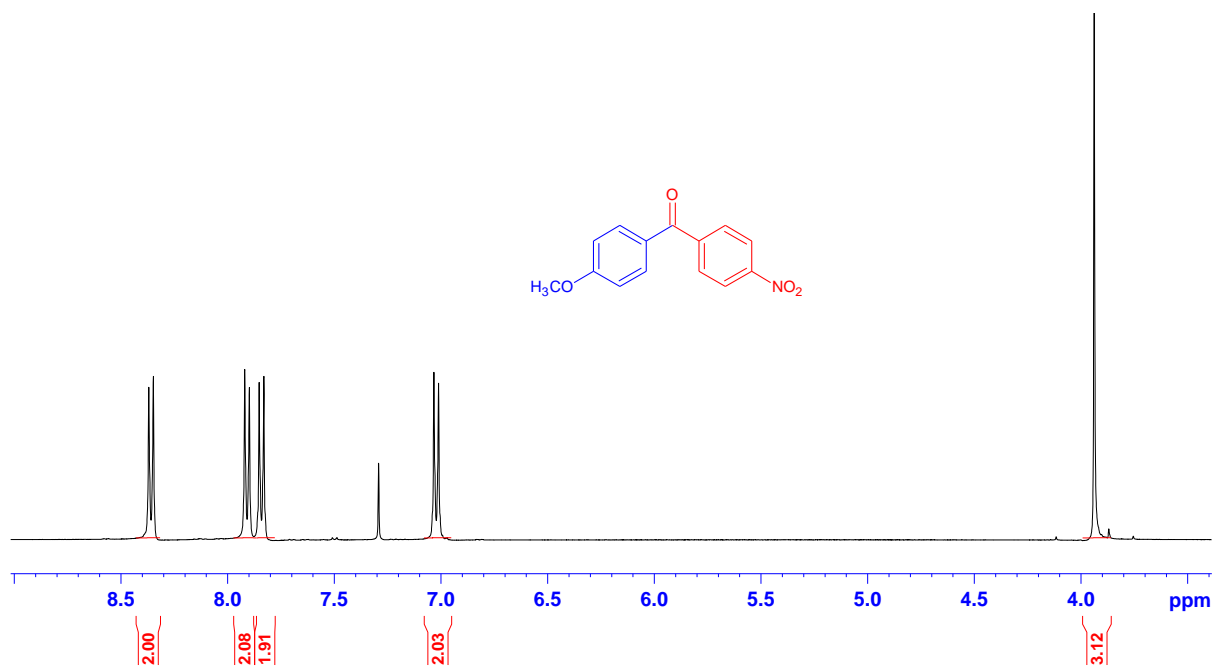
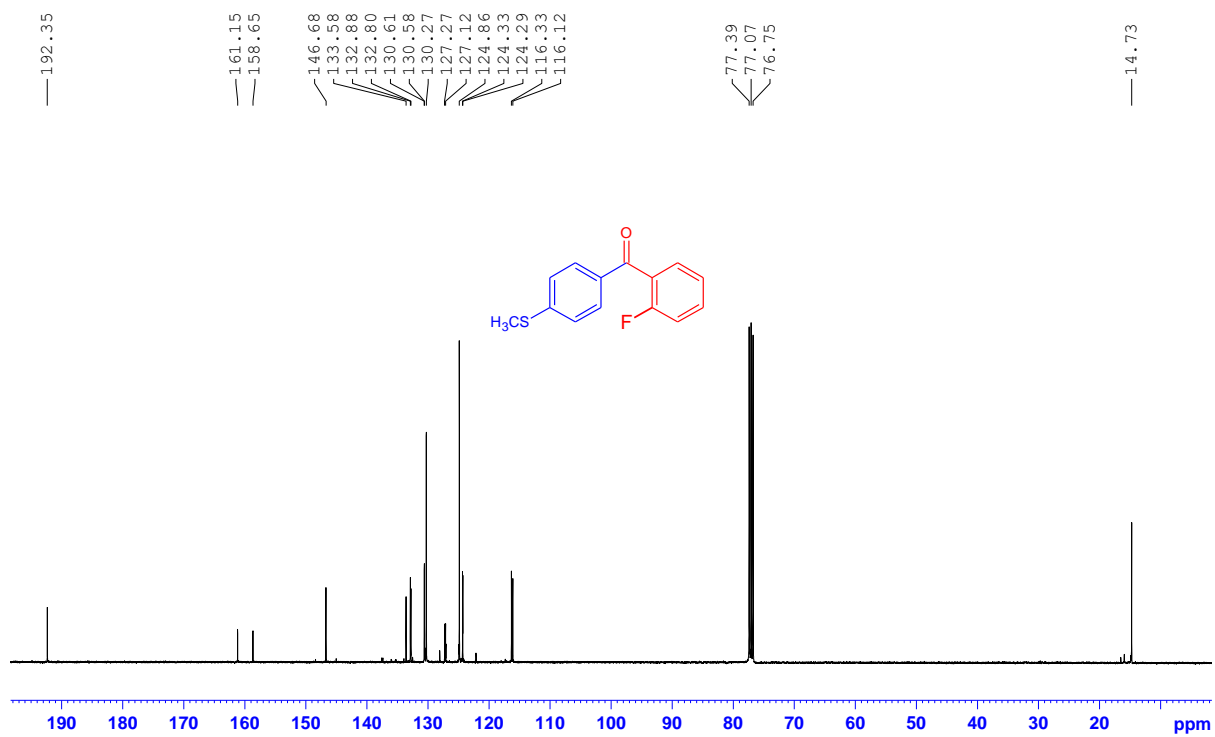


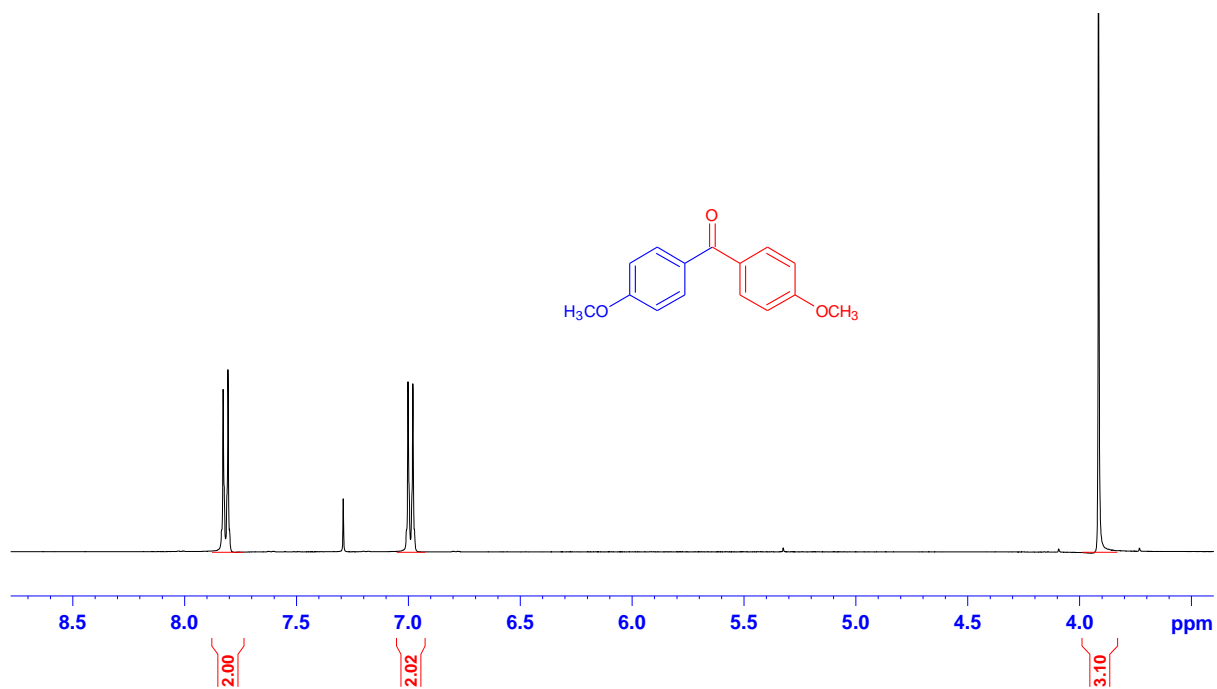
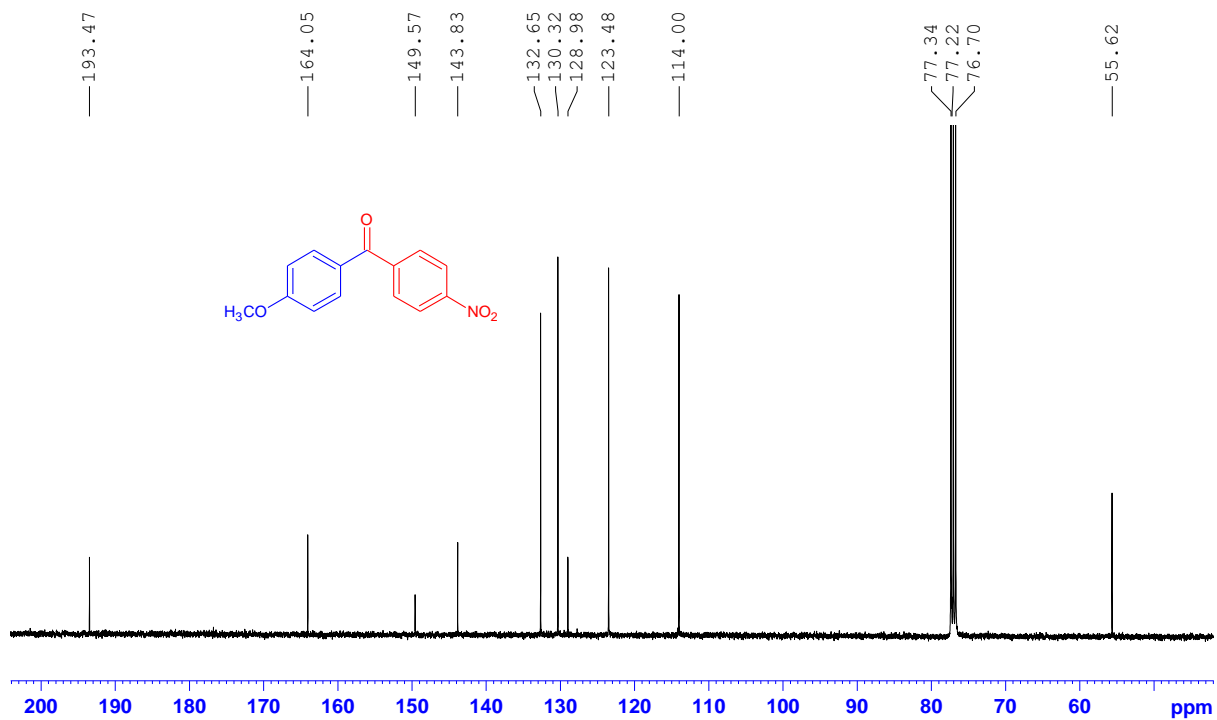


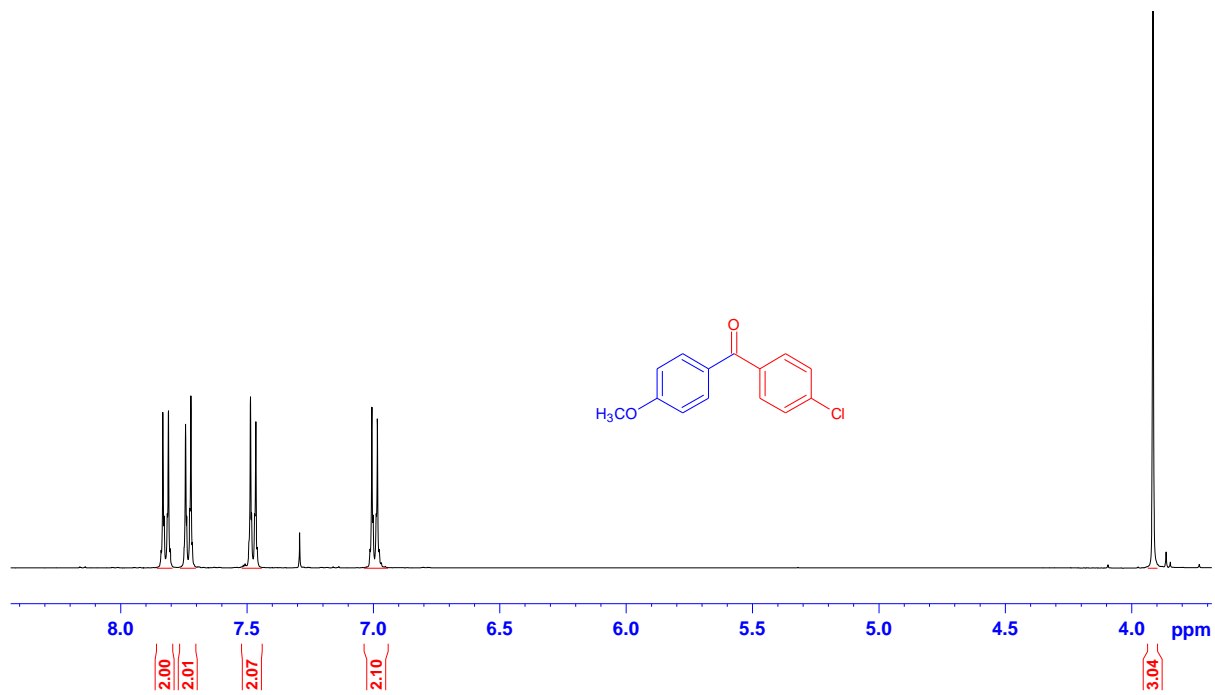
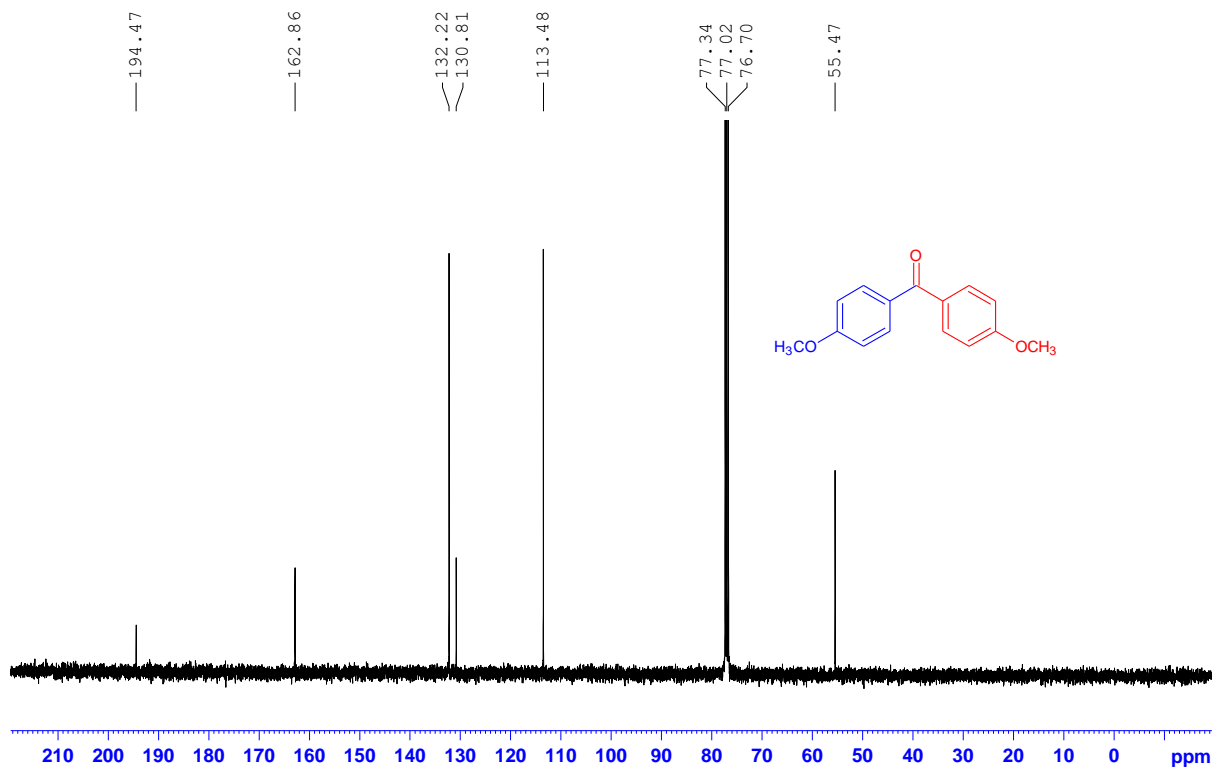


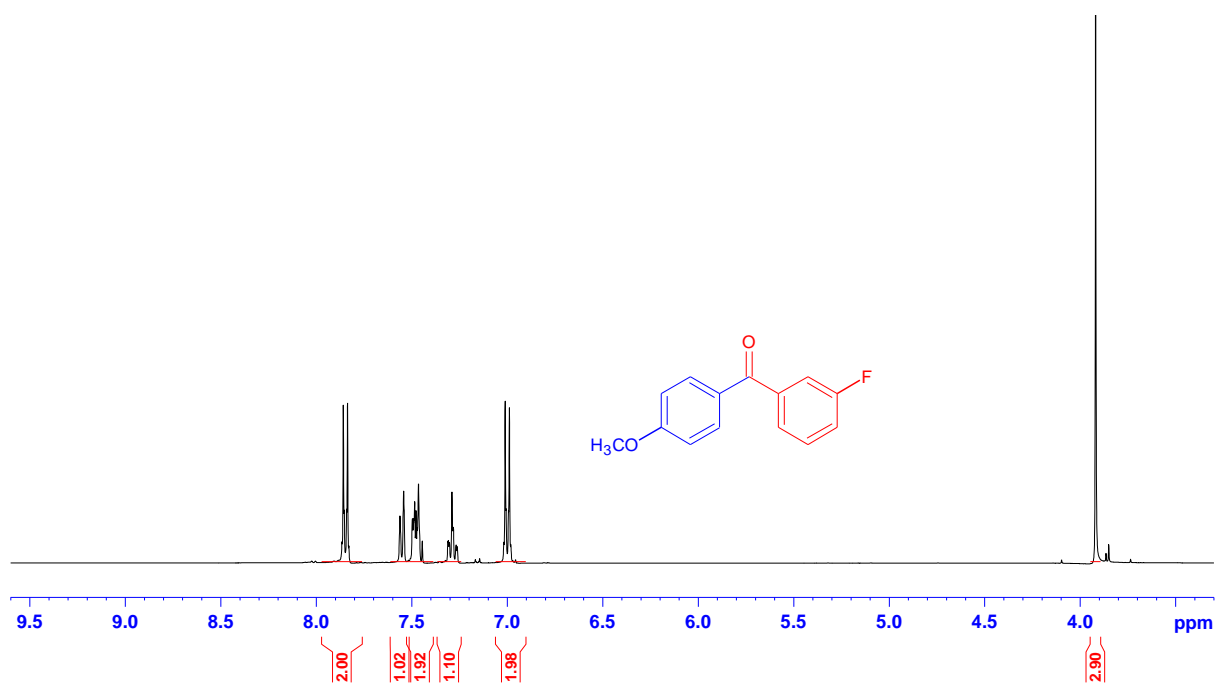
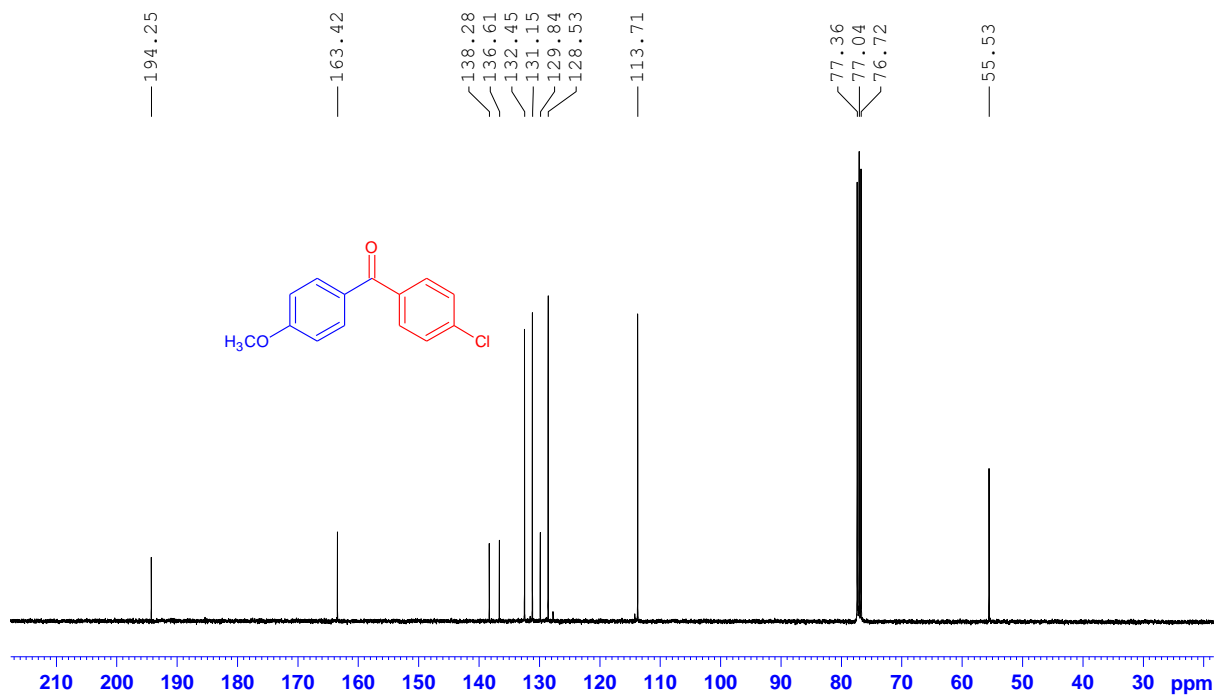




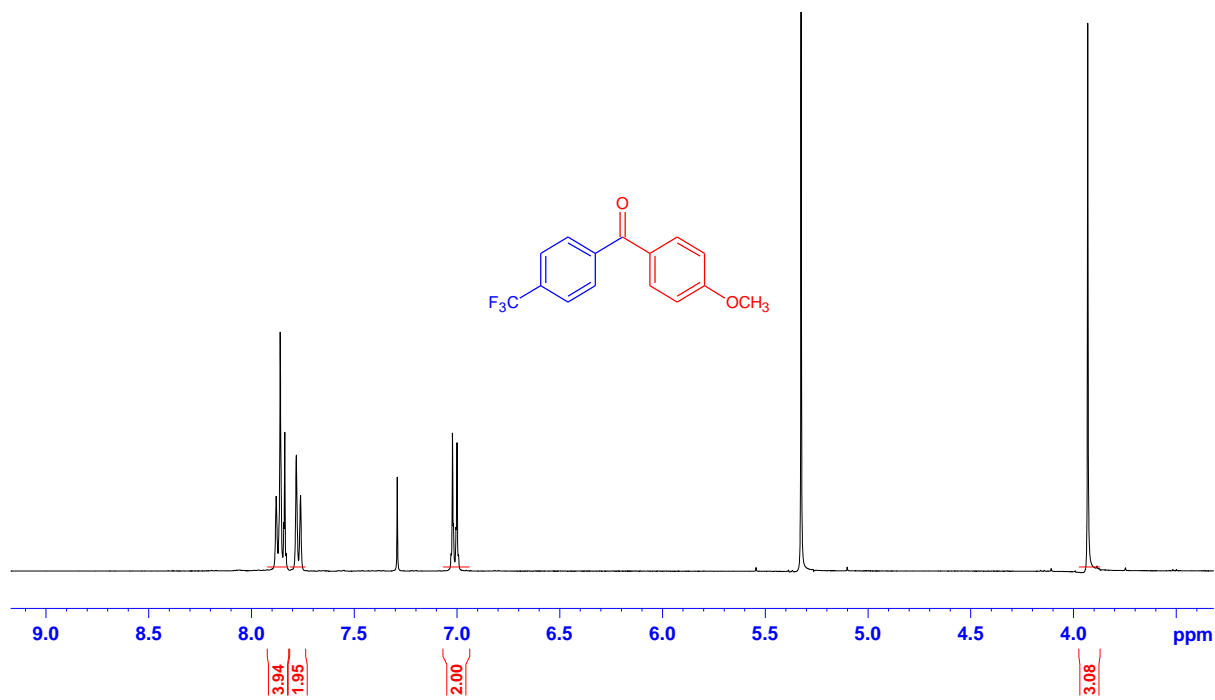
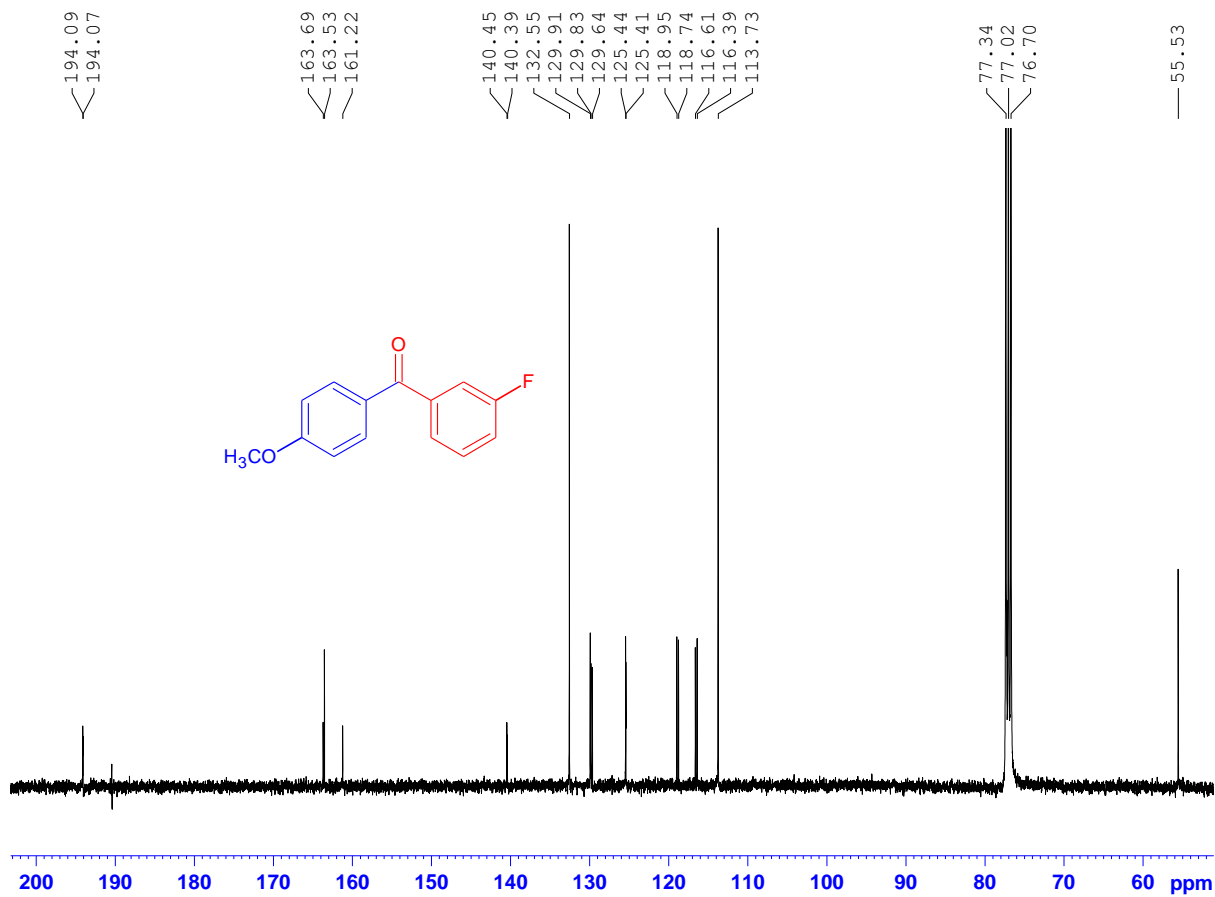


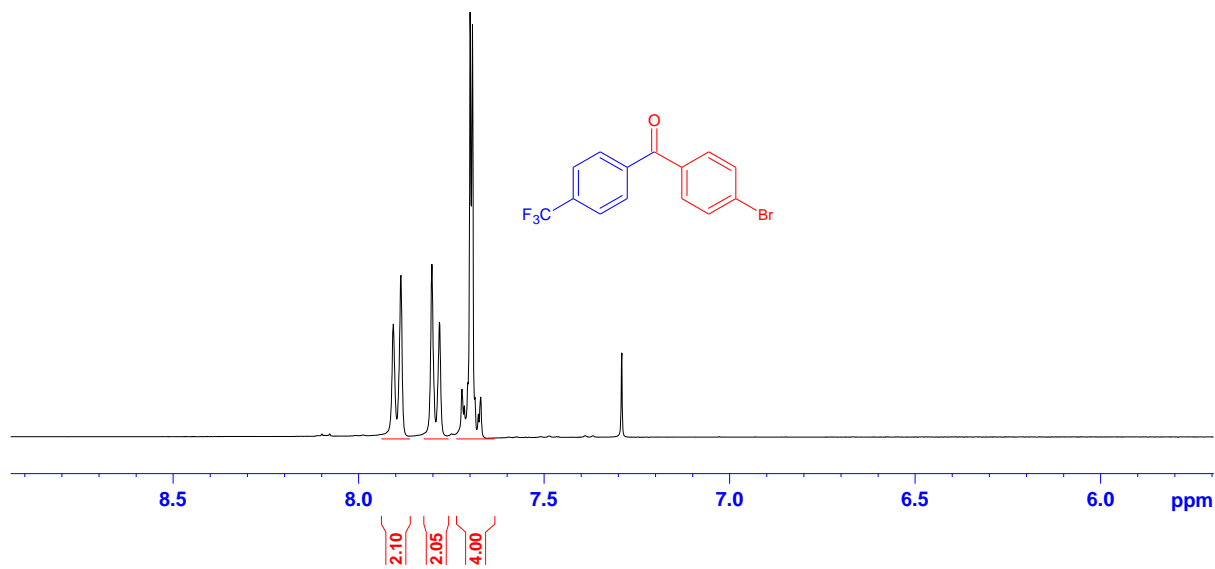
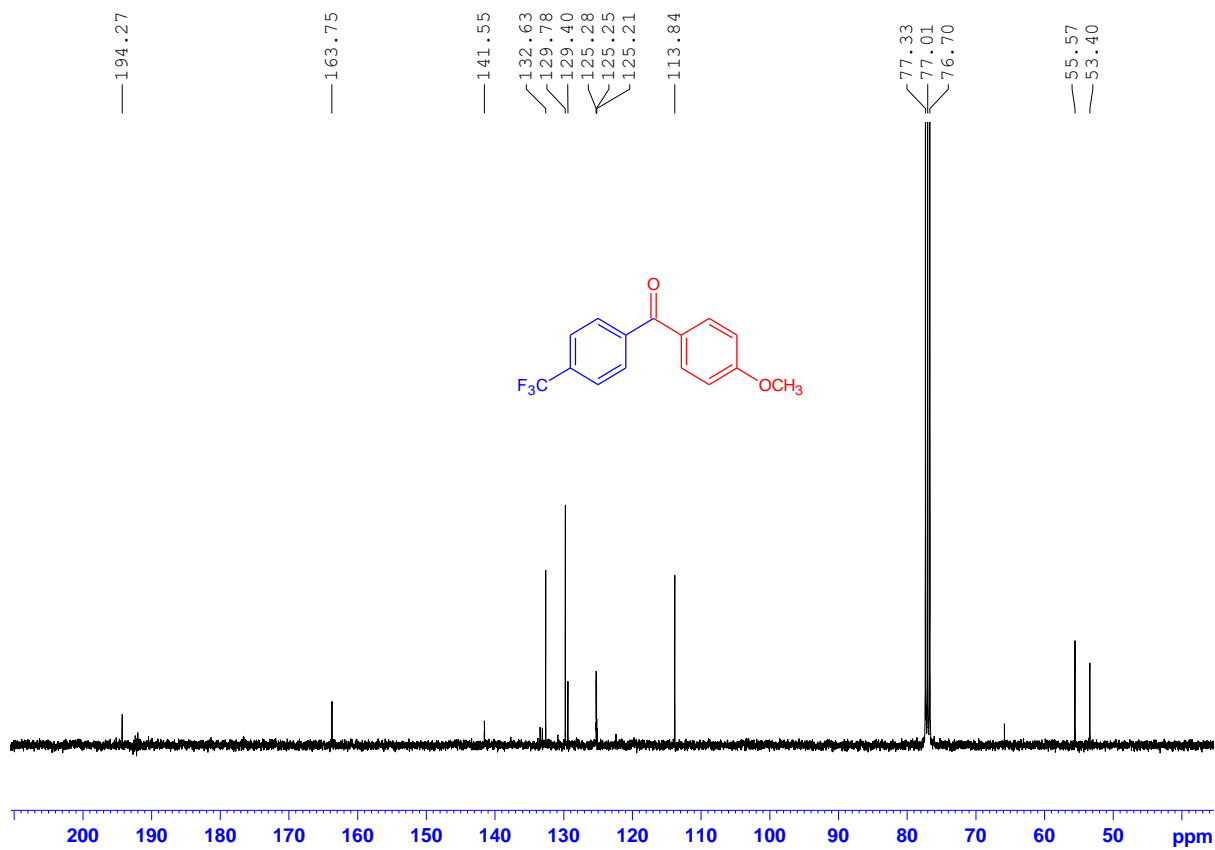


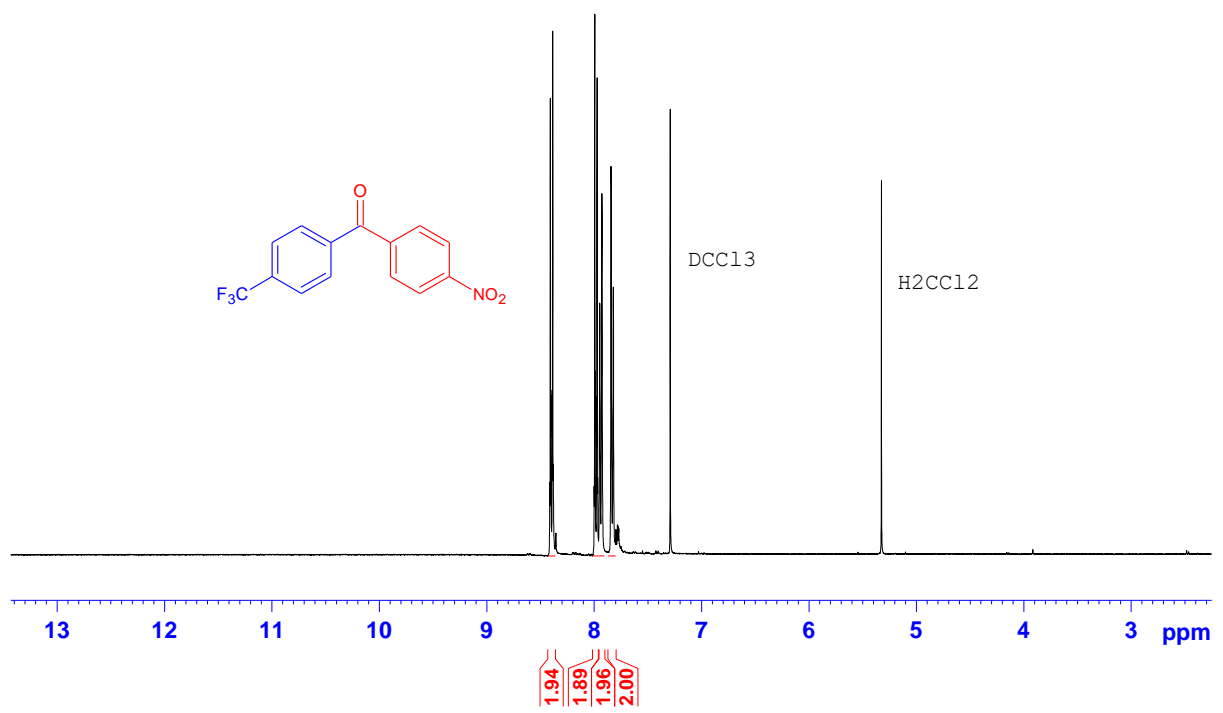
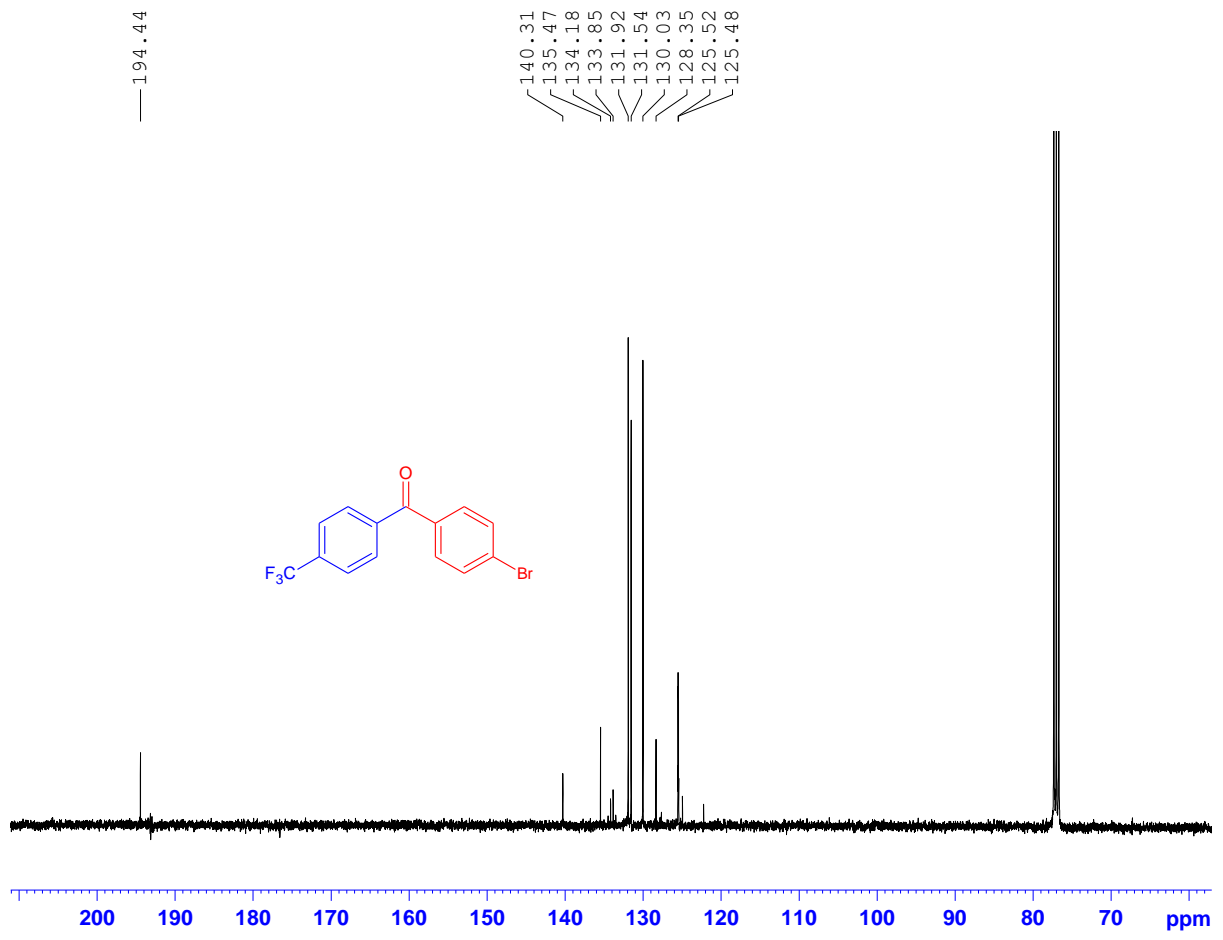


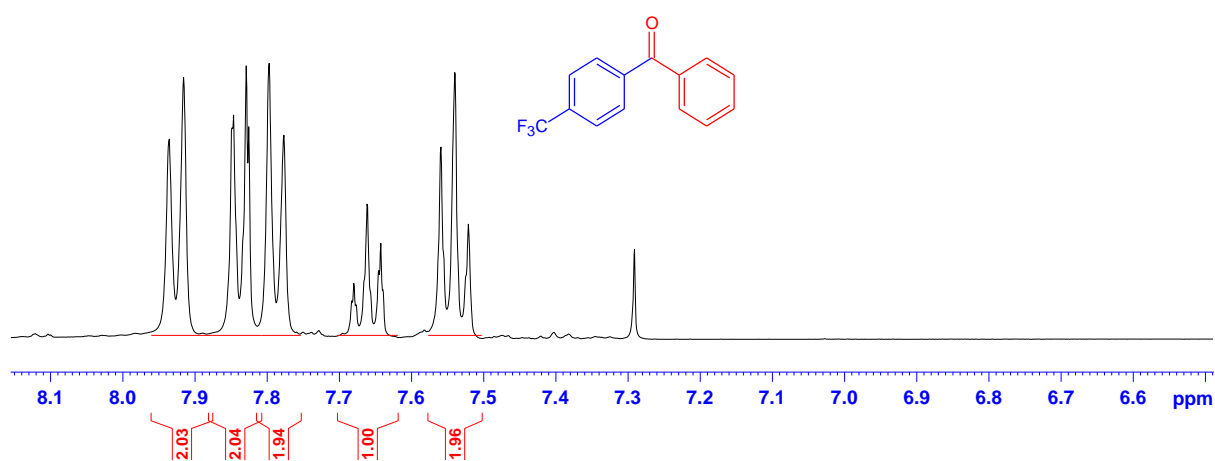
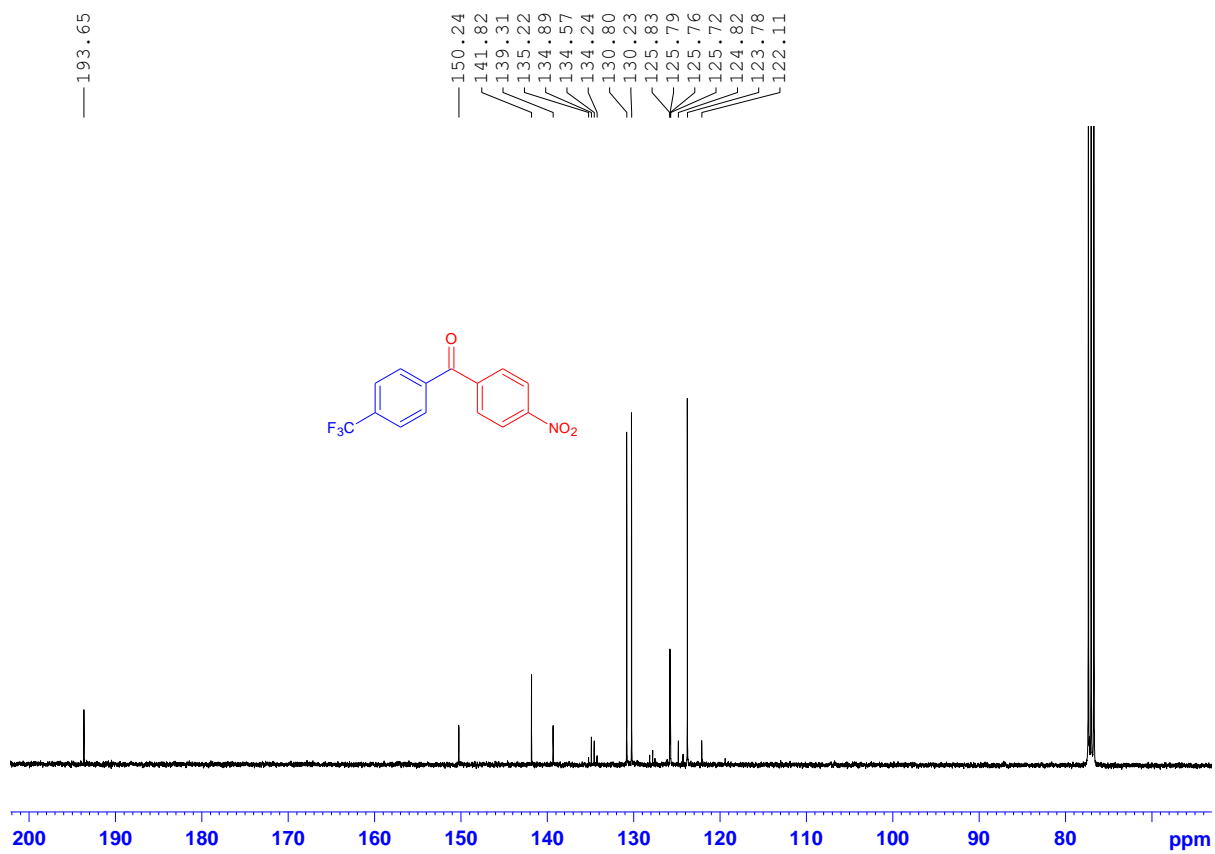


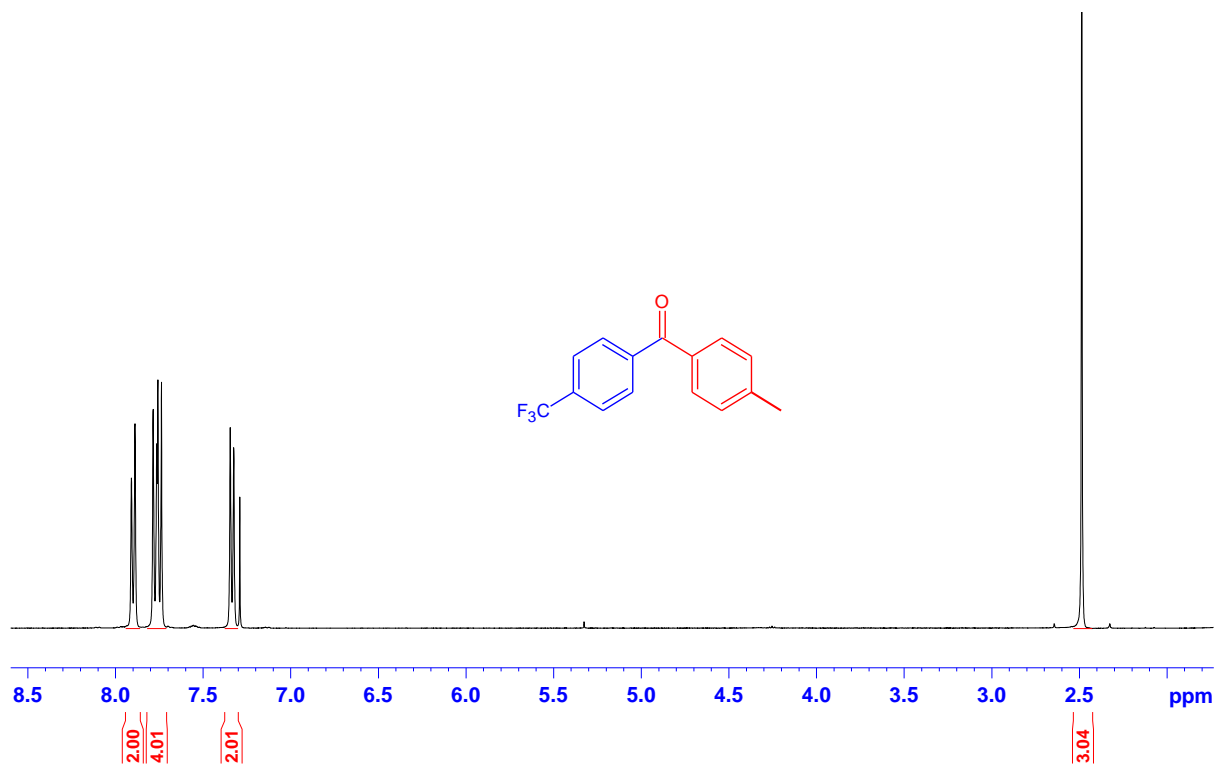
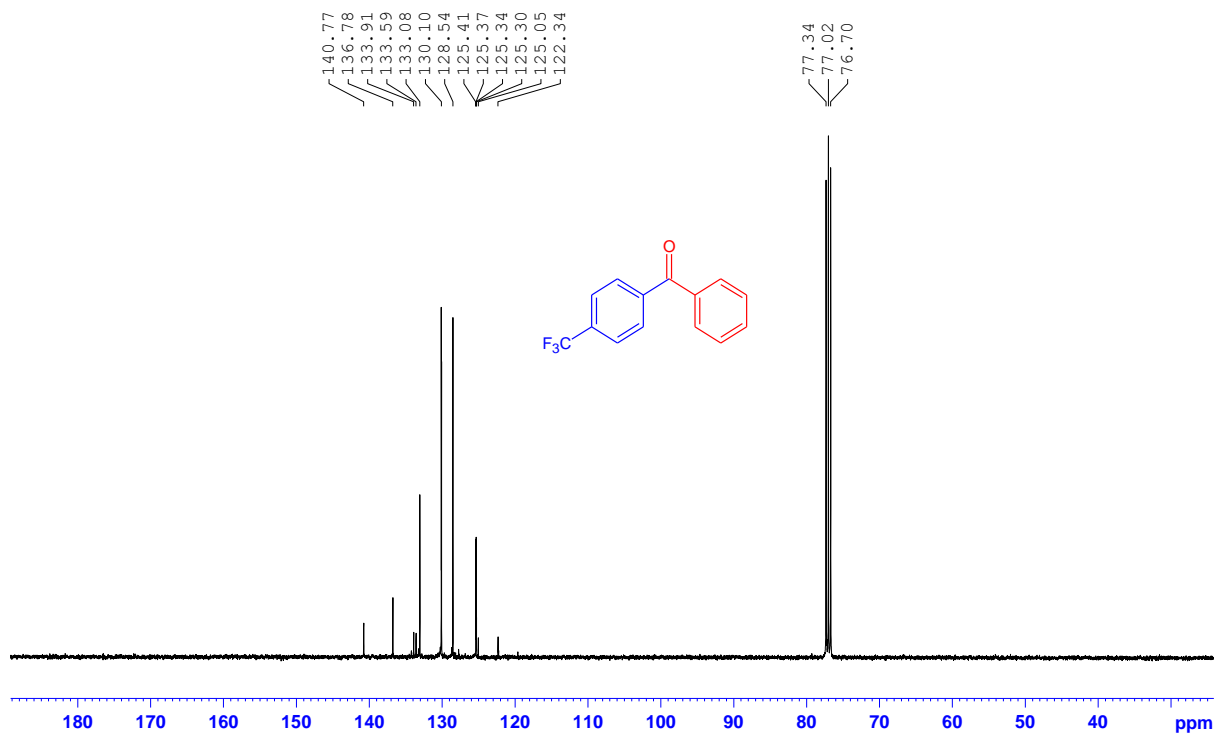


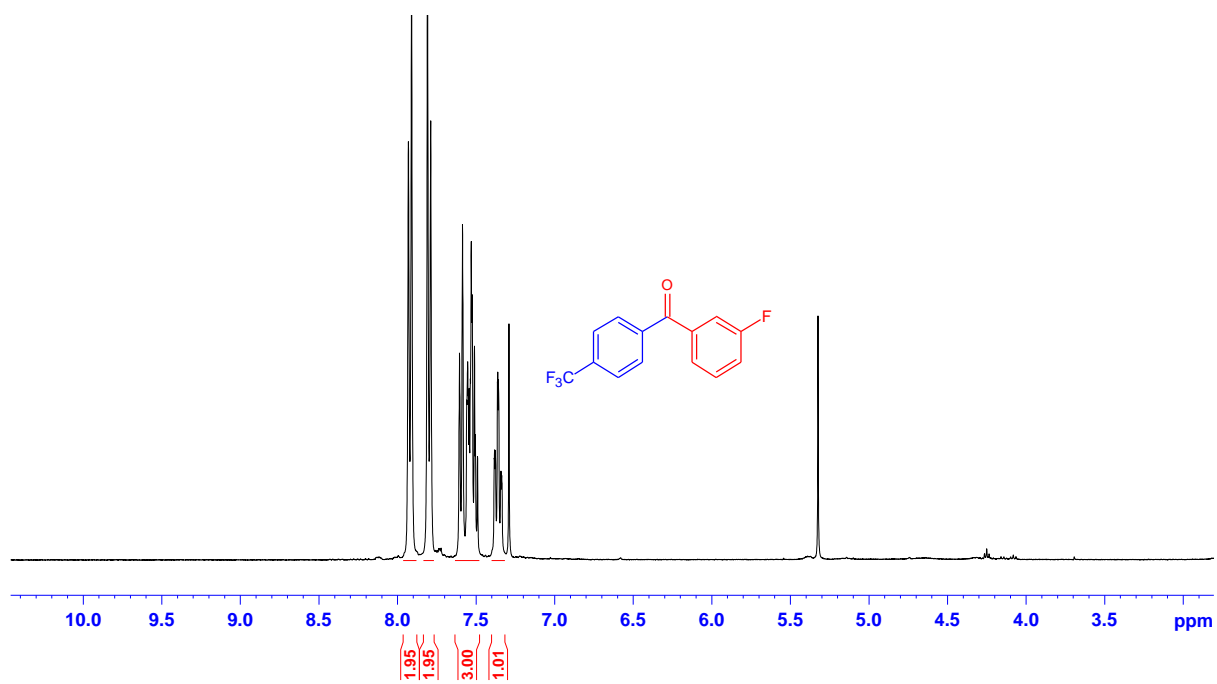
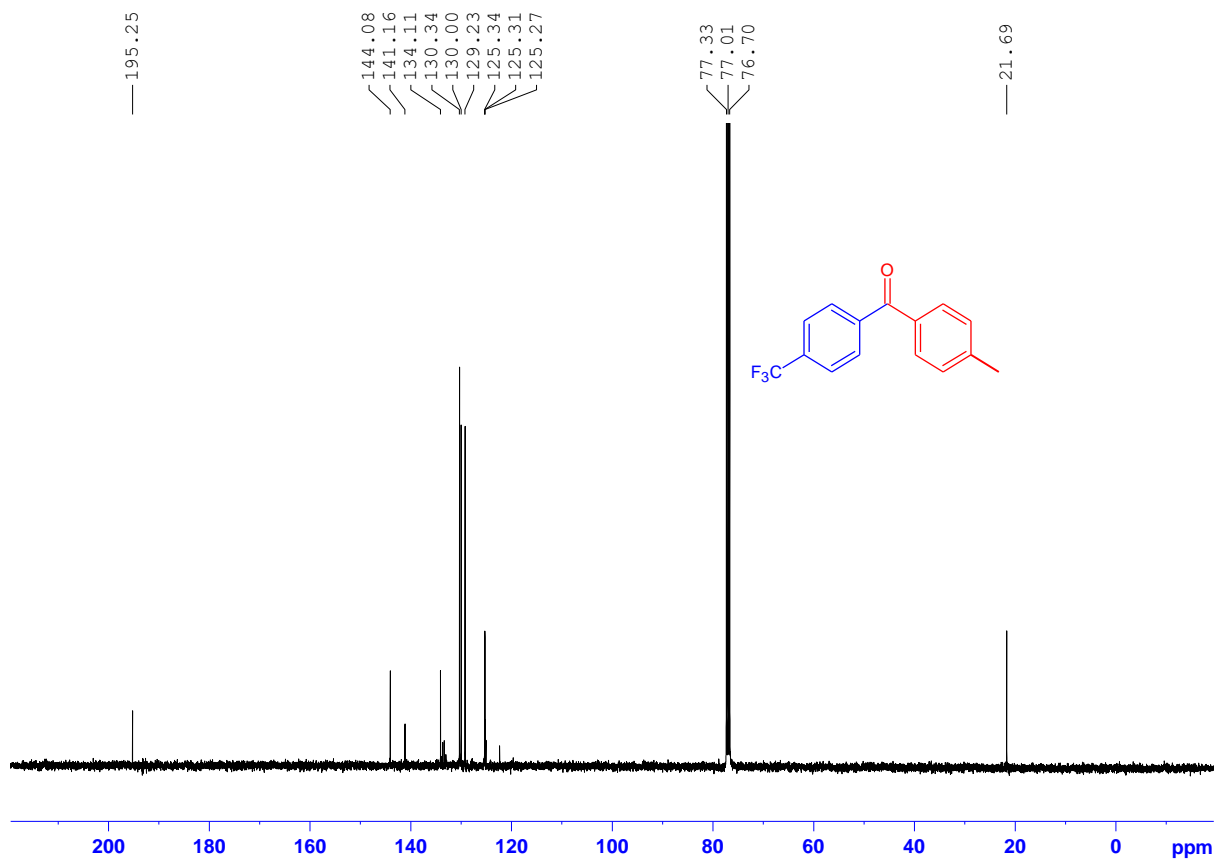


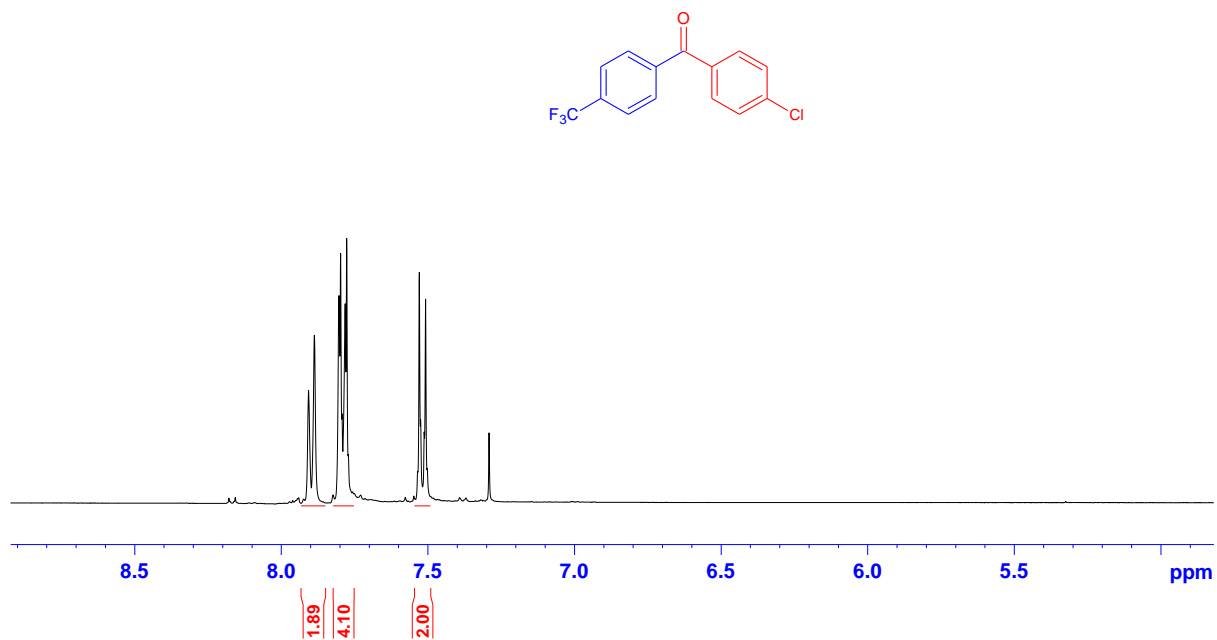
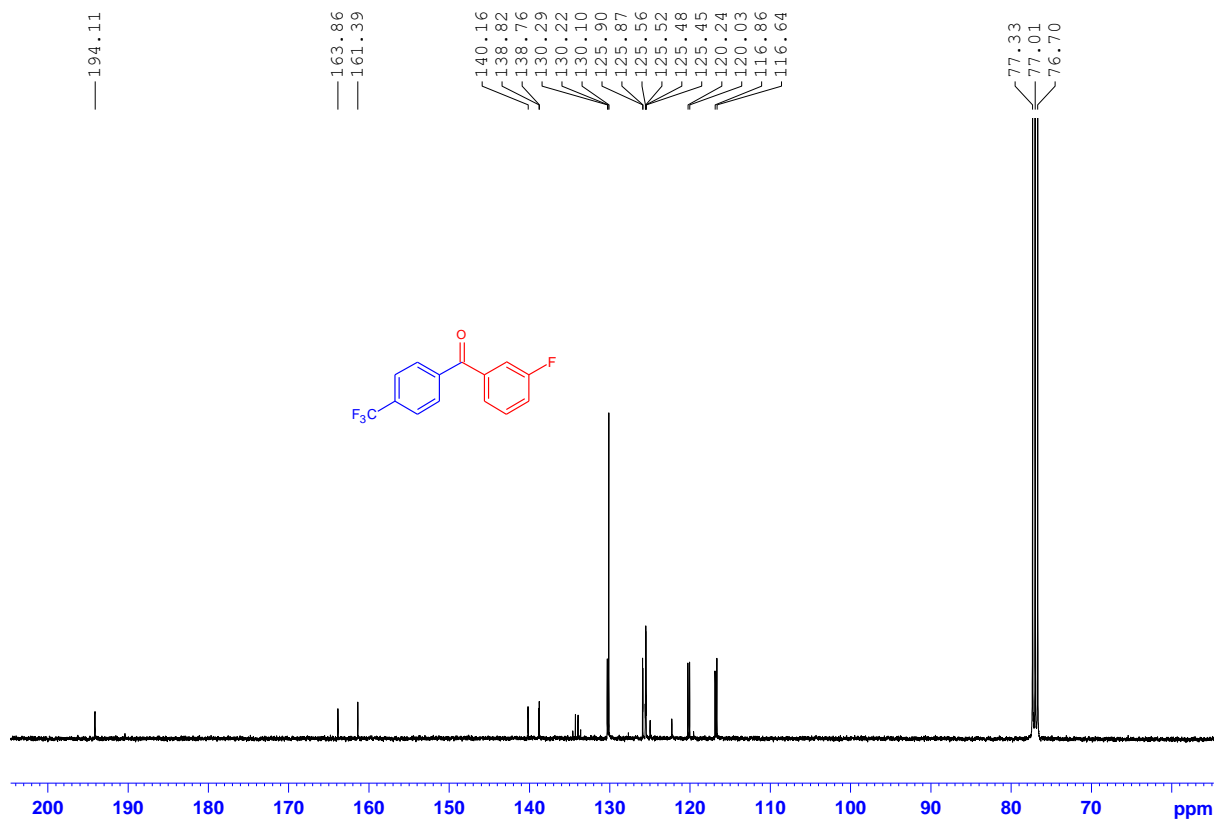












—194.27

140.38  
139.70  
134.47  
134.14  
133.82  
133.49  
131.47  
130.02  
128.93  
125.51  
125.47

