Synthesis of ketones through aerobic transition metal-catalyzed cross-coupling of thioesters

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by

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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.

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Signed [redacted] Dr Siphamandla Sithebe (Supervisor)

Abstract

Asymmetric diaryl ketones are an important class of compounds in organic chemistry due to their presence in natural products, synthesis, cosmetics as well as in biological active compounds. The aim of this project was to expand the scope of thiophilic metal carboxylates catalysts that can be applied to the aerobic Liebeskind-Srogl cross coupling reaction between various thioesters and phenylboronic acids. Thioesters bearing electron neutral, withdrawing and donating groups were successfully synthesized in yields ranging from 35 to 54%Xcv. The electron neutral thioester was used in the optimization of the aerobic Liebeskind-Srogl reaction and CuMeSal proved to be the most effective catalyst in this protocol. CuMeSal was applied in the aerobic synthesis of the asymmetric diaryl ketones bearing a wide range of functional groups including CF_3, SMe, OMe and F yielding up to 65% in 24hrs.

Aerobic Liebeskind-Srogl cross-coupling reaction was applied in the successful synthesis of chalcones, through the coupling of commercially available phenylboronic acids with previously synthesised thioesters catalysed by CuMeSal in DMF for 24hrs,furnishing desired products in poor to excellent yields 26-89%.

Acknowledgements

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Contents

List of Abbreviations

Cu	Copper
Zn	Zinc
Ag	Silver
DMF	Dimethylformamide
$AlCl_3$	Aluminium Chloride
$FeCl_3$	Iron Chloride
HCl	Hydrochloric acid
$Ga(OTf)_3$	Gallium(III) trifluoromethanesulfonate
$MeNO_2$	Nitromethane
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
$Eu(NTf)_3$	Indium(III)tris(trifluoromethanesulfonimide
THF	Tetrahydrofuran
$Fe(acac)_3$	Tris(acetylacetonato) iron(III)
CO	Carbon Monoxide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
DPPP	1,3-Bis(diphenylphosphino)propane
$AgNO_3$	Silver nitrate
Et_2O	Diethyl ether
CH_2Cl_2	Dichloromethane
TEA	Triethylamine
$Pd(OAc)_2$	Palladium acetate
PPh_3	Triphenylphosphine

K_2CO_3	Potassium Carbonate
Et_3N	Triethylamine
$PdCl_2$	Palladium Chloride
Na_2CO_3	Sodium Carbonate
CuTC	Copper(I) thiophene-2-carboxylate
$P(OEt)_3$	Triethyl phosphite
$CsCO_3$	Caesium carbonate
$Pd(MeCN)_2Cl_2$	Bis(acetonitrile)palladium dichloride
TBAF	Tetra-n-butylammonium fluoride
$P(2\text{-furyl})_3$	Tri-2-furanylphosphine
CuMeSal	Copper(I) 3-methylsalicylate
$SOCl_2$	Thionyl Chloride
ESI	Electrospray ionization
^{1} H NMR	Proton nuclear magnetic resonance
^{13} C NMR	Carbon nuclear magnetic resonance
^{19} F NMR	Fluorine nuclear magnetic resonance
$Cu(acac)_2$	Copper acetyl acetate
$Zn(OAc)_2$	Zinc Acetate
Ag ($C_7H_5O_2$)	Silver Benzoate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)

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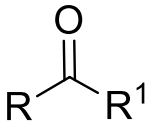
Chapter 1:Introduction:

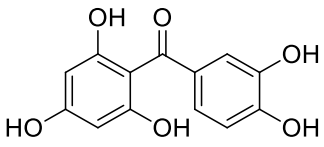
Ketones are organic compounds consisting of a carbonyl group (C=O) bonded to two alkyl or aryl groups **(Figure 1**) [1]. Ketones are an important class of organic compounds due to their functionality, ubiquity in nature as well as their frequent use in the pharmaceutical, cosmetic and textile industry[2].



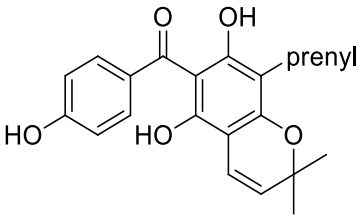
R, R^1 = alkyl, aryl

Figure 1: Ketone structure

Unsymmetrical ketone moieties have received increasing attention because of their application in cosmetics , the food industry[3] , their presences in natural products[4] and for exhibiting several biological[5] and pharmacological activities[6] . For example, benzophenone derivatives such as Macurin and Vismiapheone , isolated from the stems of the *Garcinia multiflora* [7] and *Vismia cayennensis* plants [8]exhibit cytotoxic , antiviral and antioxidative activities[7,8].



Macurin



Vismiapheone

Figure 1: Examples of Asymmetric Ketones

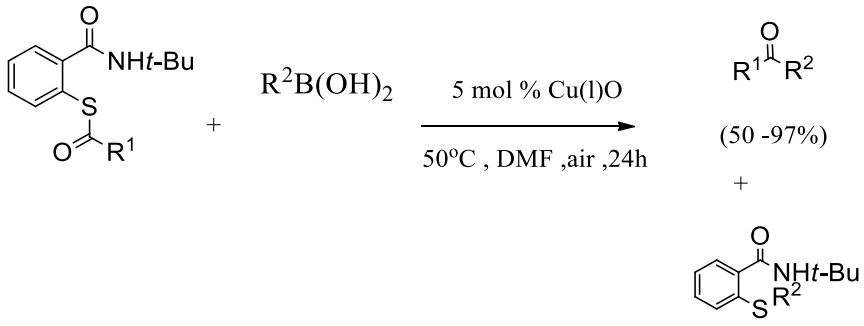
Due to their broad applications, a lot of research has focused on finding milder and more environmentally friendly methods on ketone synthesis in high yields . The traditional method applied to synthesise aryl ketones is the conversion of carboxylic acid derivatives following different routes such as Friedel-Crafts acylation[9],the use of organometallics (Grignard reagents)[10] as well as carbonylation[11].These reactions, however, have shown several drawbacks such as the use of toxic and corrosive reagent[12], the requirement of extreme reaction temperatures and production of harsh by-products [10] .

The palladium-catalysed Suzuki-Miyaura cross-coupling reaction , known for its effectiveness, has become the most frequently used reaction for the synthesis of C-C bonds[13]. The Suzuki-

Miyaura cross-coupling reaction is favoured because of its mild reaction conditions, the commercially availability of boronic acids (which are environmentally safer than other organometallic reagents), and the easy handling and removal of boron containing by-products [14]. This palladium catalysed protocol involves the coupling of organoboron compounds with aryl, alkenyl or alkynyl halide in the presence of a base to produce desired product [15].

This method does have its disadvantages , an example being the use of limitedly available, unstable and base sensitive triflates or organic halides as electrophiles[16]. To combat these issues, Liebeskind and Srogl reported on sulfur-based compounds that could be used as alternative electrophiles due to their stability, ubiquity in natural products and biological molecules[17].

The Liebeskind-Srogl reaction is a palladium catalysed, Cu(I) carboxylate-mediated cross-coupling of boronic acid with thioesters to form desired ketone [17]Villabos , Srogl and Liebeskind expanded on the aforementioned reaction and reported on a copper-templated coupling of boronic acid with a thioester under aerobic conditions referred to as the *Second generation* Liebeskind-Srogl cross-coupling reaction **(Scheme 1)**[18].



Scheme 1 : Second generation Liebeskind-Srogl cross-coupling reaction

Throughout the years researchers have mainly focused on Cu^{I} complexes (Chapter 2) as suitable catalysts in the aerobic Liebeskind-Srogl reaction. This assumption is based on previously reported methods as well as the principle of the Hard-Soft Acid Base theory, which reasons those soft acids such as Cu, Zn and Ag can form bonds with soft bases i.e., Sulphur. However, no methods have reported on the use of Zn and Ag carboxylates in the Aerobic, Transition-metal mediated Liebeskind-Srogl cross-coupling reaction. This allowed us to investigate whether other thiophilic carboxylates would be suitable as catalysts in this protocol.

Different thioesters were synthesized following previously reported methods[18,19] **(Figure 3)** (in Chapter 3) and were used in the optimization of the method .The optimized method was

applied in the coupling of boronic acids bearing electron-neutral, electron-donating and electron-withdrawing substituents with various thioesters to furnish asymmetric ketones and chalcones in poor to moderate yields.

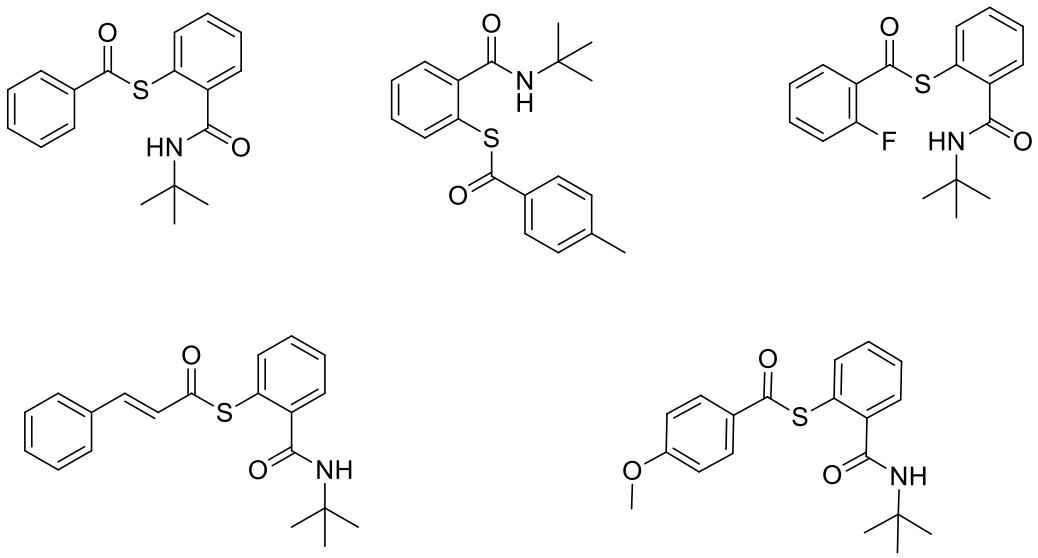


Figure 2 : Synthesized Thioesters

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Chapter 2: Literature review

2.1 Introduction

Transition metal catalyzed cross-coupling reactions are amongst the most powerful tools for the construction of complex organic compounds from simple commercially available precursors [1]. The synthesis of simple and complex biologically active organic compounds such as ketones, biaryl and functional materials heavily rely on transition metal catalyzed C-C bond cross-coupling reactions[2] .The development of synthetic procedures capable of introducing acyl functional groups to construct carbonyl organic compounds especially ketones are of great importance. Substituted aromatic ketones are of particularly important as they are building blocks present in many natural products and biologically active pharmaceutical compounds such as Sulisobenzone[3], s-Kefoprofen[4] and Sofalcone[5].(**Figure 4)**

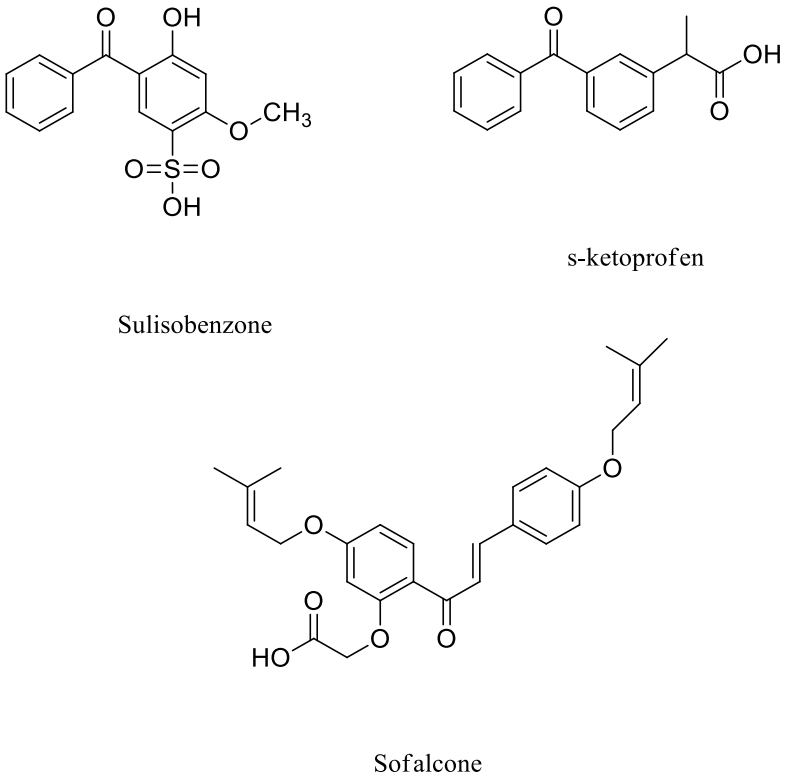
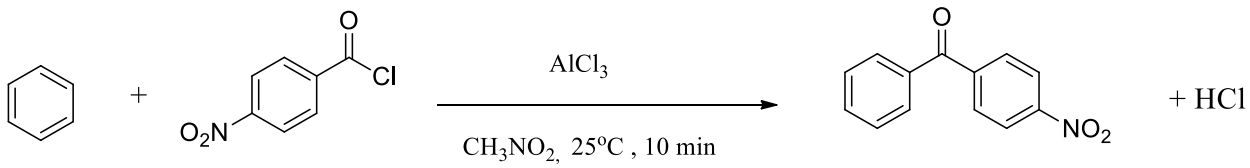


Figure 4: Examples of Substituted Aromatic Ketones

Due to the importance of ketones, there are several procedures reported in literature on the preparation of ketones including various oxidation process such as Friedel-Crafts acylation and reactions that make use of different organometallic reagents as nucleophiles. Friedel-Craft acylation is one of the oldest carbon-carbon bond forming reactions[6] which involves the reaction of nucleophilic benzene derivatives**(1)**with electrophilic acyl chlorides**(2)**in the

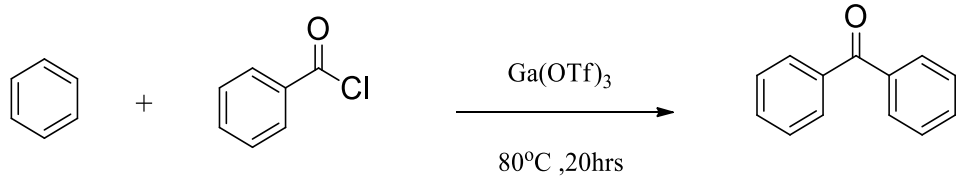
presence of a strong Lewis acid catalyst , usually $AlCl_3$ or $FeCl_3$, to produce ketone**(3) (Scheme 2)**[7]. Although Friedel-Crafts acylation produces ketones in moderate to excellent yields there are several drawbacks associated with this reaction such as the use of corrosive and polluting Lewis acids[8] which usually have to be added in excess[9], harsh reaction conditions[10] and production of corrosive HCl by-products [11].



1 **2** **3** (54.6-97.1%)

Scheme 2

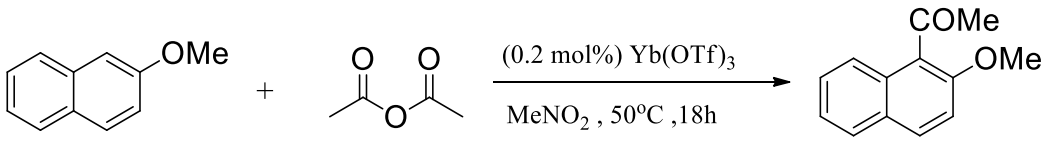
To overcome the use of a harmful and corrosive catalyst ($AlCl_3$ or $FeCl_3$), environmentally friendly lanthanide trifluoromethanesulfonates are used as catalysts[12]. Prakash and co-workers developed a method for the acylation of aromatic compounds **(1)** with benzoyl chloride **(4)** in the presence of a catalytic amount of gallium trifluoromethanesulfonates to produce desired products **(5**) in moderate to good yield. Unlike $AlCl_3$, gallium trifluoromethanesulfonates is not water sensitive and can be recovered from an aqueous solution after drying. The catalyst can be used several times without any loss in catalytic activity **(Scheme 3)**[13].



1 **4** **5** (49-97%)

Scheme 3

The use of acyl chlorides as nucleophiles also presented some limitations as they are easily hydrolysed to carboxylic acids in the presence of water. To overcome this obstacle, Kawada and co-workers used more stable acid anhydrides as acylating agents instead of acyl chlorides[14].2-Methoxynaphathalene (**6)** is acylated by acetic anhydride **(7)** in the presence of catalytic amount of ytterbium trifluoromethanesulfonates in $MeNO_2$ producing the desired products **(8)** in moderate to good yield **(Scheme 4)** [14].

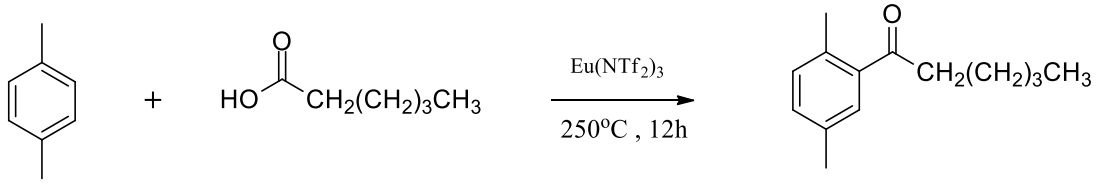


6 **7** **8** (51-78%)

Scheme 4

$Yb(OTf)_3$ is ineffective in the acylation of unsubstituted benzene derivatives, however, it is effective when benzene derivatives with electron-donating groups are used as nucleophiles. $Yb(OTf)_3$ is not water sensitive as it can be reused more than two times while maintaining its catalytic activity [14].

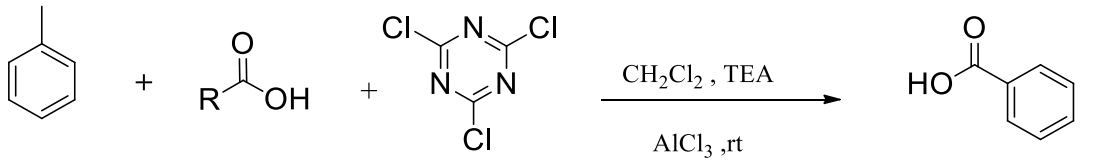
In an attempt to synthesize ketones from Friedel-Crafts acylation, Kwamura and co-workers developed a procedure which uses aliphatic carboxylic acid as electrophiles. In these reactions, a range of aliphatic carboxylic acids **(9)** are reacted with *p*-xylene derivatives **(10)** in the presence of $Eu(NTf_2)_3$ to produce desired ketones **(11)** in good yields **(Scheme 5)**[15]



9 **10** **11** (73-91%)

Scheme 5

The use of high temperature of up to 250°C for 12 hours was however a concern. To improve on those reaction conditions, Kangani and co-workers developed an acylation reaction of toluene **(12)** with a carboxylic acid **(13)** in the presence of cyanuric chloride **(14)** at room temperature to give the desired product **(15)** in high yields **(Scheme 6)**[16].

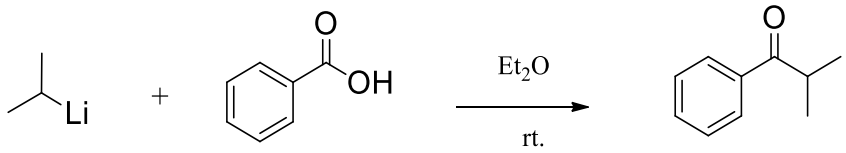


12 **13** **14** **15** (85 -95%)

Scheme 6

The 1:1:1 molar reaction of cyanuric chloride, carboxylic acid, and triethylamine at room temperature results in an acid chloride which proceeds to acylate the toluene. This reaction make use of $AlCl_3$ as catalyst resulting in a HCl by-product which is buffered by the triethylamine [16].

The synthesis of ketones is not only limited to using nucleophilic benzene derivatives as in Friedel-Crafts acylation. Organometallic reagents **(16)** can also be cross-coupled to carboxylic acid derivatives **(15)**, producing ketones in good to excellent yields **(17) (Scheme 7)**[17].

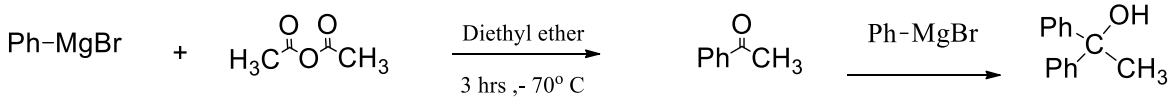


16 **15** **17** (60%)

Scheme 7

The first example of this kind of chemistry was invented by Freund when he demonstrated that the reaction of acyl chlorides with dimethyl and diethylzinc produced ketones[18]. Following this discovery, several other scientists disclosed that the organometallic compounds of copper [19], cadmium [20], magnesium[21], zinc[22] and aluminium[20] are also effective nucleophiles when coupled with carboxylic acid derivatives. However, only the use of organomagnesium, organozinc and organocadmium reagents gave good to excellent yields [23].

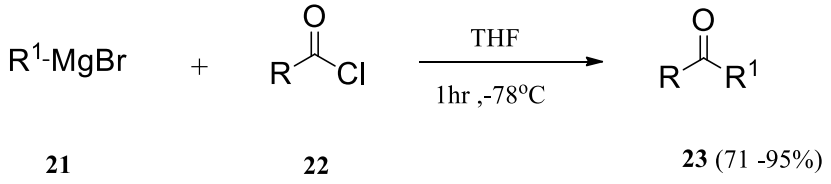
Organomagnesium halides also known as Grignard reagents are the most commonly used organometallic reagents due to their ease of preparation and broad application in organometallic and organic synthesis[24]. Newman and co-workers reacted a Grignard reagent **(18)** with an ether solution of acetic anhydride **(7)** to give corresponding ketone **(19)** in moderate to high yields **(Scheme 8)**[25].



18 **7** **19** (42-79%) **20**

Scheme 8

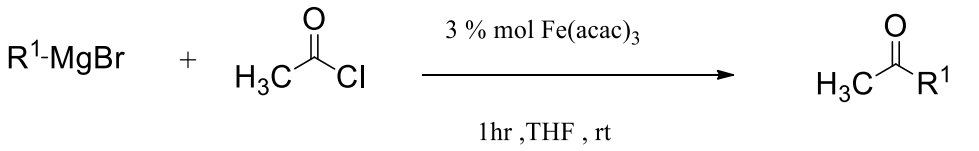
The limitations of this protocol are the formation of tertiary alcohol **(20)** due to the Grignard reagent **(18)** reacting with the ketone **(19)** product. Sato and co-workers were able to overcome this problem through the slow addition of the Grignard reagent **(21)** in THF to excess acid chloride **(22)** in THF to give ketones **(23)** in almost quantitative yields **(Scheme 9)** and produced less than 1% of alcohols in most of the reactions[26]. The use of THF as a solvent played a significant role in the suppression of alcohol side products because when the same reaction was carried out, using diethyl ether as the solvent, a higher percentage of alcohol by-products was formed[26].



21 **22** **23** (71 -95%)

Scheme 9

Even though the method reported by Sato and co-workers gave ketones in good to excellent yields it requires an excess amount of acid chloride and must be conducted at -78°C. Fiandanese and co-workers reported on an improved alternative reaction of 1 equimolar of Grignard reagent **(21)** and acyl chloride **(24)** in the presence of $Fe(acac)_3$ at room temperature to give ketones **(25)** in good to excellent yields **(Scheme 10)**[27]**.**

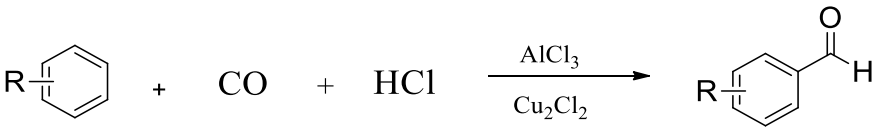


21 **24** **25** (63-92%)

Scheme 10

The transition metal catalyzed cross-coupling reaction of organic electrophiles with organometallic reagents in the presence of carbon monoxide is a viable synthetic method for the preparation of unsymmetrical ketones [28]. This method, known as carbonylation, is the reaction responsible for the introduction of a carbonyl group into a parent molecule as a

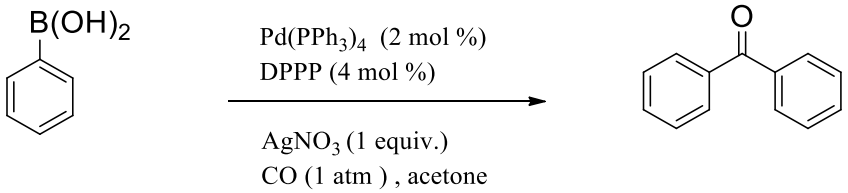
carbonyl source. Carbonylation reactions plays an important role in industry as it is used to covert various bulk chemicals into a variety of useful products applicable in our everyday lives such as carboxylic acid, ketones, aldehydes etc[29]. This transformation is attractive due to its simplicity, efficiency, economic viability and it gives desired product in excellent yields [30].



Scheme 11

However, this transformation does have its limitations as it requires a constant rate of pressurized toxic carbon monoxide and high temperature [30].

Palladium catalysed carbonylation reactions are the most popular transition metal catalyzed synthesis of ketones initially pioneered by Heck and co-workers in the early 1970s[31] and continued by Negishi and co-workers in the 1980s [32]. Continuing with the work reported by Heck, Li and co-workers recently described the treatment of phenylboronic acid **(26)** with CO at atmospheric pressure to give symmetrical diary ketones **(5) (Scheme 12)** [33].Usually , this reaction is conducted in the presence of two substrates ,i.e. organoboronic acid and a acyl halide to get unsymmetrical ketones , however in this case symmetrical ketones were produced.

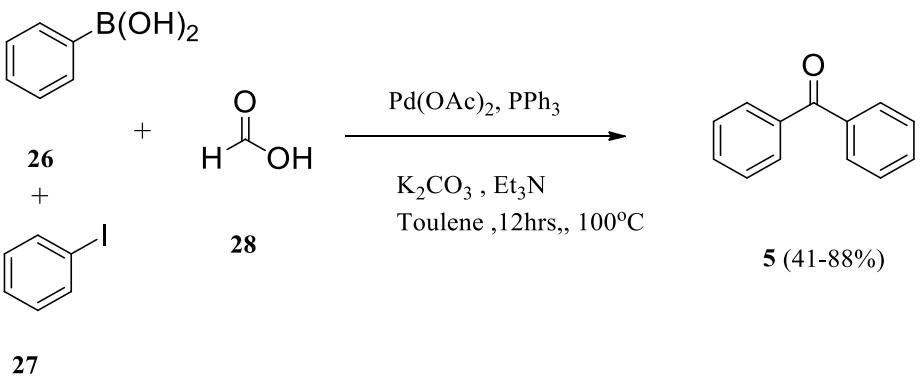


26

5 (49 -87%)

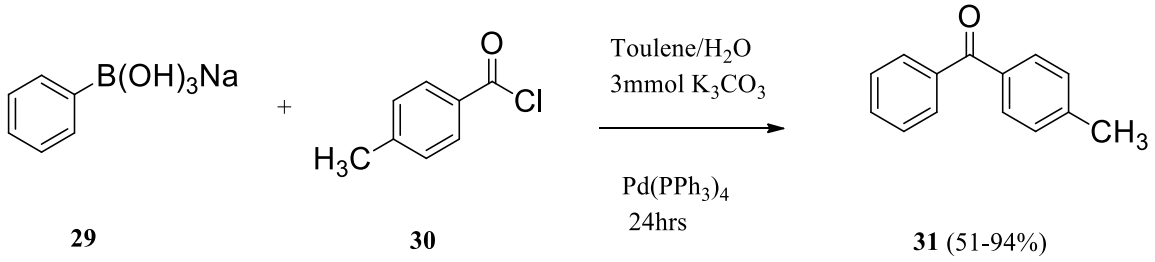
Scheme 12

The use of CO as a carbonyl source makes the operation and handling of carbonylation reaction unattractive as it is not user friendly, particularly in large industrial scales. As a result Qui and co-workers developed a CO free coupling of an aryl halide **(27)** and boronic acid **(26)** using formic acid **(28)** as CO source to produce desired diary ketones **(5)** in moderate to excellent yields **(Scheme 13)** [34].



Scheme 13

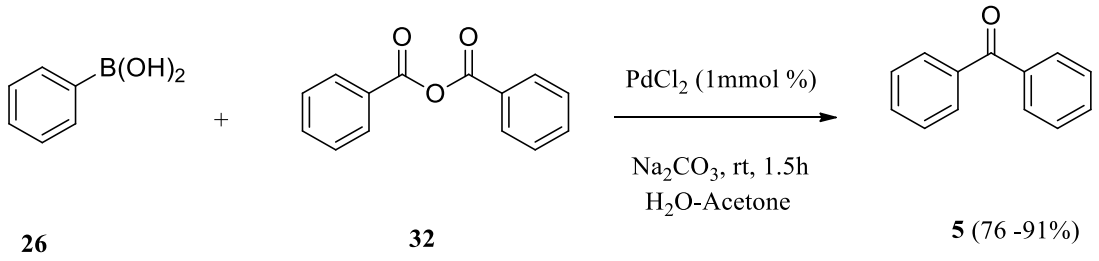
Pd-catalyzed Suzuki cross-coupling reactions of carboxylic acid derivatives with boronic acid or borate esters in the presence of excess amount of base, is also a well-known procedure for the synthesis of ketones particularly because the starting materials are readily available, non-toxic, and stable towards moisture. Hajipor and co-workers reported the Pd-catalyzed cross-coupling reaction of boronic acid derivatives **(29)** with acyl halides **(30)** to give the desired diaryl ketones **(31)** in excellent yields.**(Scheme 14)**[35]**.**



Scheme 14

In the optimization of the method reported by Hajipour, 1 mmol of K_3CO_3 resulted in conversion of 89% but the use 3 mmol increased the conversion percentage to 94%[35].

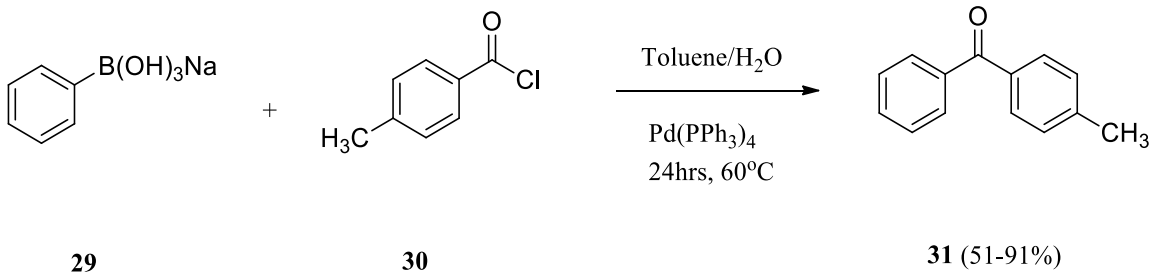
The traditional Suzuki-Miyaura cross-coupling acylation reaction usually makes use of unstable acyl chlorides as electrophiles. As part of an ongoing development in finding more stable alternative electrophiles, a variety of acyl sources such as carboxylic anhydrides[36], carboxylic acids[37], amides[38] and thiol esters[39] have since been widely explored as potential acylating agents. Xin and co-workers reported on the Suzuki acylation reaction using benzoic anhydride as a electrophile[36]. In this reaction, Xin reported that an excess amount of arylboronic acid **(26)** with 1 equivalent of benzoic anhydride **(32)** in the presence of Na_2CO_3 to produce the expected diaryl ketone **(5)** in quantitative yields **(Scheme 15)**[36]**.**



26 **32** **5** (76 -91%)

Scheme 15

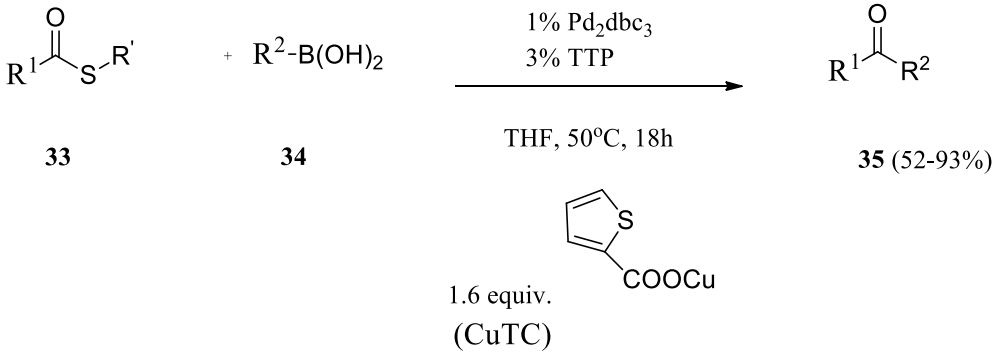
Most Pd-catalyzed Suzuki- Miyaura cross-coupling reactions require a base to transform, *in-situ*, boronic acid to a better nucleophilic borate. The use of free base has however, proven to be problematic particularly when base sensitive substrates are reacted. An example of this is in the synthesis of 4-amino or 4-hydroxybenzophenone under basic conditions produces a complex mixture of by-products as a result of deprotonation of the hydroxyl or amino group leading to undesired products [40]. To overcome this obstacle Sithebe *et al* developed a base free Suzuki-Miyaura acylation reaction in which activated borates **(29)** are reacted with acyl chlorides **(30)** at 60°C, furnishing ketones **(31)** in moderate to excellent yields. In this way, base sensitive amino and hydroxyl groups were catered for **(Scheme 16)**[41].



29 **30** **31** (51-91%)

Scheme 16

In the efforts to find a base-free transition metal-catalyzed cross-coupling method for the construction of C-C bond, Liebeskind and Srogl reported a mechanistically unique and unprecedent Pd-catalyzed Cu^{I}-carboxylate-mediated cross-coupling reaction between thioester **(33)** and boronic acid **(34)** to form ketones **(35)** in moderate to excellent yields **(Scheme 17)** [42].



Scheme 17

2.2 Liebeskind-Srogl Cross-coupling Reaction

A key feature of the reaction is the requirement of stoichiometric amounts of thiophilic Cu[1] carboxylates, such as CuTC, as metal cofactor. Over the years the scope of this reaction has been extended and subsequent studies have shown that commercially available Copper (I)-3-methylsalicylate and Copper(I) diphenylphosphinate can be used as metal cofactors in the cross-coupling reaction [43]

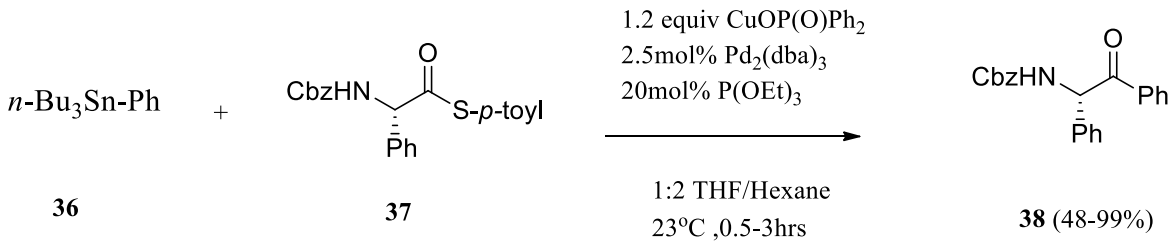
Copper(I)-3-methylsalicylate

Copper(I) diphenylphosphinate

Figure 5 : Cu (I) co-factors

Nucleophilic substrates in the Liebeskind-Srogl coupling are not only limited to the use of organoboron derivatives as over the years several other nucleophilic reagents such as organostannes[44] ,arylsiloxanes as well as aryl organoindium have been reported as efficient nucleophiles in this cross-coupling reaction.

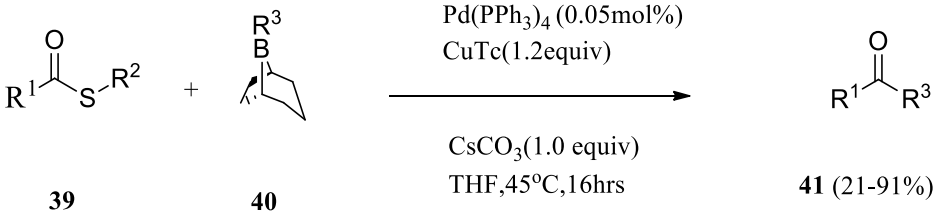
With the intention to synthesize *N*-protected α-amino ketones with high enantiopurity, Liebeskind and co-workers developed the Cu(I) diphenylphosphinate (CuDPP)-mediated, palladium-catalyzed coupling of a variety of aryl, heteroaryl and alkenyl substituted tri-n-butylorgannstannes **(36)** and α-amino acid thioesters **(37)** resulting in α-amino ketone products **(38)** in moderate to excellent yields **(Scheme 18)**[44].



Scheme 18

The viability of π-deficient heteroarylstannes is an advantage to this protocol compared to the related boronic acid systems[44].

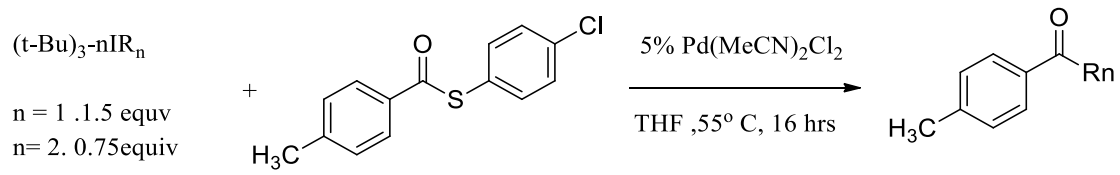
Breaking away from the conventional Liebeskind-Srogl cross-coupling reaction, Yu and co-workers reported the coupling of a thioester **(39)** and B-alkyl-9-BBN derivatives **(40)** in the presence of a base, $CsCO_3$, resulting in desired alkyl-alkyl and aryl-alkyl ketones **(41)** in poor to excellent yields **(Scheme 19)** [45]



Scheme 19

Yu and co-workers observed that the addition of 1 equiv. of $CsCO_3$ to the coupling of the thioester and B-alkyl-9-BBN derivatives significantly improved the yields of the products[45]. According to Yu and co-workers a base is essential in this coupling as it activates the organoborane coupling partner. The presence of a base, however, reported to cause decomposition of the thioesters.

To overcome this challenge Fausett and co-workers reported that primary, secondary and aryl organoindium compounds **(42)** are more convenient nucleophiles when coupled with thioesters **(43)** because they don't have to be activated by a base to form desired ketones **(44)** in moderate to excellent yields **(Scheme 20)**[46].

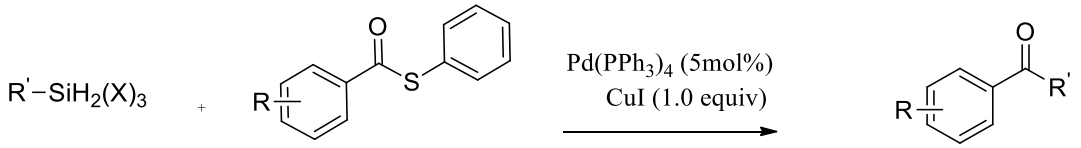


42 **43** **44** (55-95%)

Scheme 20

The Liebeskind-Srogl cross-coupling reaction typically requires a Cu co-catalyst to break the S-C bond but interestingly the Pd-catalyzed cross-coupling method reported by Fausett and co-workers is not Cu[1]-mediated[45]. Indium is thiophilic which means that the organoindium reagent is able to form a bond with the sulphur present in the thioester leading to the cleavage/breaking of the S-C bond and so no Cu co-catalyst is required for this step[46].

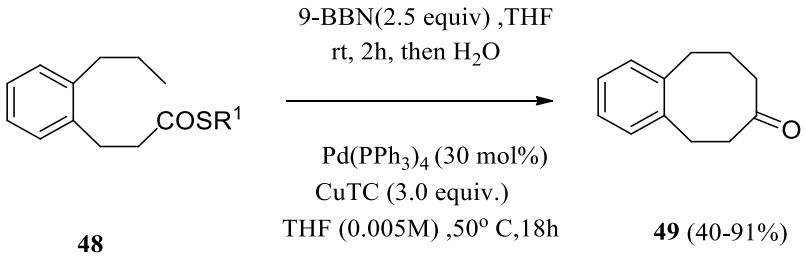
Over the years the expansion of the Liebeskind-Srogl coupling reaction scope has led to several reports of various organometals i.e., organotin, organoindium and organoboron, as efficient nucleophilic coupling partners. However, some of the organometallic are toxic, unstable, and difficult to prepare[47]. In search of a more convenient and environmentally safe nucleophilic coupling partner, Van de Eycken's research group developed a so called Libeskind-Hiyama-type coupling reaction in which organosiloxane **(45)** is efficiently coupled with thioesters **(46)** furnishing desired ketones **(47)** in good to excellent yields **(Scheme 21)**[47].



45 **46** **47** (86 -96%)

Scheme 21

Nakada and co-workers were the first to report a one-pot hydroboration/intramolecular Liebeskind-Srogl cross-coupling reaction of ω-alkenyl thioester **(48)** with 9-BBN for the synthesis of medium-sized carbocyclic ketones **(49)** in moderate to excellent yields **(Scheme 22)**[48]**.**

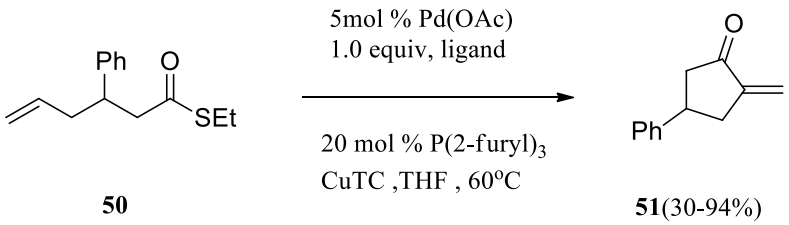


48 **49** (40-91%)

Scheme 22

ω-alkenyl thioesters with substituents in the *ortho* position are more likely to undergo ring-closing reactions[48].

In 2013, Du Bois and co-workers reported on a intramolecular cross-coupling of thioesters **(50)** with olefins that resulted in cyclic ketones **(51)** in moderate to excellent yields **(Scheme 23)**[49]



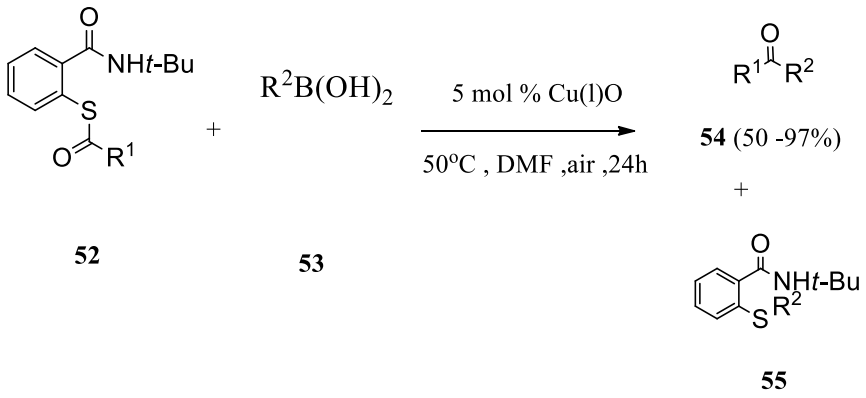
50 **51**(30-94%)

Scheme 23

This method took advantage of the unique reactivity of thioesters with Pd catalysts with low oxidation states and Cu^1 co-catalyst to form acyl-metal species[49]. Trapping the acyl-metal intermediates with the alkene function group resulted in the corresponding exomethylene cycloalkanone product **(57)**. When α-substituted thioesters were used as electrophilic reagents in this intramolecular cross-coupling reaction the yields were slightly low. This is due to the competing decarbonylation and the resultant β-hydride elimination[49]. As a result ,co-ordinating groups such as hydroxy groups were introduced to the β-carbon to stabilize the acyl-Pd intermediate in order to suppress these side reactions[49].

The requirement of an excess amount of thiophilic Cu^I carboxylate, also known as *First-Generation Liebeskind-Srogl cross-coupling,* was not favourable in an industrial setting as Cu^I-carboxylate was required in excess. Villaboos and co-workers made improvements on the First Generation Liebeskind-Srogl cross-coupling reaction and reported on a Cu^l -catalyzed cross-coupling of thiol esters **(52)** and organoboronic acids **(53)** under aerobic conditions, in which

only a catalytic amount of Cu^{I} carboxylate is required to give ketones **(54)** in moderate to excellent yields **(Scheme 24)** known as the Second Generation Liebeskind-Srogl Cross-Coupling reaction [50]**.**

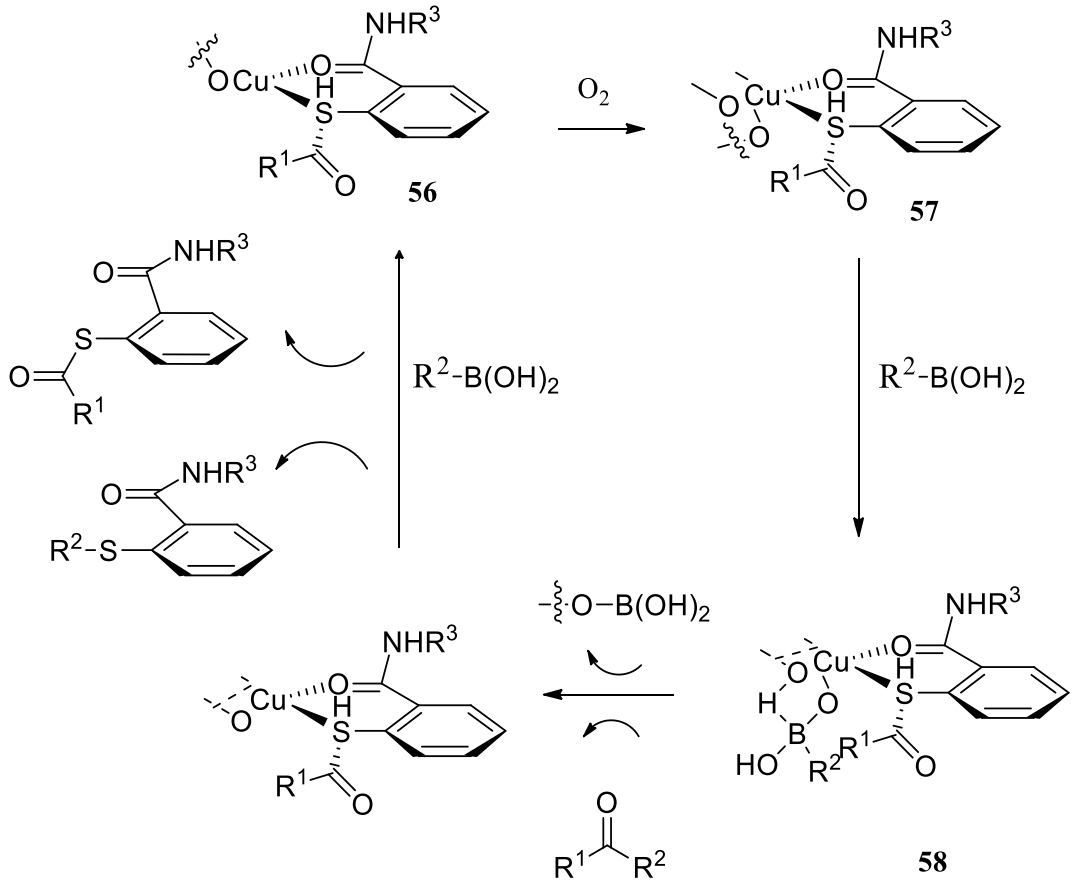


Scheme 24

A sacrificial second equivalent of boronic acid is essential as it serves to scavenge the thiolate from the reaction cycles thus shifting the equilibrium towards the product[50].

The mechanism of this aerobic cross coupling reaction was studied and explained by Villabos and co-workers. According to Villabos and co-workers, the absence of Pd in the catalytic sequences as well as the lack of any precedent for oxidative addition of the S-C bond to Cu^{I} make a traditional oxidative addition-transmetallation-reductive elimination sequences highly unlikely. Control experiments suggests that the stoichiometric amount of the Cu^{I} carboxylate co-factors pairs with the generated thiolate through a thermodynamically strong Cu-thiol esters bond, while the borophilic carboxylate pairs with the $-B(OH)_2$ moiety to form a thermodynamic sink[50].

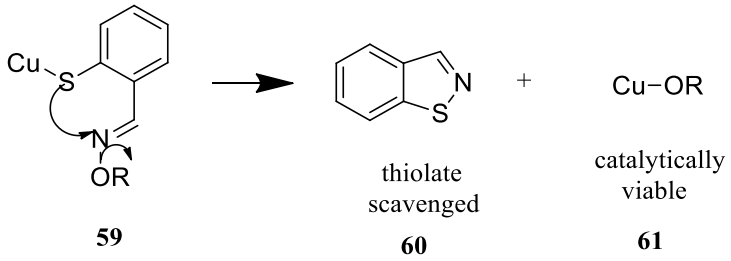
Closely looking at previously documented studies of proposed Cu^{I} dioxygen reactions, Villabos and co-workers proposed that the mechanism proceeds via three stages. The reaction is initiated by the oxidation of Cu^{I} intermediate to Cu^{II} or Cu^{III} intermediates **(56)** which are easily accessible through low energy intervention. The pairing of the borophilic carboxylate with boronic acid allows the coupling of the adjacent nucleophilic organoboron moiety with the acyl group from thioester thus eliminating ketones and a higher oxidation $Cu^{II/III}$ thiolate **(57)**. The last step of the mechanism is the reaction of the generated high oxidation Cu-thiolate with the sacrificial boronic acid producing the thiolate ether and the regeneration of Cu^{I} for re-entry into the catalytic cycle **(58) (Scheme 25)**.



Scheme 25

Upon further investigation of the *Second Generation Liebeskind-Srogl* protocol scope, Villalobos noted that only a specific thioester with -NHt-Bu pendent positioned appropriately participated in efficient Cu-catalysed cross-coupling to form desired ketone product[50].

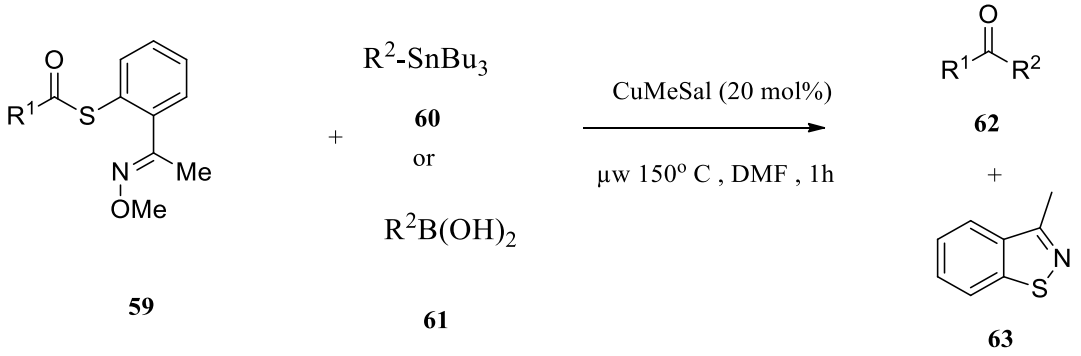
An intense understanding of the First and Second generation desulfitative cross coupling reaction raised two critical questions: Can the desulfitative of the boronic acids and thiorganics be effective using only catalytic amount of Cu^{I} precursors and without the addition of the second, sacrificial, equivalence of boronic acid? These questions were addressed by Zhang *et al* when they developed a metallothionein system in which the N-S bond cyclizes to form a thiolate scavenger **(60)** and Cu **(61)** for catalysis[51]**(Scheme 26)**.



Scheme 26

Unlike the Second generation desulfitative coupling protocol, which is limited to only boronic acids as nucleophiles, the current metallothionein desulfitative coupling can also accommodate organostannanes as efficient nucleophilic coupling partners.

In this protocol, a corresponding thiol ester **(59)** is reacted with 1 equivalence of boronic acid **(61)** or organostannane **(60)** in the presence of catalytic amount of Cu^{I} precursor in the microwave producing the desired ketone **(62)** in excellent yields as well as thiolate scavengers **(72)**.[51] **(Scheme 27)**

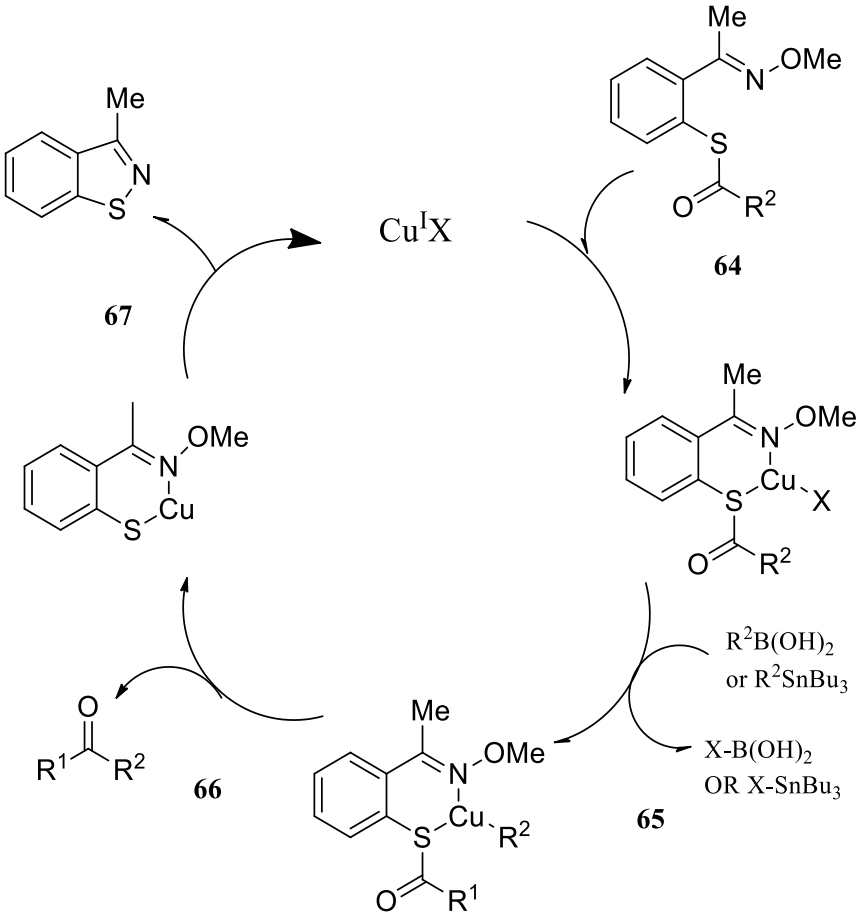


Scheme 27

The catalytic mechanism of metallothionein desulfitative cross coupling is unique in a way that high oxidation $Cu^{II/III}$ states are not required.

The catalytic cycle is initiated by the coordination of Cu^{I} to the thiol ester-oxime to form a S, N-chelation **(64)**. The S, N-chelation undergoes transmetallation from either boron or tin to Cu^{I} which allows the organocopper R^2 and the thiol ester carbonyl carbon to be in proximity **(65)**. The induced electrophile activation of the thiol ester along with the proximity effect is expected to furnish a ketone through the reaction of the generated organocopper reagent and a Cu^{I}-thiolate is eliminated **(66)**. At this point in the Second Generation Liebeskind cross coupling reaction the catalytic cycle would halt as there is no effective means to scavenge the thiolate from Cu to regenerate a Cu oxygenate. However, in this transformation the Cu^{I}-thiolate reacts

with the internal oxime functionality effectively trapping the thiolate as a benzoisothiazole and an active Cu oxygenate catalyst that re-entries the catalytic cycle **(67)**[51] (**Scheme 28**).



Scheme 28

The discovery, development, and advancement of Libeskind Srogl cross-coupling reaction has, without a doubt, expanded the scope of the cross-coupling methodologies available in organic synthesis. The most outstanding and a unique fixture of the Libeskind Srogl cross-coupling reaction, amongst other coupling reaction reactions, is the mild reaction conditions, the broad scope of substrates and the uniqueness of the mechanism. Despite these advantages, the use of expensive Cu^1 carboxylates as co factors as well as reaction promoters is one of the drawbacks that requires further developments. As a result, the pursual of other cheaper copper percussors or thiophilic elements which can promote the reaction at low loading and higher catalytic activity would be of great achievements in this realm.

To the best of our knowledge there are no procedures in literature which describe the use of other thiophilic metal carboxylates as catalysts in the Aerobic Libeskind-Srogl cross-coupling reaction in the synthesis of ketones. In this study we study the efficiency of thiophilic (Ag and

Zn) carboxylates as catalysts in this cross-coupling protocol based on the Hard-Soft Acid-Base theory.

2.3 Aims and objectives

The aims of the project were to:

- synthesize and characterize (using ^{1}H and ^{13}C NMR techniques, mass spectrometry as well as Infrared) different thioesters bearing N-tert-butyl pendant following reported procedures.
- find optimal reaction conditions for the synthesis of ketones from the synthesised thioester bearing *N*-tert-butyl pendant using cheap Cu^{1}-carboxylate and
- investigate the suitability and catalytic activities of other thiophilic metal carboxylate (Ag and Zn)
- Synthesise different ketones from the optimal reaction conditions and characterised them.

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Chapter 3: Results and Discussion

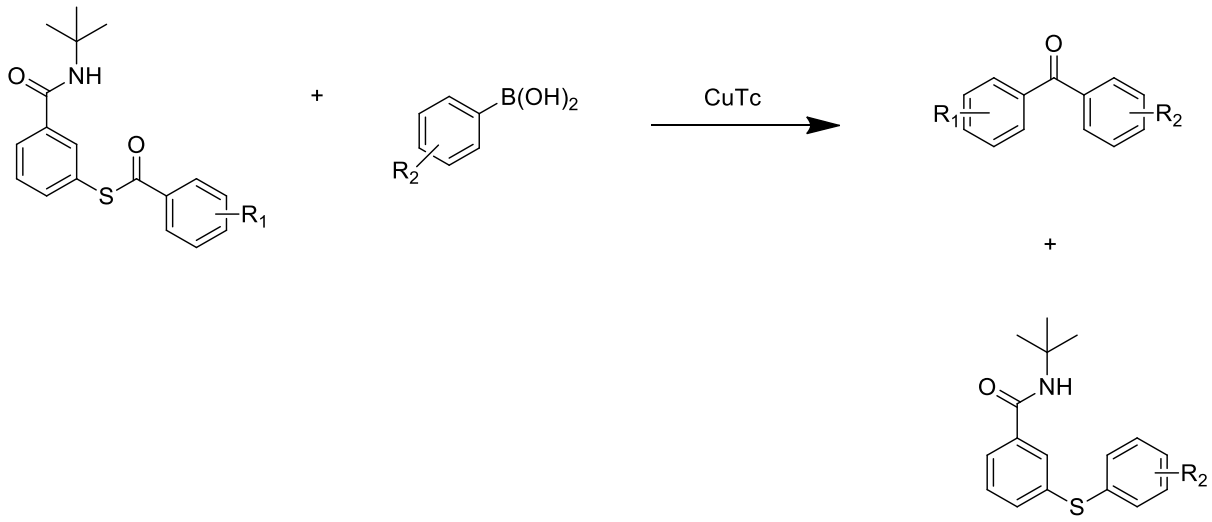
Due to the wide occurrence of asymmetric diaryl ketone moiety in a variety of natural products[1], fragrances[2], dyes [3], pharmaceuticals and biological active compounds as well as in organic synthesis, a lot of research has gone into finding milder and more environmentally friendly methods to synthesize asymmetric diaryl ketones in high yields. The synthesis of diaryl ketones, using transition metal catalysed cross-coupling reactions has been extensively explored, with one of the most frequently used method being the Suzuki-Miyaura cross-coupling reaction[4]. The Suzuki-Miyaura cross-coupling reaction involves the coupling of an organoboron derivative with different electrophiles in the presence of a base and catalyst. The reaction conditions of this protocol, however, do not accommodate base sensitive substrates.

To find a more suitable cross-coupling reaction which can also accommodate base sensitive substrates, an alternative Liebeskind and Srogl cross-coupling reaction was reported and it is based on a base-free copper-mediated coupling of thioester with organoboron derivatives. According to the HSAB theory copper, a soft acid, is thiophilic and so it would form a strong bond with sulphur, a soft base, resulting in cleavage of the S-C bond allowing for the formation of the ketone product.

In this study we investigate the effectiveness of thiophilic metal carboxylates (such as Copper acetate, Silver benzoate and Zinc acetate) in the Liebeskind-Srogl coupling reaction to find optimal reaction conditions for the synthesis of ketones from electrophilic thioesters and nucleophilic organoboron compounds.

3.1 Synthesis of Thioesters

Initially the thioesters were synthesised using readily available reagents following previously reported methods.[5] Villabos and co-workers synthesised various thioesters which were used as efficient electrophiles in aerobic Liebeskind-Srogl coupling reactions resulting in substituted diaryls. In the study Villabos and co-workers noted that the thioesters bearing a NH-^{t}Bu pendent positioned on the *ortho*-position relative to the thioester functionality participated efficiently in Cu-catalysed cross-coupling to form asymmetric ketones. A sacrificial second equivalent of boronic acid was required to scavenge the thiolate from the reaction cycle resulting in the generation of the Cu-catalyst as well as thioether side product (**Scheme 29**).

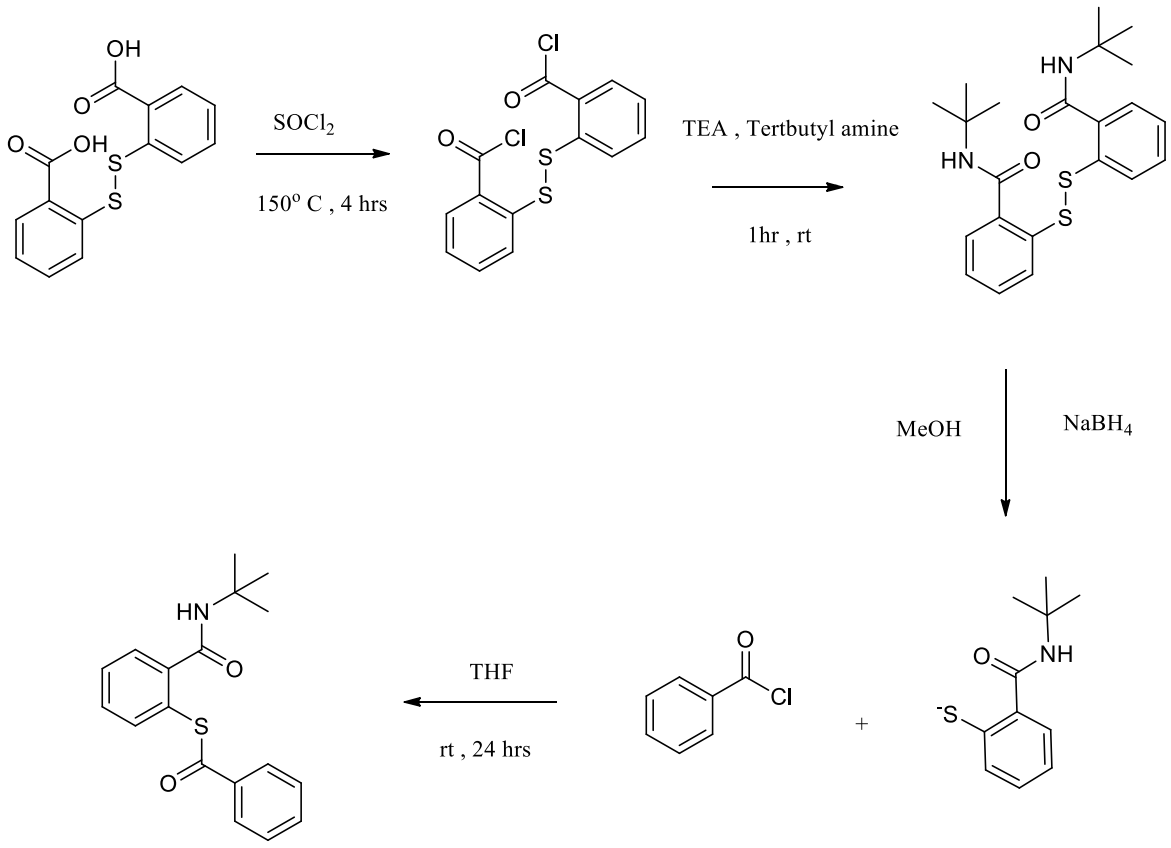


Scheme 29

3.1.1 The synthesis of thioesters

Following the procedure reported by *Liebeskind et al*, the thioesters were successfully isolated as light-yellow crystalline powder at 49-54 % yields **(Scheme 30**). Purification of the desired products were obtained after column and radial chromatography. The resulting pure products were confirmed using ^{1}H, ^{13}C and ^{19} F NMR spectra were consistent with the desired products, showing expected peaks (see appendix A)

A typical synthesis of the desired thioesters was initiated by chlorination of dicarboxylic acid using thionyl chloride at elevated temperatures. After complete evaporation of thionyl chloride, the resulting diacyl chloride was treated with a base, triethyl amine, followed by the addition of a nucleophilic tertbutyl amine to form the desired diamide moiety. The reduction of disulfide bond using a mild reducing agent (sodium borohydride), in protic solvent, results in the thiolate ion which were reacted with appropriate acyl chloride furnishing the desired thioesters in low to moderate yields (**Scheme 31**).



Scheme 31

3.1.2 Synthesis of S-(2- (tert-butylcarbamoyl) phenyl) benzothioate

S-(2- (tert-butylcarbamoyl) phenyl) benzothioate **(68)** was prepared in isolated yield of 49% as mustard powered product. The structure was confirmed through the elucidation of ^{1}H NMR, ^{13}C NMR spectrum as well as liquid chromatography-mass spectrometry. The ^{1}H NMR spectrum of S-(2-(tert-butylcarbamoyl) phenyl) benzothioate **(68)** showed a singlet resonating at δ_H 1.32 ppm which integrates for 9 protons corresponding to the three methyl groups of *tert*-butyl functionality. The spectrum showed a broad singlet peak resonating at δ_H 6.00 ppm integrating for only one proton .The broad singlet was assigned to the -*NH* and is consistent with the peak reported in literature [6]. The aromatic region of the spectrum shows multiplets integrating a total of 9 protons which is consistent with the anticipated structure **(Figure 6)**.

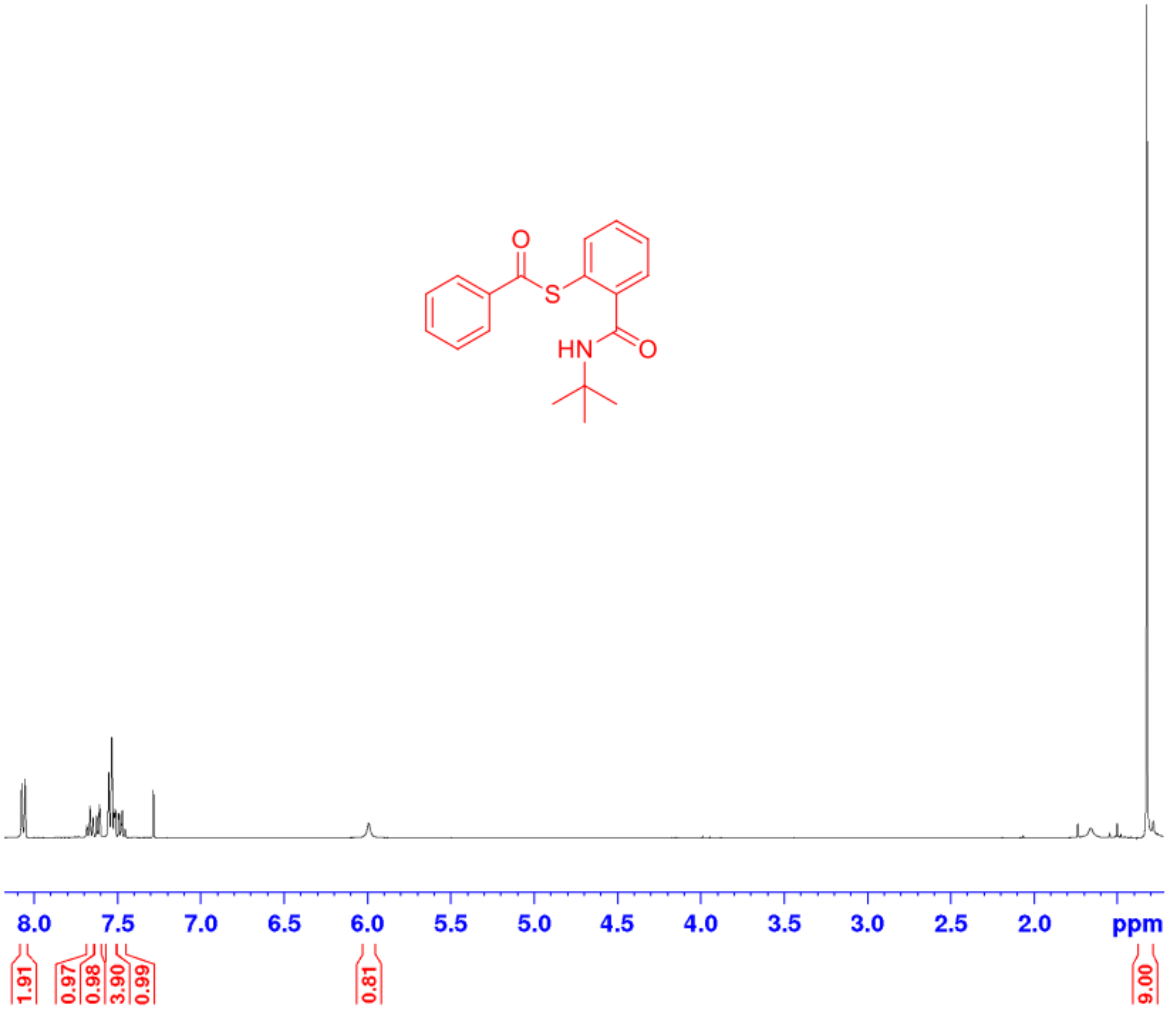


Figure 6: The ^{1}H NMR of compound **68**

The ^{13}C NMR spectrum of compound **(68)** has a 14 carbon peaks **(Figure 7).** A carbon peak resonating at δ_C 20.58 ppm is assigned to the three methyl carbons on the *tert*-butyl group. The peak appearing, more downfield relative to the methyl peak, at 31.79 ppm can be assigned to the tertiary carbon bonded to the three methyl groups. The two distinct peaks appearing further downfield, at 167.80 ppm and 192.17 ppm are assigned to an amide carbonyl carbon and thioester carbonyl carbon, respectively .The rest of the peak are in the range 123.41 -144.18 ppm are assigned to the aromatic carbons presents on the two benzene rings **(Figure 7) .**

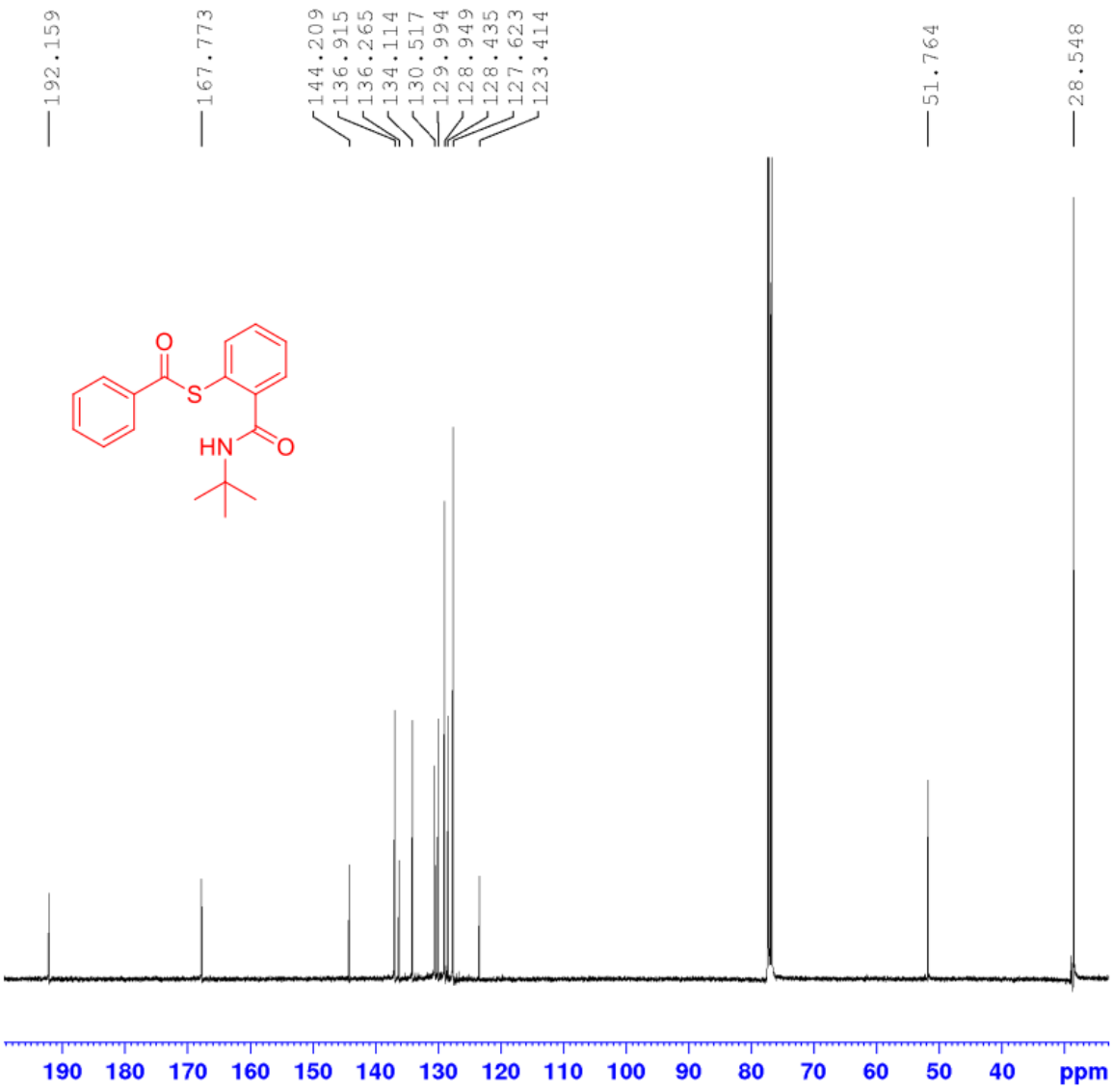


Figure 7: The ^{13}C NMR of compound 68

The mass spectrum of S-(2- (tert-butylcarbamoyl) phenyl) benzothioate **(68)** was obtained from the LCMS spectrum **(Figure 8)** confirming the structure of the thioester. ESI+ (positive mode) showed a sodium and acetonitrile adduct at *m/z* 377.05 (Calculated for $C_{18}H_{19}NO_2S$ + Na+ ACN) . Due to the formation of a stable sulphur-sulphur bond in open air, a dimer formed during the ionisation of the compound resulting in a peak adduct at *m/z* 649.15 (Calculated for $C_{36}H_{38}NO_4S_2$ + Na) **(Figure 8)**.

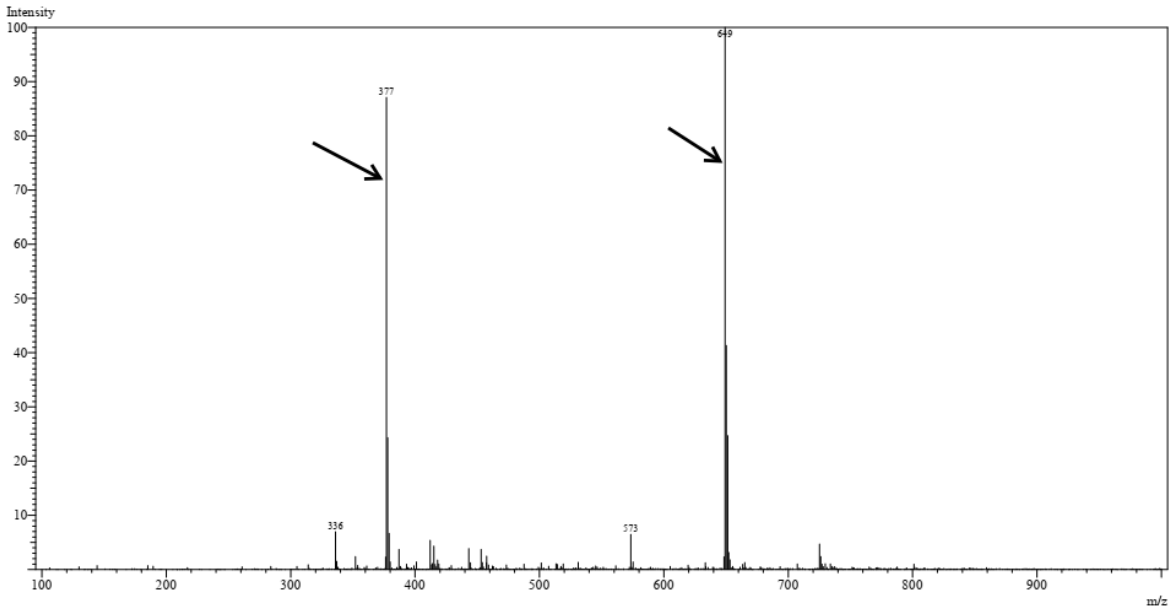


Figure 8: LCMS spectrum of compound 68

3.1.3 Synthesis of S-(2-(tert-butylcarbamoyl)phenyl) 4-methylbenzothioate

S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate **(70)** was successfully synthesised and obtained as a light-yellow crystalline powder. The ^{1}H NMR spectrum showed a singlet at δ_H 2.46 which integrated to 3 protons corresponding to the methyl group attached to the thioester functionality. The multiplet peaks resonating downfield in the region δ_H 7.97 – 7.31 are due to the aromatic protons which is consistent with the peaks reported by Villabos [6] **(Figure 9)**.

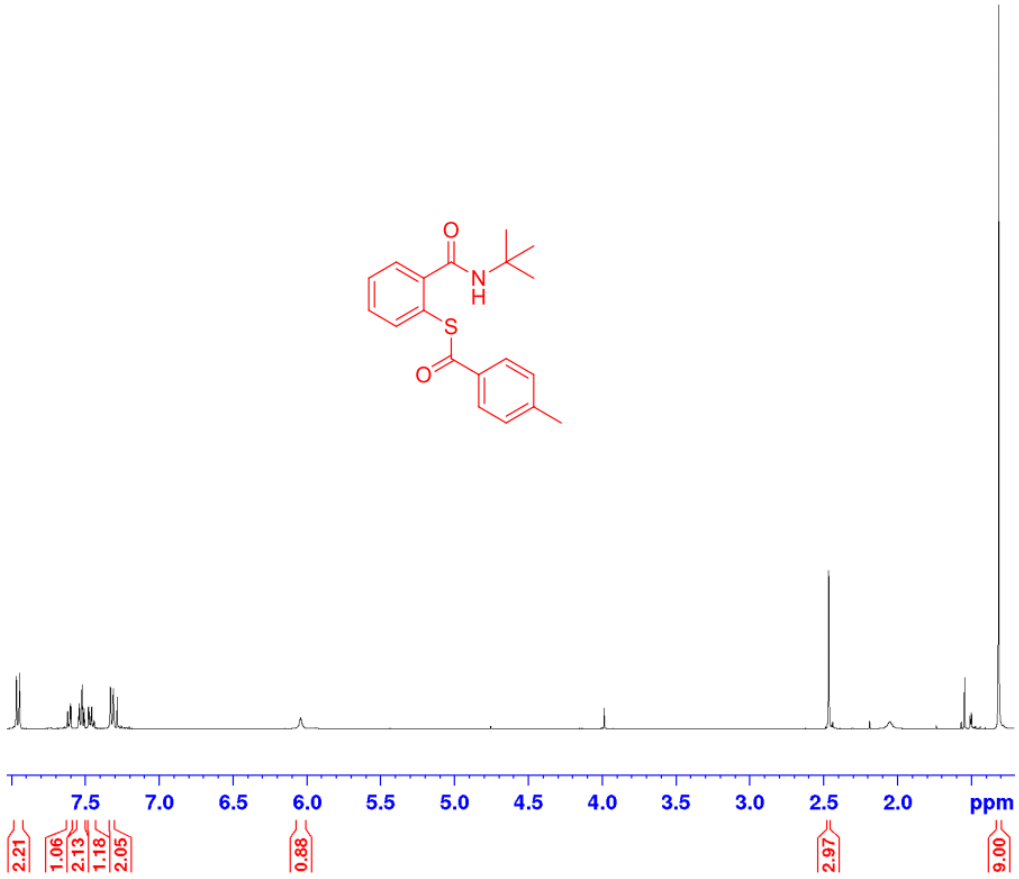


Figure 9: The ^{1}H NMR of compound 70

Due to overlapping the ^{13}C NMR spectrum of compound **(70)** showed 15 peaks **(Figure 10)**. The peak resonating upfield at δ_C 28.53 is assigned to the methyl carbon on the thioester functionality. Peaks appearing at δ_C 167.85 and 191.85 are assigned to the amide carbonyl carbon and thioester carbonyl carbon, respectively **(Figure 10)**.

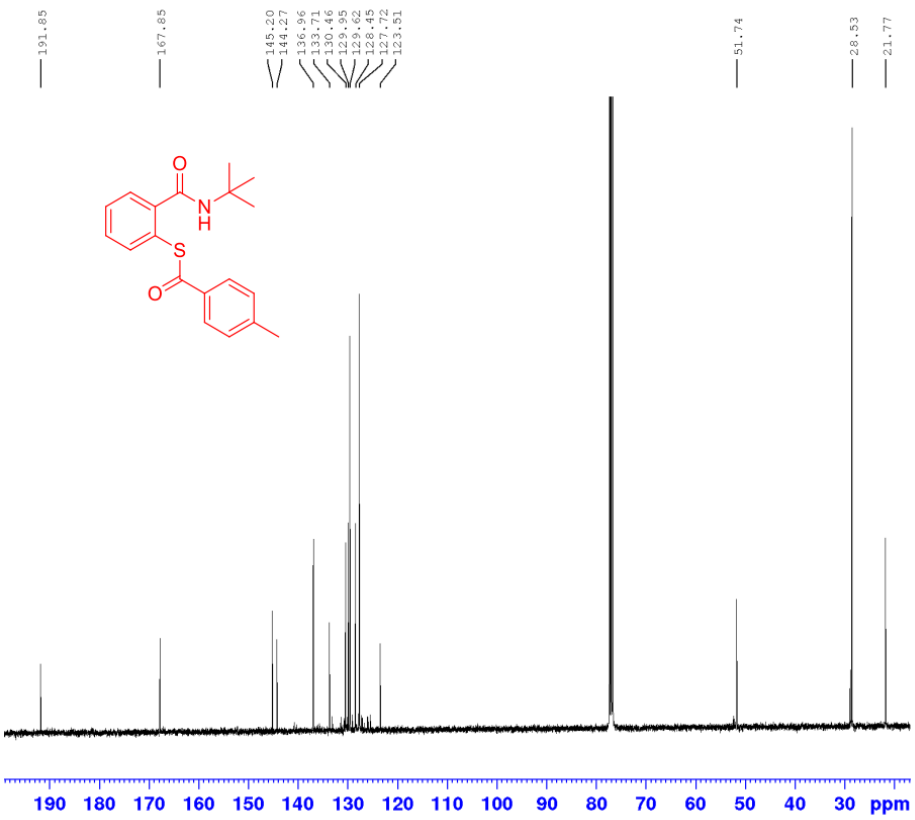


Figure 10: The ^{13}C NMR of compound 70

The ESI+ (positive mode) **(Figure 11)** showed a sodium and acetonitrile adduct at *m/z* 391.20 (Calculated for $C_{19}H_{21}NO_2S$ + Na+ ACN) . The ESI+ (positive mode) also showed a sodium adduct at *m/z* 677.30 (Calculated for $C_{38}H_{42}NO_4S2$ + Na) owing to the presence of a dimer.

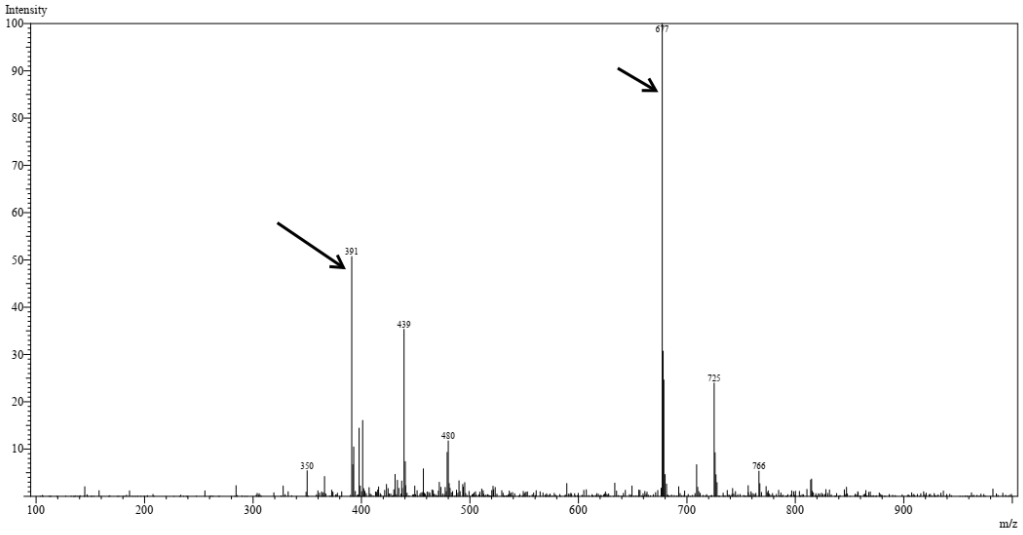


Figure 11: LCMS spectrum of compound 70

Following the method reported above the following five thioesters were synthesised and characterised (**Figure 12**)

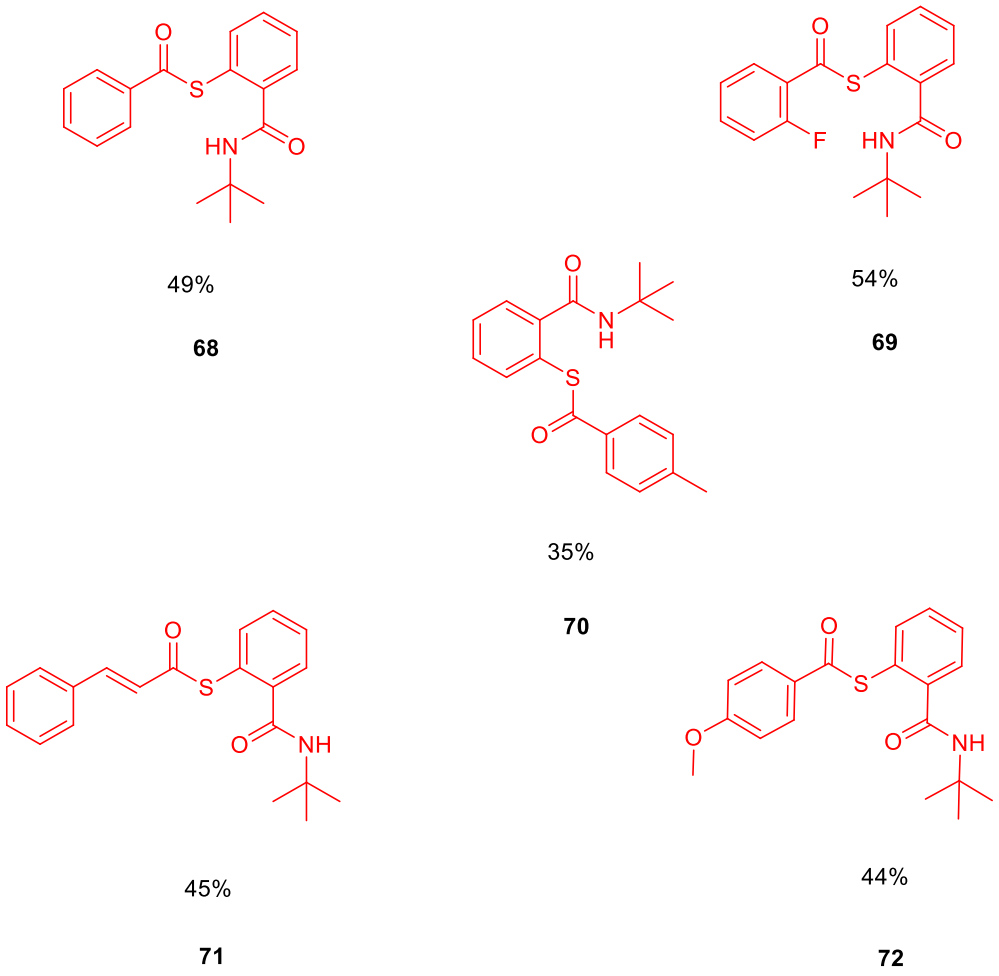
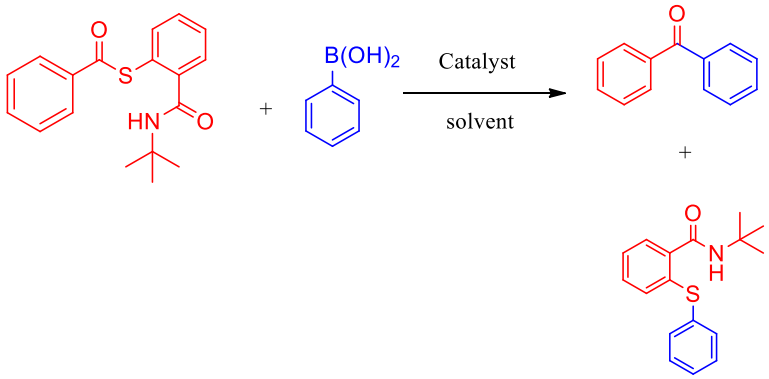


Figure 12: Prepared thioesters

3.2 Optimisation of reaction conditions.

With the desired thioesters successfully synthesized, the next step of the project was to find optimal reaction conditions for the synthesis of ketones **(Scheme 32)** .



Scheme 32

Table 1: Optimalisation of reaction conditions

Entry	Solvent	Temperature	Catalyst	Yields	
				Ketones	Thioether
1	DMF	50°C	-	0	0
2	DMF	50°C	Cu $(OAc)_2$	43	28
3	DMF	50°C	$Cu(acac)_2$	-	-
4	DMF	50°C	Zn $(OAc)_2$	-	-
5	DMF	50°C	$Ag(C_7H_5O_2)$	-	-
6	DMF	50°C	CuTC	21	41
7	DMF	50°C	CuMeSal	65	56
8	DMF	50°C	CuMeSal(anaerobic)	20	15

Table 1 shows the conducted optimisation reaction using different reaction conditions and reagents. The reaction of thioester **68** with phenyl boronic acid in the absence of a catalyst yielded no ketone nor thioether product **(Table 1, entry 1)** . This observation was, however, not surprising since the catalyst is needed to promote the reaction. Liebeskind and Srogl had similar findings as their controlled experiments revealed that both carboxylate counterion and Cu^1 cation were indispensable in this protocol[7]. The addition of catalytic amount $Cu(OAc)_2$ promoted the reaction only furnishing the desired diaryl ketone in 43% yields and corresponding thioether in 28% yield **(Table 1, entry 2)**, the production of the desired ketone using $Cu(OAc)_2$ as a catalyst motivated us as $Cu(OAc)_2$ is cheaper than the catalyst used in the literature . $Cu(acac)_2$ catalyst failed to promote the coupling reaction under Liebeskind-Srogl as no product formation was observed **(Table 1, entry 3)**. This might be due to the excess

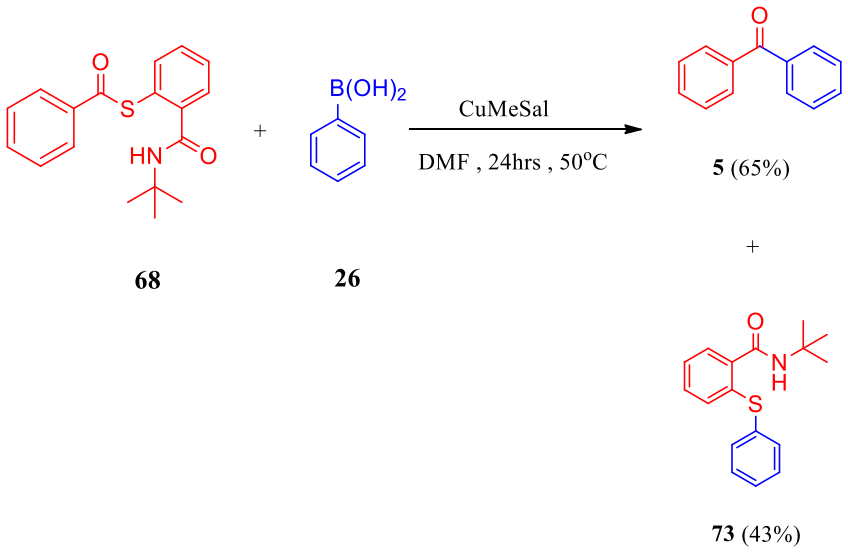
binding of the acac ligands on the Cu metal centre which then hinders the catalytic cycle. Attempts to use other thiophilic transition metal carboxylates such as Zn and Ag did not seem to promote the coupling reaction under the proposed reaction conditions, despite the common use of these transition metal in desulfitative coupling reactions **(Table 1, entries 3-5)**.

CuTC initiated the coupling reaction producing more thioether (41%) than the ketone (21%) (**Table 1, entry 6**). CuMeSal showed to be the most effective catalyst in the coupling reaction, like Villabos' observations. The reaction is initiated by the oxidation of the Cu^{I} to $Cu^{II/III}$ making the pairing with the boronic acid possible explaining why a decrease in yield (20%) was observed when the reaction was conducted under inert atmosphere.

With the optimised reaction conditions at hand, the scope of thioesters and boronic acids both bearing electron-donating and electron-withdrawing substituents were investigated and results are summarized in **Table 2** .

3.2.1 Synthesis of Benzophenone

Benzophenone and *N*-(tert-butyl)-2-(phenylthio) benzamide were prepared in the isolated yield of 65% and 43 % as a white crystalline powder from the reaction of compound **76** and phenylboronic acid **(26) (Scheme 33)** .



Scheme 33

The structures of compounds **5** and **73** were confirmed using ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of benzophenone (**5)** showed signals resonating in the aromatic region δ_H 7.81-7.27 which integrated for 5 protons due to the symmetrical nature of compound **5** similar to that reported by Villabos[6] **(Figure 13)**.

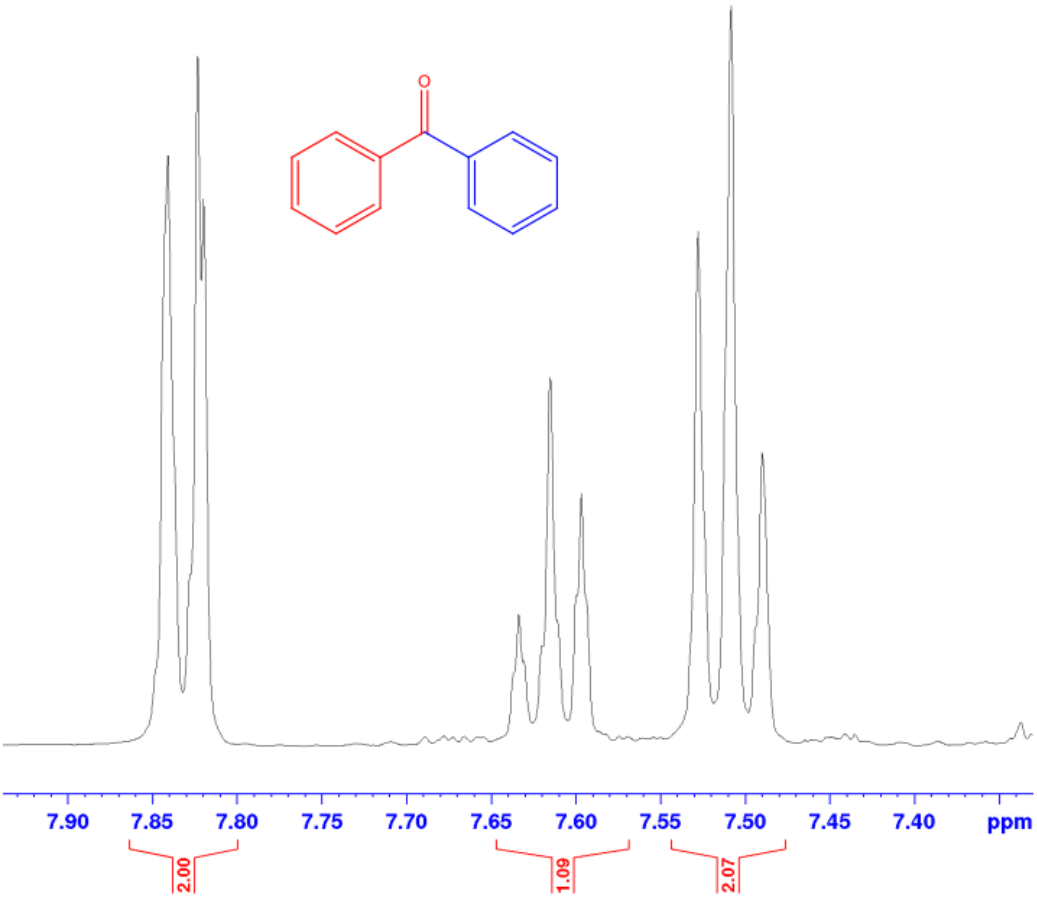


Figure 13: ^{1}H NMR spectrum for compound 5

The ^{13}C NMR spectrum of compound **5** has five peaks as expected **(Figure 14)**. The distinct peak appearing further downfield at δ_c 196.74 is assigned to the carbonyl carbon of the ketone functionality **(Figure 14)**.

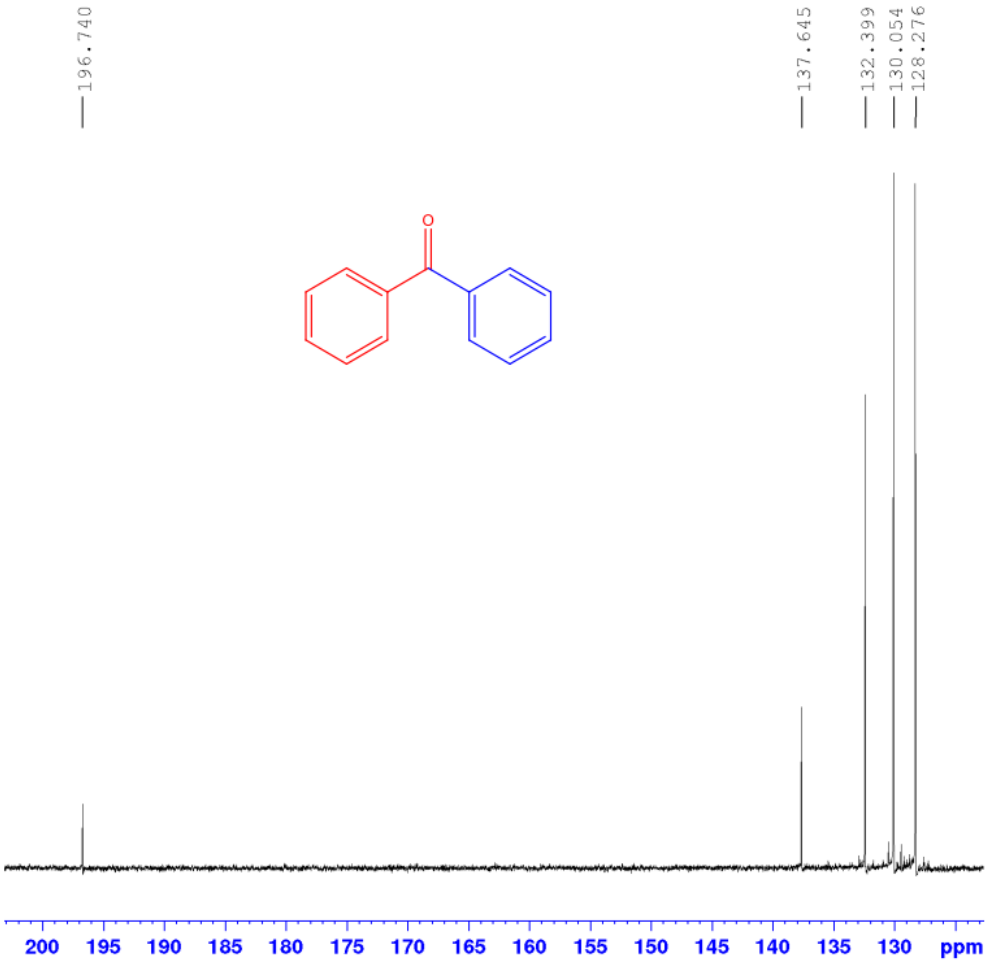


Figure 14: ^{13}C NMR spectrum for compound 5

The ^{1}H NMR spectrum of *N*-(tert-butyl)-2-(phenylthio) benzamide **(73)** showed a singlet at δ_H 1.38 ppm integrating for 9 protons owing to the three methyl groups of the *tert*-butyl functionality and a broad peak at δ_H 6.24 ppm integrating for one proton and is assigned to *NH* group of the amide functionality **(Figure 15)**.

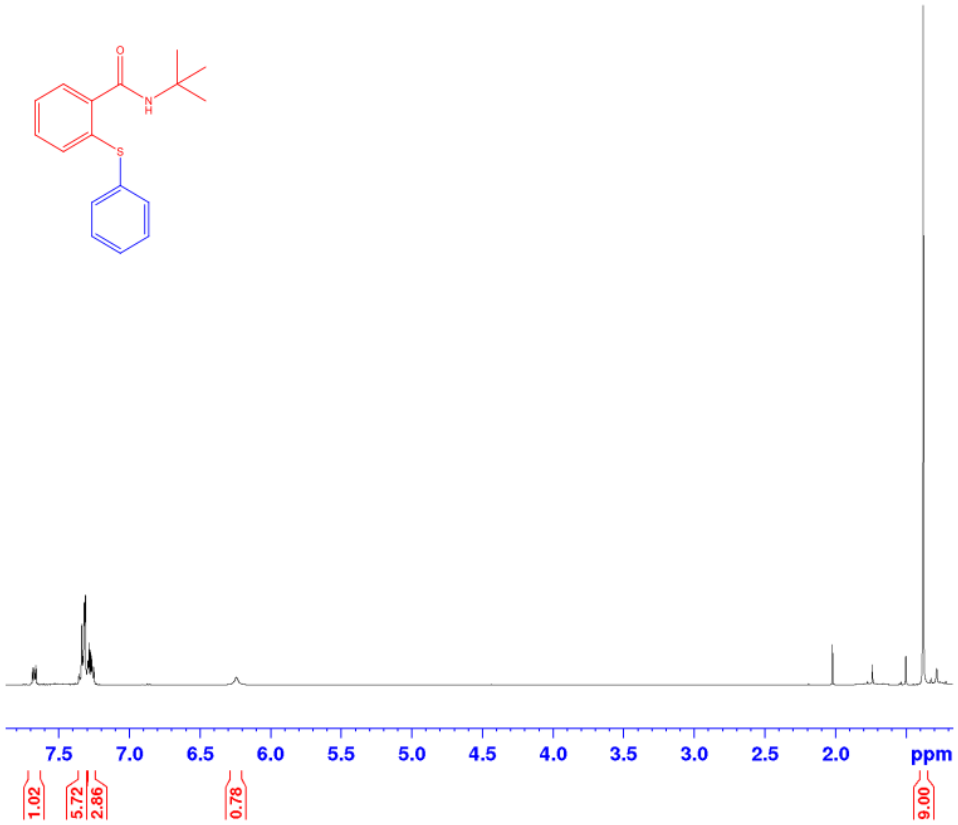
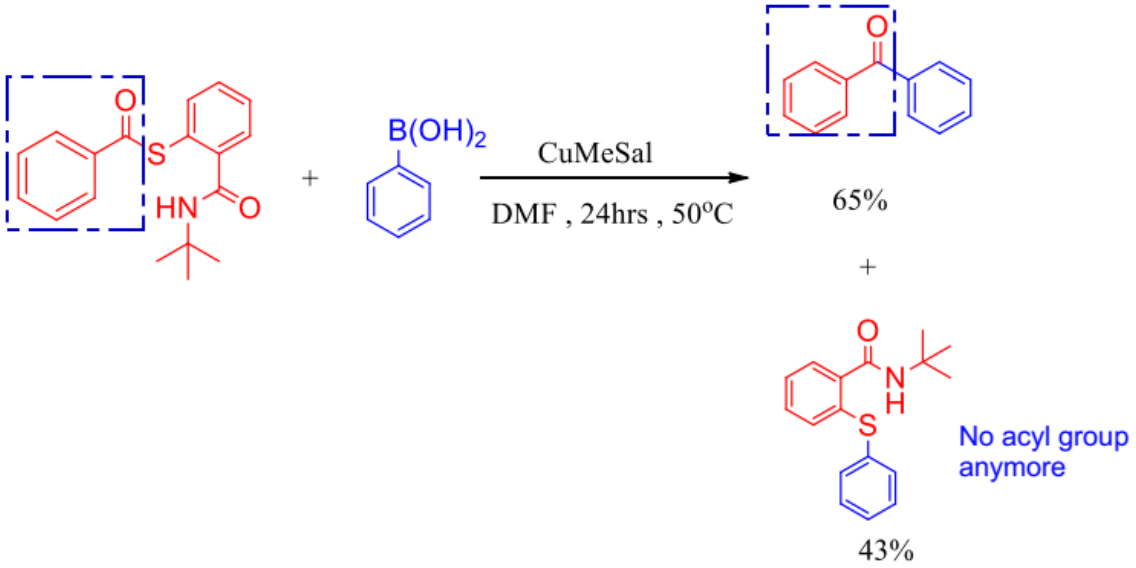


Figure 15: ^{1}H NMR spectrum for compound 73

The ^{13}C NMR spectrum of compound **73** shows 12 peaks **(Scheme 16)**. The carbon peak resonating at δ_C 28.61 ppm is assigned to the three methyl carbons in the tert-butyl group. The peak appearing further downfield, relative to the methyl carbons, at δ_C 51.92 ppm is assigned to the tertiary carbon attached to the three methyl groups. When comparing the ^{13}C NMR spectrum of compound **73** with compound **68**, it is noted there is a disappearance of carbonyl peak at 192.17 ppm from the spectrum of thioether **73** relative to the thioester **68 (Scheme 34)** This observation confirms a successful transfer of the acyl group from the thioester to the nucleophilic phenyl boronic acid to form the desired ketone. The peak resonating at δ_C 166.94 ppm is assigned to the amide carbonyl carbon (**Scheme 34**)


B(OH)2
CuMeSal
DMF , 24hrs , 50°C
65%
43%
No acyl group anymore

Scheme 34

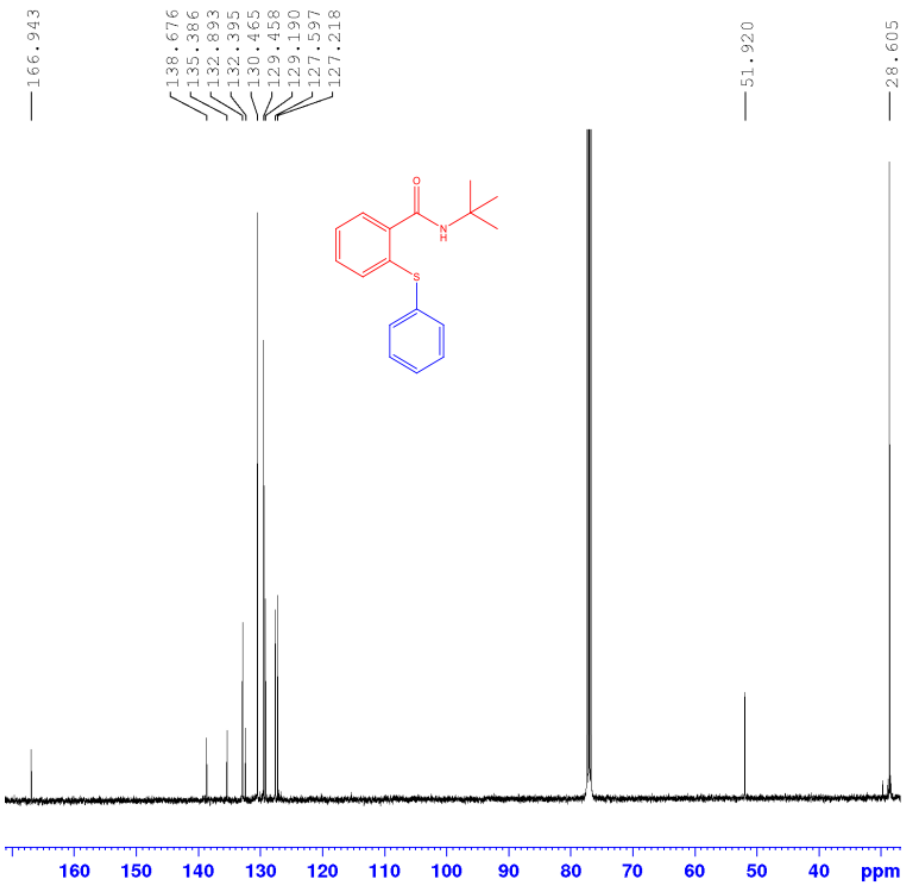
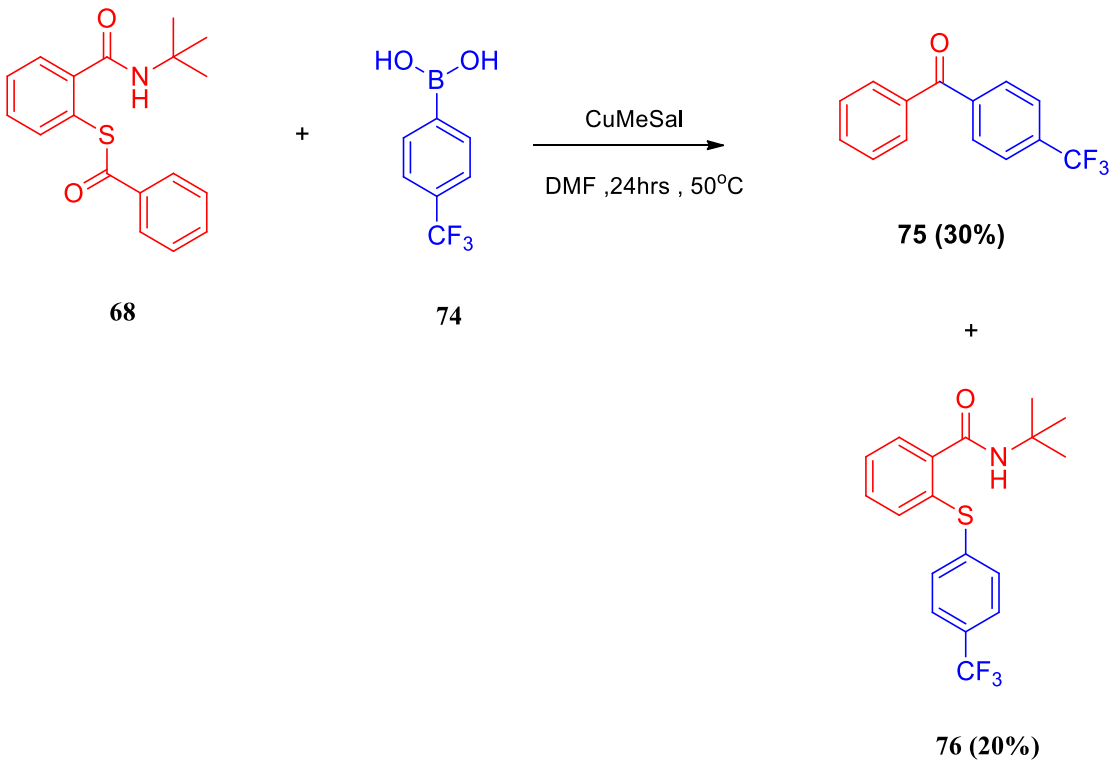

166.943
138.676
135.386
132.893
132.395
130.465
129.458
129.190
127.597
127.218
51.920
28.605
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

Figure 16: ^{13}C NMR spectrum for compound 73

3.2.2 The synthesis of phenyl(4-(trifluoromethyl)phenyl) methanone

The coupling of compound **68** with a phenylboronic acid bearing an electron-withdrawing trifluoromethyl group **(74)** furnished an asymmetric ketone **75** and thioether **76** in poor yields, 30% and 20% respectively. The trifluoromethyl group induces a strong withdrawing inductive effect in the phenylboronic acid thus increasing its acidity [8] thus reducing compound **74** efficiency as a nucleophile in the coupling reaction. The low yields of the desired ketone product were also a result of an incomplete reaction as evidenced by the appearance of the starting thioester spot on the TLC after 24 hours or reaction time **(Scheme 35)**.



Scheme 35

Phenyl(4-(trifluoromethyl) phenyl) methanone **(75)** was obtained as a light-yellow powder and through ^{1}H NMR spectrum analysis its structure was confirmed .Peaks resonating in the region δ_H 7.92 -7.51 ppm integrating for 9 protons are assigned to the aromatic protons in the two benzene rings (**Figure 17)**.

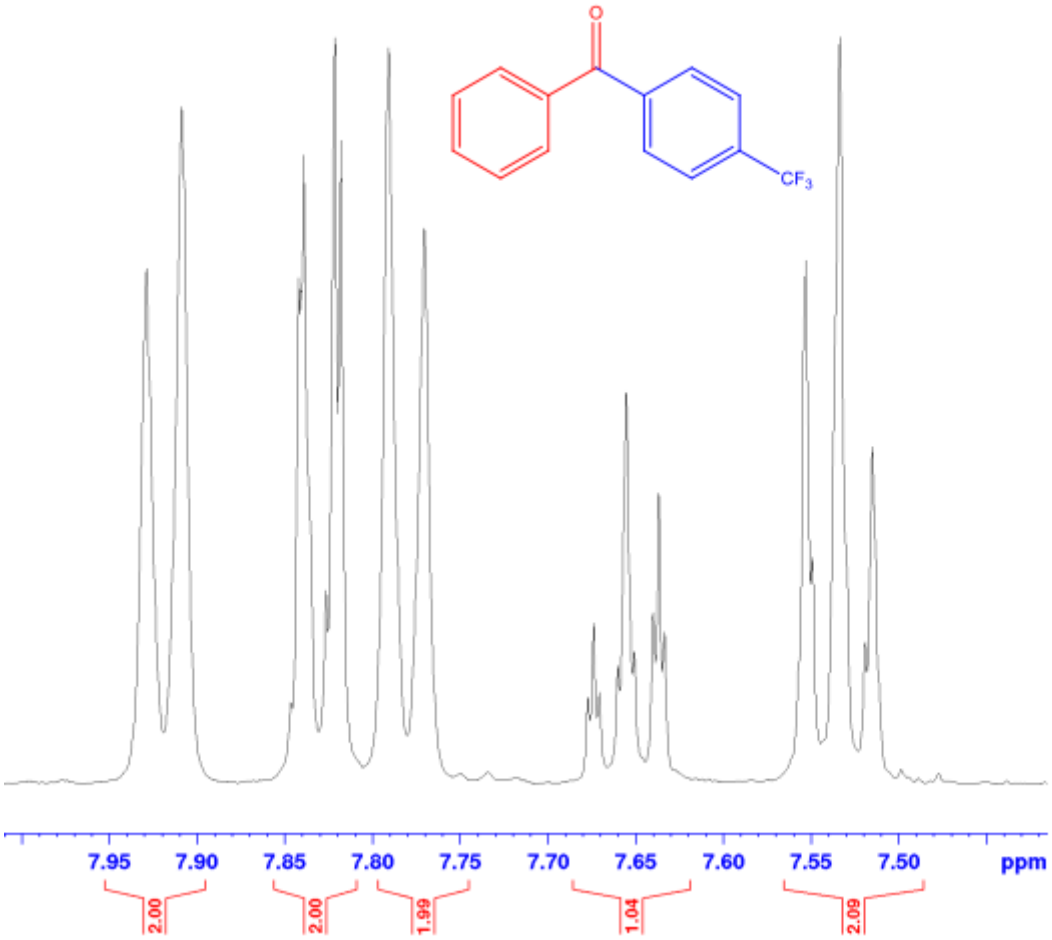


Figure 17: ^{1}H NMR spectrum for compound 75

S-(2-(tert-butylcarbamoyl) phenyl) benzothioate **(76)** was obtained as a light-yellow crystalline powder and its structure was confirmed by the ^{1}H NMR spectrum **(Figure 18)**. A singlet at δ_H 1.34 ppm integrating for 9 protons is assigned to three methyl groups of the tert-butyl functionality and peaks resonating downfield in the region δ_H 7.70-7.28 ppm are due to the aromatic protons and integrate for 8 protons.

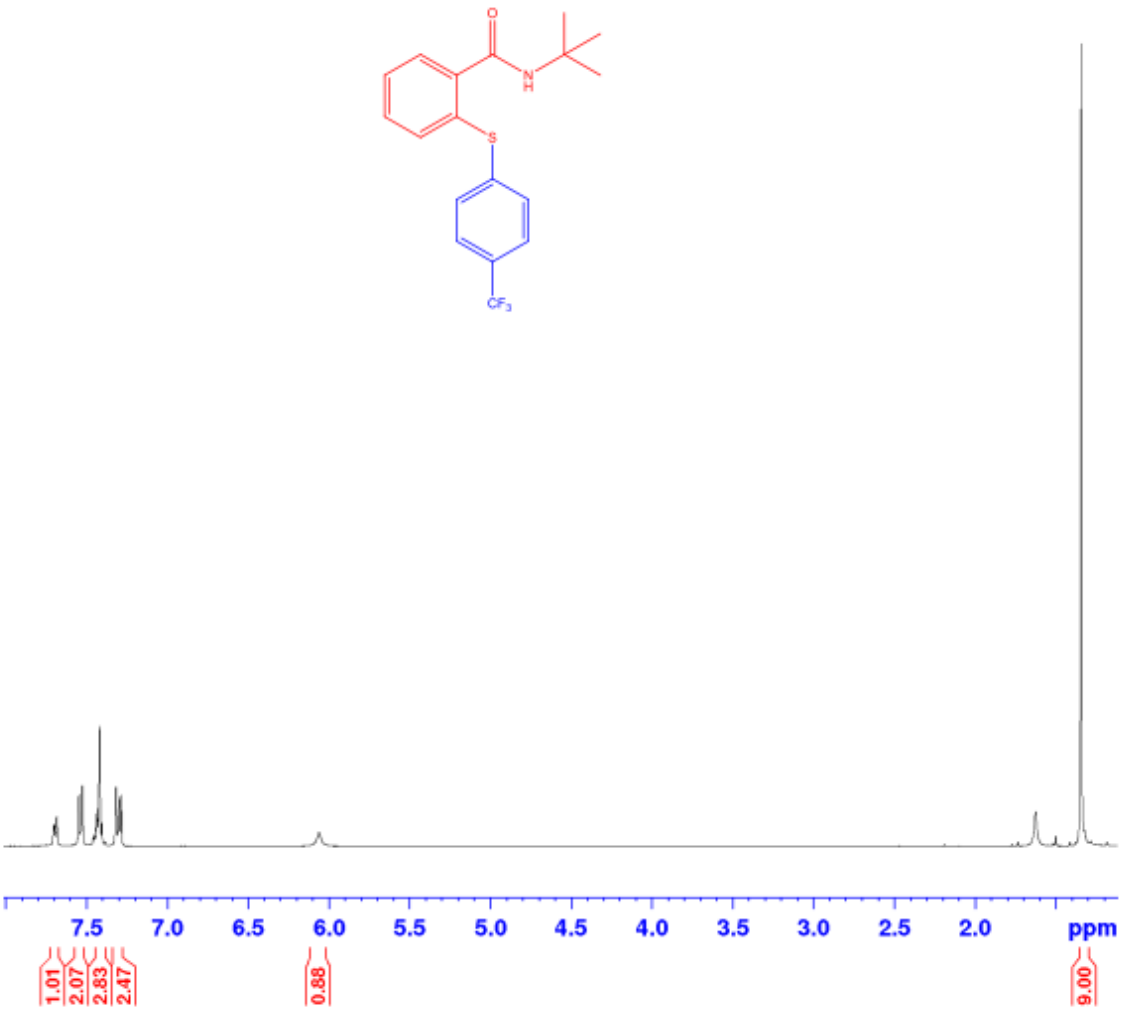
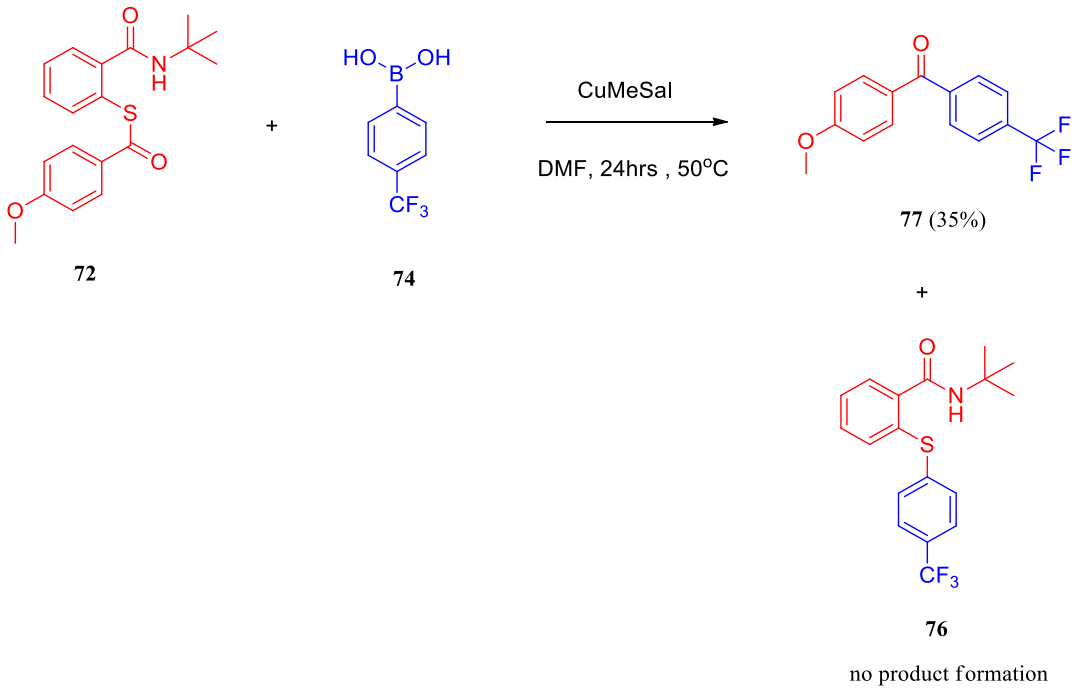


Figure 18: ^{1}H NMR spectrum for compound 76

3.2.3 Synthesis of (4-methoxyphenyl) (4-(trifluoromethyl)phenyl) methanone

The cross-coupling reaction of boronic acids bearing electron withdrawing functional groups are reported to proceed slower that those bearing electron-donating functional groups because electron-withdrawing groups decreases the nucleophilicity of the carbon atom directly bonded to the boron atom[8]. This effect is reported to slow the transmetallation of the nucleophilic moiety to the catalytic transition metal which decreases the yield of the desired product by promoting formation of side product (through protodeboration reaction)[9]. To test this hypothesis, boronic acid bearing a strongly electron-withdrawing trifluoromethyl group was reacted. The reaction of S-(2-(tert-butylcarbamoyl)phenyl)4-methoxybenzothioate **(72)** with 4-trifluorophenyboronic acid **(74)** went smoothly affording the desired ketone product **(77)** in an unsatisfactory 35% yield. The low yield indeed confirms the hypothesis reported in the

literature. It was also strange to observe that the corresponding thioether **(76)** was not detected in the reaction mixture after the completion of the reaction mixture **(Scheme 36)**.



72 + 74

Scheme 37

The ^{1}H NMR and ^{13}C NMR of the desired ketone **77** is consistent with the structure, **Figure 19 and 20**.

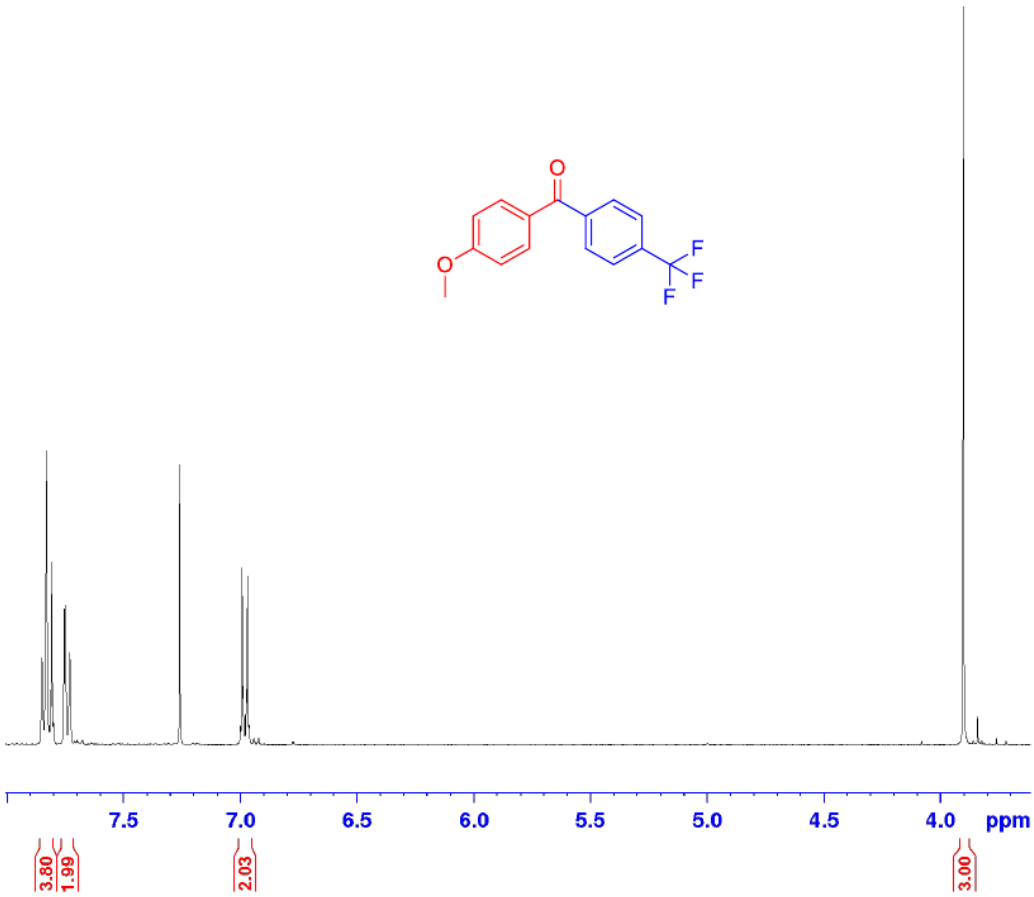


Figure 19: ^{1}H NMR spectrum for compound 77

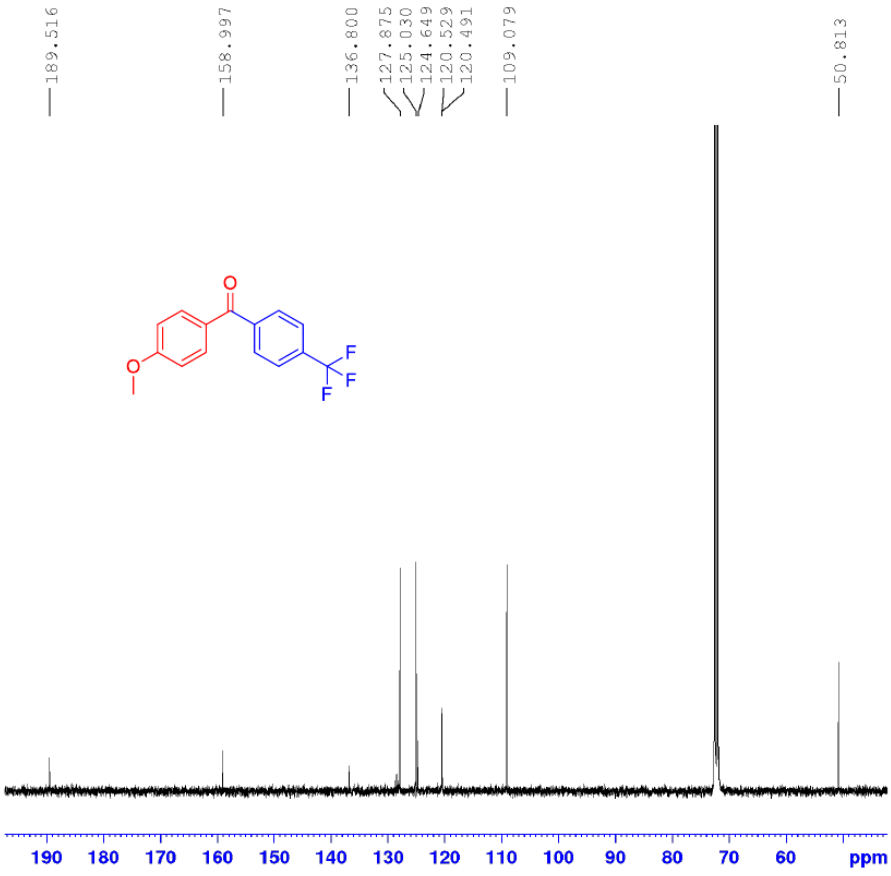
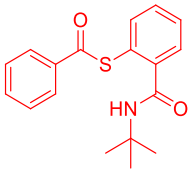
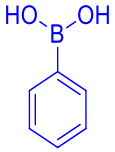
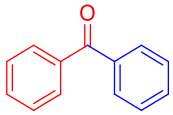
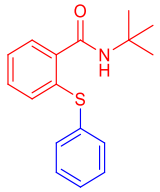
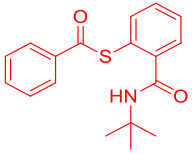
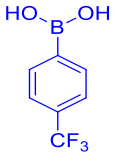
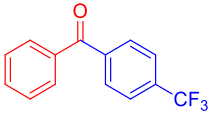
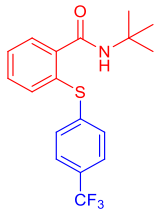
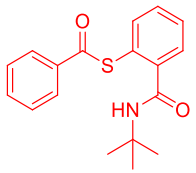
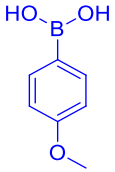
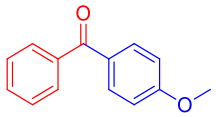
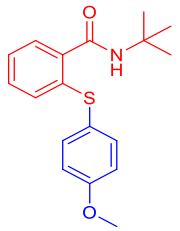
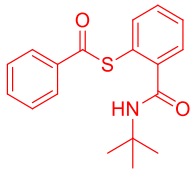
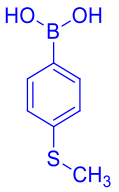
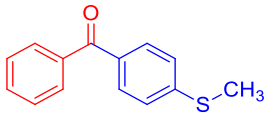
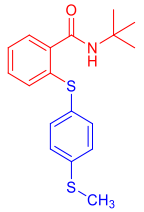
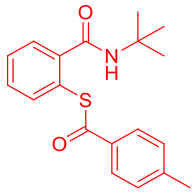
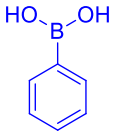
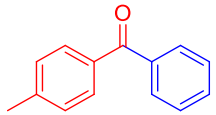
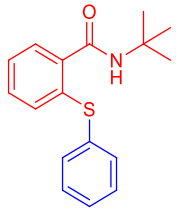
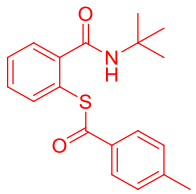
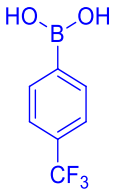
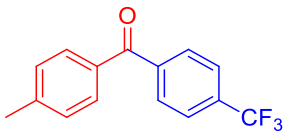
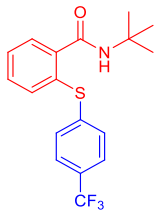
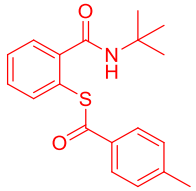
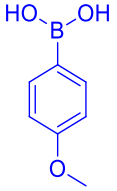
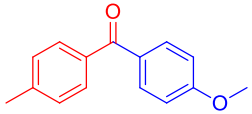
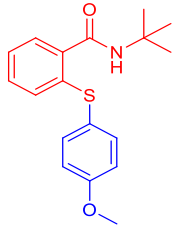
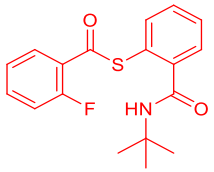
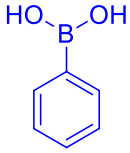
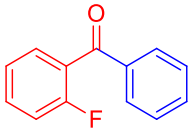
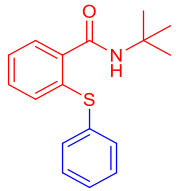


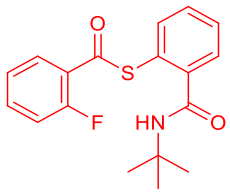
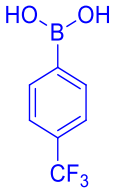
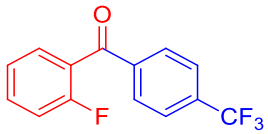
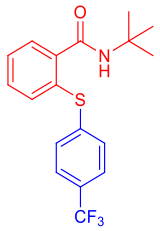
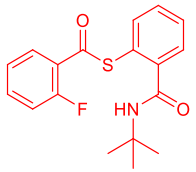
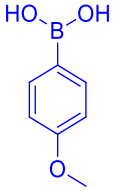
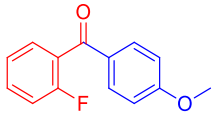
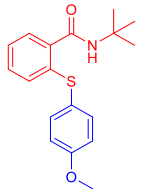
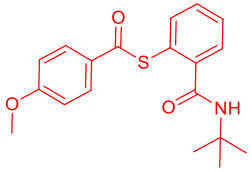
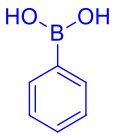
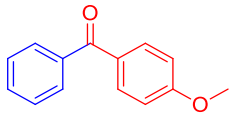
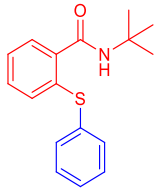
Figure 20 : ^{13}C NMR spectrum for compound 77

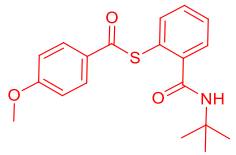
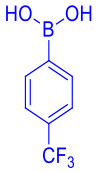
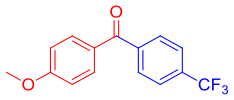
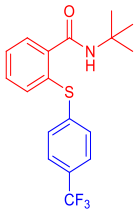
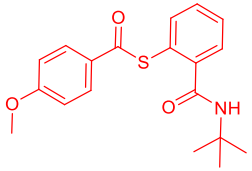
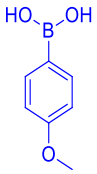
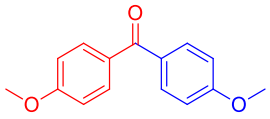
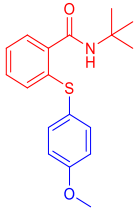
Table 2: Aerobic, copper-catalyzed acylation reactions of phenylboronic acids with thioesters

Entry	Thioester	Boronic acid	Products			
			Ketone	Yield%	Thioether	Yield%
1	 **68**	 **26**	 **5**	65	 **73**	43
2	 **68**	 **74**	 **75**	30	 **76**	22

3	 **68**	 **77**	 **78**	38	 **79**	53
4	 **68**	 **80**	 **81**	38	 **82**	53
5	 **70**	 **26**	 **83**	39	 **73**	57

6	 **70**	 **74**	 **84**	20	 **76**	49
7	 **70**	 **77**	 **85**	35	 **79**	14
8	 **69**	 **26**	 **86**	26	 **73**	37

9	 **69**	 **74**	 **87**	58	 **76**	47
10	 **69**	 **77**	 **88**	41	 **79**	43
11	 **72**	 **26**	 **89**	35	 **73**	29

12	 **72**	 **74**	 **77**	27	 **76**	N.R
13	 **72**	 **77**	 **90**	N.R	 **79**	N.R

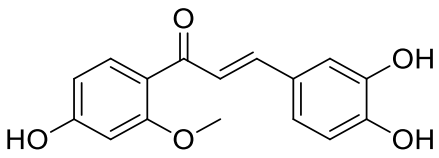
[a] Reaction conditions: thioester (1mmol), boronic acid (2.5mmol), CuMeSal (5%mmol) , DMF (5 mL) , 50°C ,24hrs .[b , c] Isolated yields

The cross-coupling reactions of boronic acid bearing electron-donating groups (i.e., methoxy and methylthio) with thioester substituted with electron-neutral hydrogen atom was not favourable producing the desired ketones in poor 38% yields (**Table 2, entries 3 and 4**).

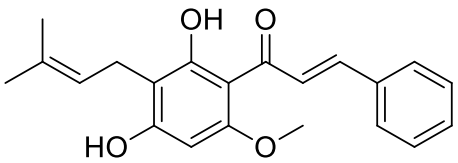
On the other hand, the thioester *para*-substituted with an electron-donating methyl group also sluggishly coupled with boronic acid bearing electron neutral as well as donating functionalities furnishing the desires ketones in 39% and 35% yields, respectively (**Table 2, entries 5 and 7)**. However, the reaction of the same thioester *para*-substituted with an electron-donating methyl group with boronic acid bearing a strongly deactivating trifluoromethyl group struggled to pass the activations energy thus producing (4-methylphenyl) (4-(trifluoromethyl) phenyl) methanone in only 20% yield, (**Table 2, entry 6).** The poor yields obtained for (4-methylphenyl) (4-(trifluoromethyl)phenyl) methanone may be attributed to the incomplete reaction evidenced by the presence of the starting material after the reaction time .

3.3 Aerobic, Cu-catalysed synthesis of Chalcones

Chalcone are aromatic ketones with two aromatic rings linked through a three carbon α,β-unsaturated carbonyl system i.e. 1,3-diphenyl-2-propene -1-one[10] . The chemistry of chalcones has been of great interest to organic chemists due to their open chain mode and the ability to modify their skeletal structure[10] to produce a new class of organic compounds such as isoxazoles[11], pyrazoles[12] and azachalcones[13] . Chalcone are also the main biogenetic precursors for the synthesis of flavonoids and isoflavonoids which are customary constituents of the human diet[14]. Chalcones have received special attention, not only from the synthetic and biosynthetic perspectives[15] but also for their diverse and interesting biological activities and potential therapeutic and pharmacological properties[15] . Chalcones have shown a variety of biological activities such as antibacterial[16], anti-HIV[17] and anti-inflammatory[18] just to mention a few. An example of this is the Sappan chalcone, which is a known constituent of Sappan Ligum has shown anti-inflammatory activity[19] while Xanthohumol has been reported to have anti-cancer as well as anti-HIV-1 properties[17] (**Figure 20).**



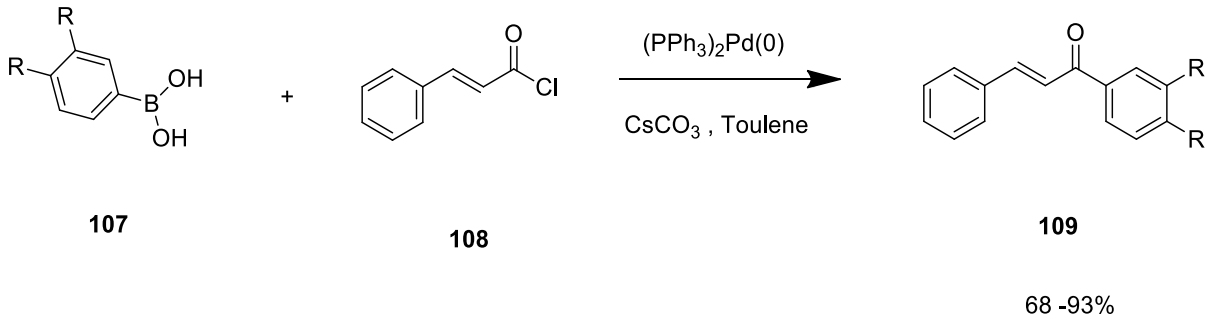
Sappanchalcone



Xanthohumol

Figure 20: Examples of Chalcones

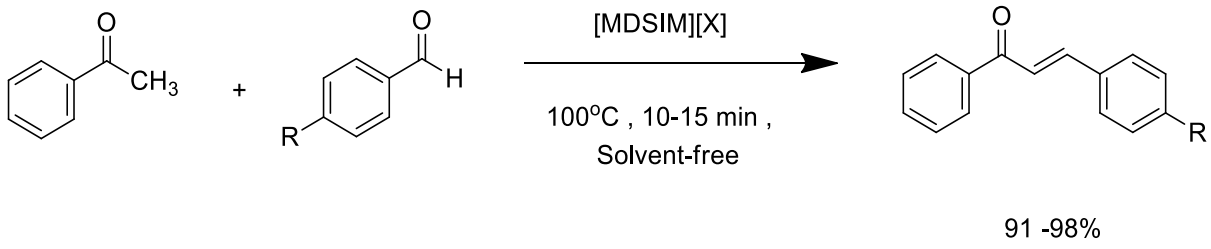
Owing to their attractive properties as well as their importance in the pharmaceutical industry, a lot of methods have been reported on the synthesis of various chalcones . In 2003 Eddarir and co-workers , using a method previously reported by McCarthy *et al* [20], manged to synthesis various chalcones through the coupling of phenylboronic acids **(107)** with cinnamoyl chloride **(108)** to produce the desired product **(109)** in moderate to excellent yields[21] (**Scheme 37)**.



107 **108** **109**

Scheme 37

The bulk of reported chalcones and their derivatives are produced using the Claisen-Schmidt reaction in a polar solvent. A recent and modified Claisen-Schmidt reaction is reported by Das and co-workers and it is a solvent-free reaction between benzaldehyde and acetophenone, in the presence of an ionic liquid catalyst [MDSIM][X] ,which leads to various chalcones in excellent yields 91 -98% [22] (**Scheme 38)**.



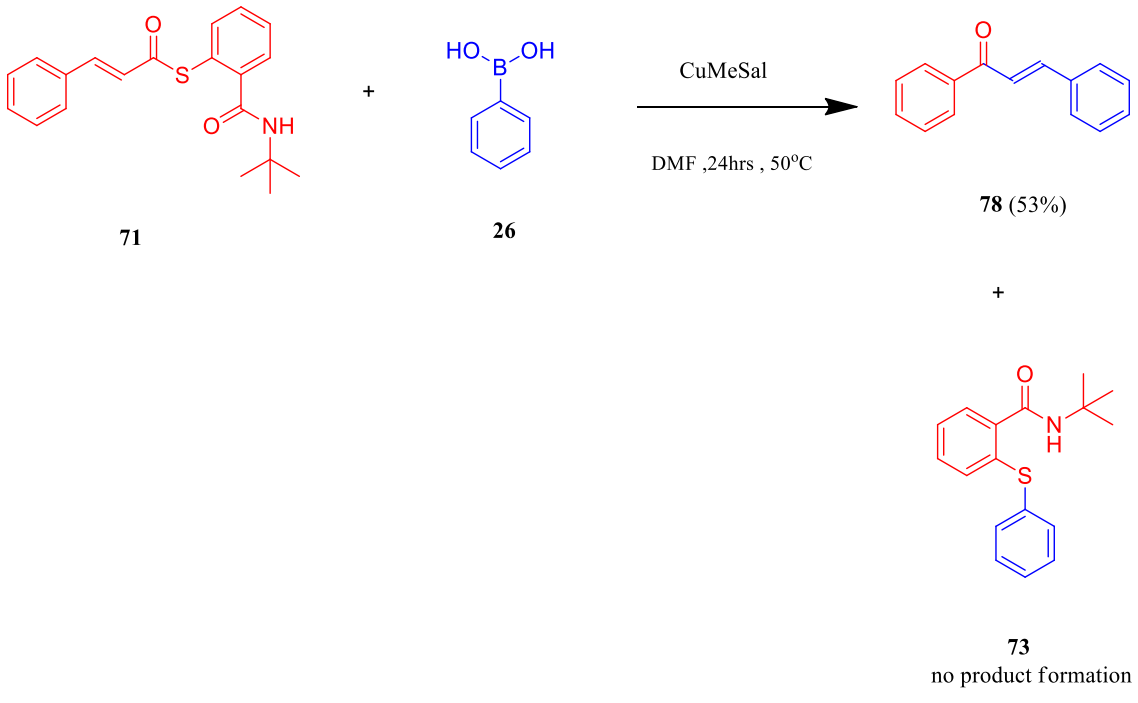
Scheme 38

To the best of our knowledge, the Liebeskind-Srogl reaction has never been used in the synthesis of chalcones, as a result, a successful application of Liebeskind-Srogl reaction in the synthesis of chalcones will be of great advantages in terms of expanding the scope of method used for the preparation of chalcones. In addition, using Libeskind-Srogl cross-coupling reaction is advantageous compared to the traditional methods because of its relatively mild reaction conditions and no base is required (especially for base sensitive functionalities) in the reaction so the scope of reagents that can be used in this procedure is significantly increased.

Below we report on the successful synthesis of chalcone derivatives using the Liebeskind-Srogl cross-coupling reaction.

3.3.1 Synthesis of (E-) 1,3-Diphenyl-2-propen-1-one

(E-)1,3-Diphenyl-2-propen-1-one (**78)** was synthesized from the reaction of (E)-S-(2-(tert-butylcarbamoyl) phenyl) 3-phenylprop-2-enethioate **(71)** and phenylboronic acid **(26)** in DMF. The desired product **78** was obtained in moderate yield 53% after purification through column chromatography **(Scheme 39).**



71 **26** **78** (53%) + **73**
no product formation

Scheme 39

To confirm a successful synthesis of (*E*-)1,3-Diphenyl-2-propen-1-one **(91)**, a small sample of the product was analysed using both ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum showed a total of 12 protons consistent with the number of protons expected from the desired product **(91)**. The aromatic region of the spectrum revealed multiplet peaks in the region 7.40-7.70 ppm, these peaks are assigned to the aromatic protons on both aromatic rings. A broad doublet (which resembles two singlets) resonating at 7.80-7.88 ppm has a J = 15.7 Hz which signifies the *trans* configuration of the vinyl protons (**Figure 22**).[23]

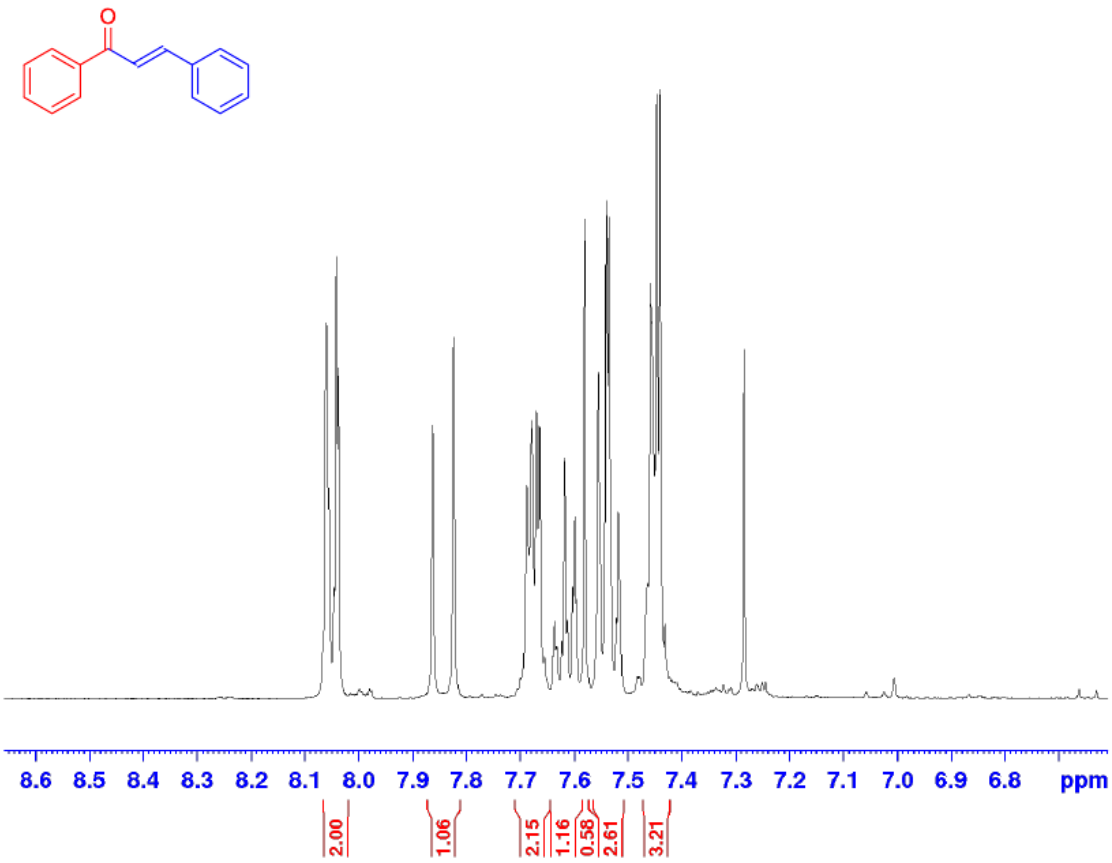


Figure 22: ^{1} H NMR spectrum for compound 78

The ^{13}C NMR of compound **78 (Figure 23)** showed 11 peaks. Peaks resonating at 122.17 ppm and further downfield at 144.89 ppm are assigned to the 2 carbons of the vinyl group. The peak resonating at 190.63 ppm is assigned to the carbonyl carbon of the ketone functionality. Peaks

resonating from 128.46 to 138.25 ppm are a result of the carbons in the 2 benzene rings.

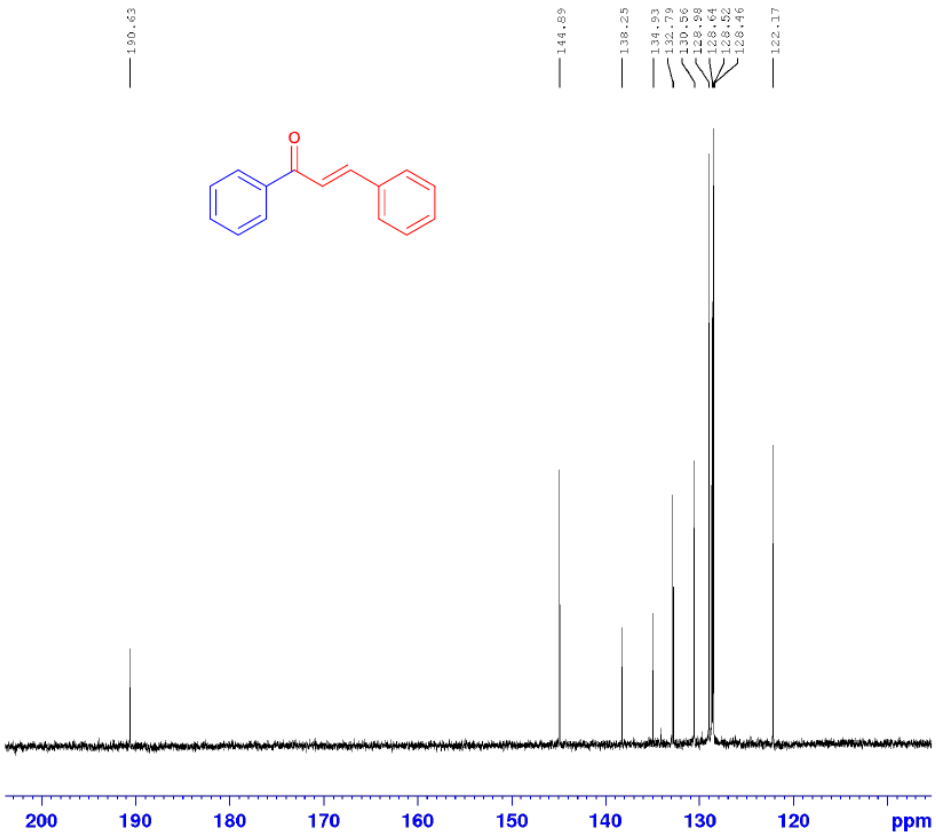
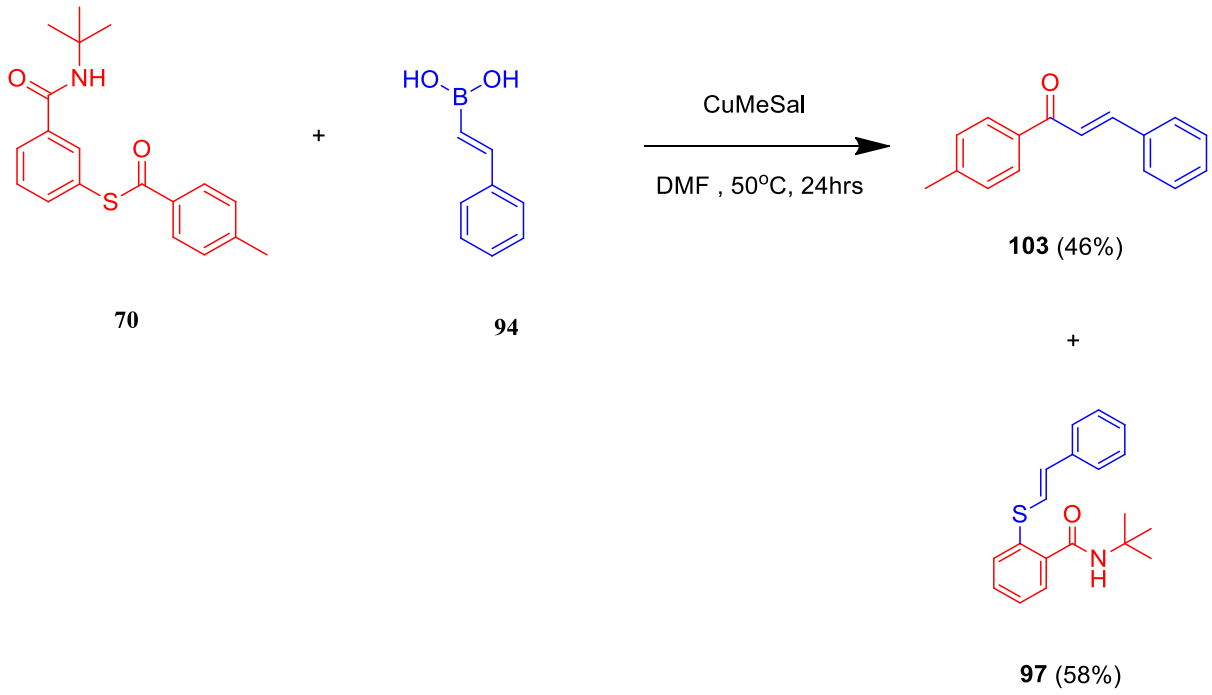


Figure 23: ^{13}C NMR spectrum for compound 78

A successful synthesis of (*E*)1,3-Diphenyl-2propen-1-one using Libeskind Srogl cross-coupling reaction was a great achievement given that this reaction has never been used in the synthesis of chalcones. With the first successful reaction at hand, other chalcones bearing electron withdrawing and electron donating functional groups were synthesised.

3.3.2 Synthesis of (E)-3-phenyl-1-(p-tolyl)prop-2-en-1-one

The coupling of compound **70** with trans-2-vinylphenylboronic acid **(94)** furnished (E)-3-phenyl-1-(p-tolyl)prop-2-en-1-one **(103)** and (E)-N-(tert-butyl)-2-(styrylthio)benzamide **(97)** as a light-yellow crystalline powder with a yield of 46% and 37% , respectively. [6] The increase in yield could be due to the presence of the electron-donating vinyl group[24] which is able to activate the aromatic ring through a resonance donating effect **(Scheme 40)**.



Scheme 40

The ^{1}H NMR spectrum **(Figure 3.19)** of compound **103** showed a singlet resonating at δ_H 2.47 ppm integrated for 3 protons corresponding to the methyl substituent on the aromatic ring. Peaks resonating at 7.58 and 7.98 ppm are assigned to the 2 protons of the vinyl group.

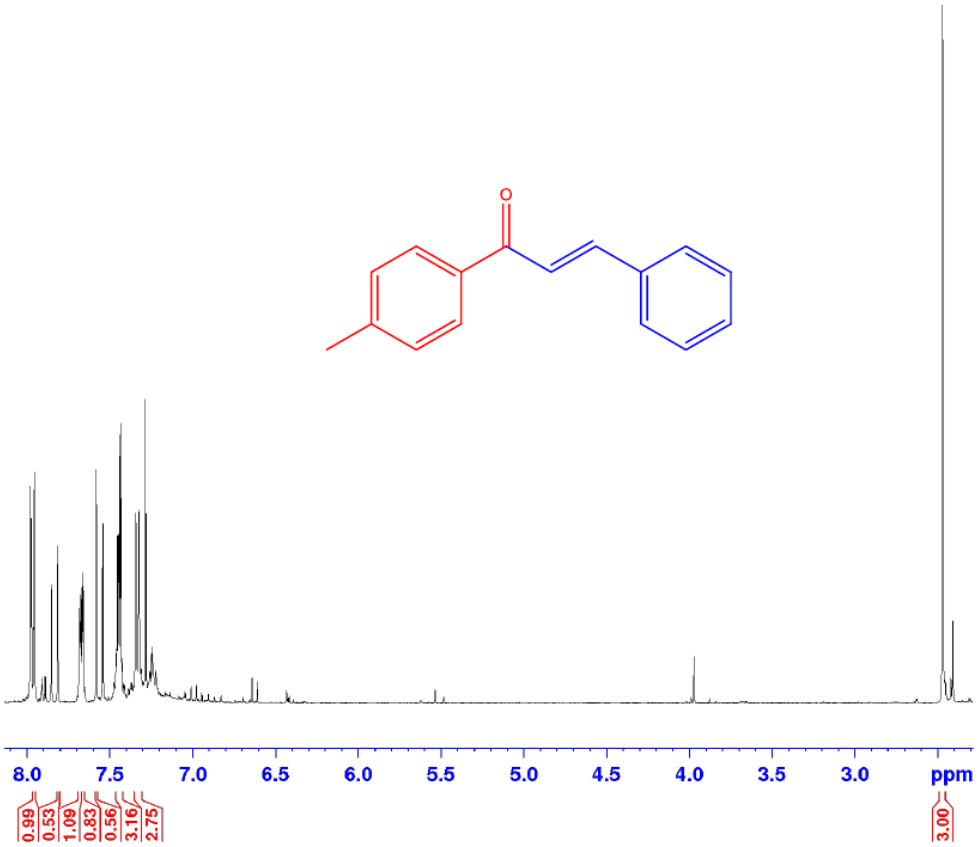
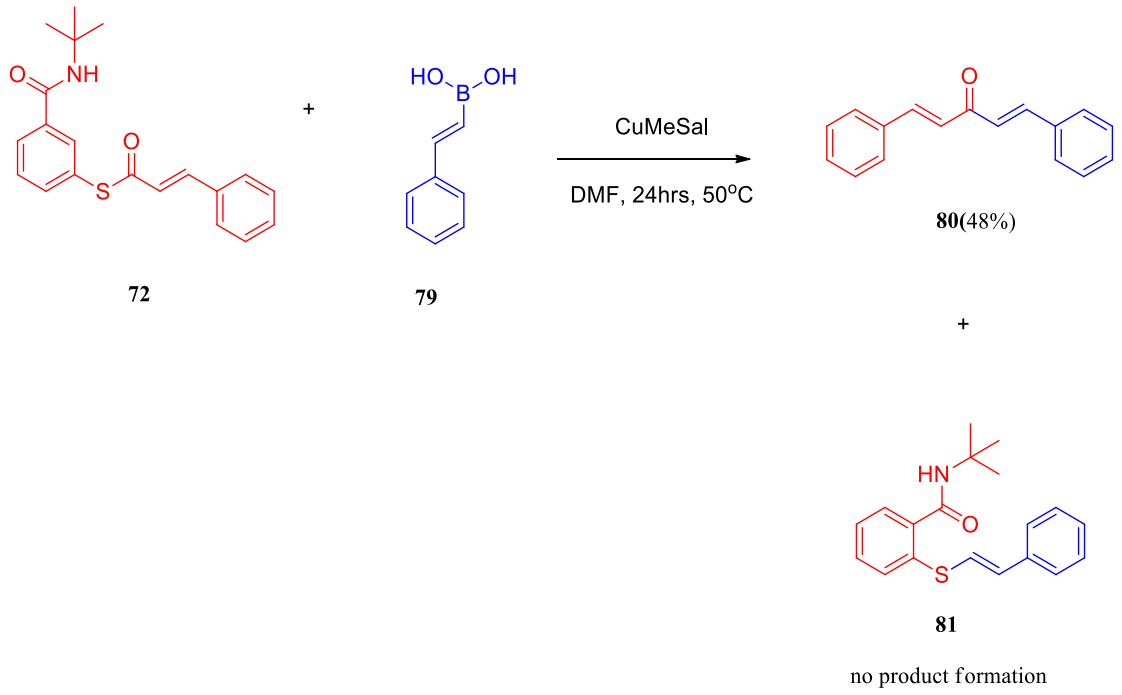


Figure 24: ^{1}H NMR spectrum for compound 103

3.3.3 Synthesis of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one

The coupling of compound **72** with 2-transvinylphenylboronic acid **(79)** furnished desired product, (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one **(80)** in low 48% yield. The formation of the expected thioether **81** was not observed during a TLC analysis. The reason as to why other thioethers are not detected on TLC analysis is not yet known **(Scheme 41)**



Scheme 41

^{1}H and ^{13} C NMR spectrum of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one **(80)** was less complex given its symmetric structure. The ^{1}H NMR spectrum showed five aromatic protons resonating in the range 7.4-7.70 ppm. The two vinyl protons are distinct, with the vinyl proton close to the carbonyl resonating downfield at about 7.79 ppm and the other vinyl proton resonating a little upfield at about 7.12 ppm. Both vinyl protons have a coupling constant (*J*) close to 15 Hz signifying that they have adopted a *trans*-configuration.

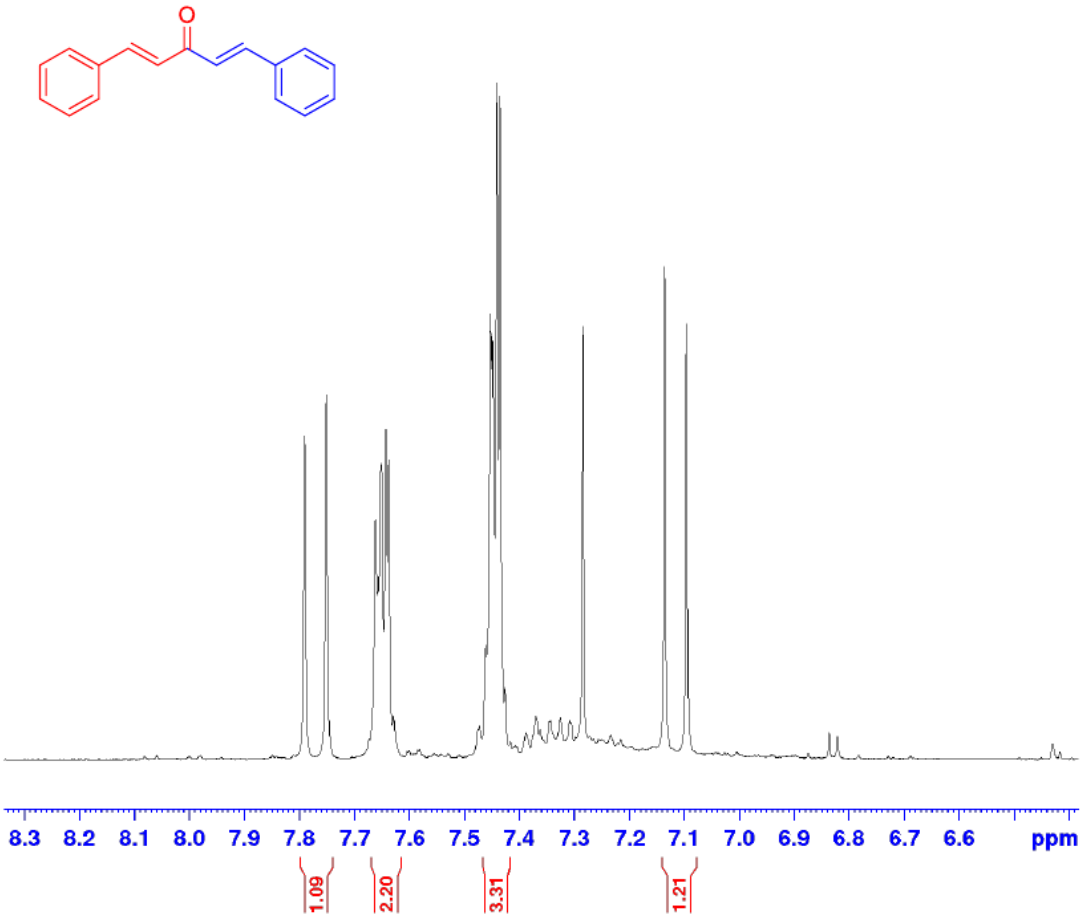


Figure 25: ^{1}H NMR spectrum for compound 80

The, ^{13}C NMR spectrum of compound **80 (Figure 26)** only showed 7 peaks as expected. The peaks resonating at 125.46 and 143.33 ppm assigned to the 2 carbons of the vinyl group. A peak, further downfield , resonating at 188.94 ppm corresponding to the carbonyl carbon .

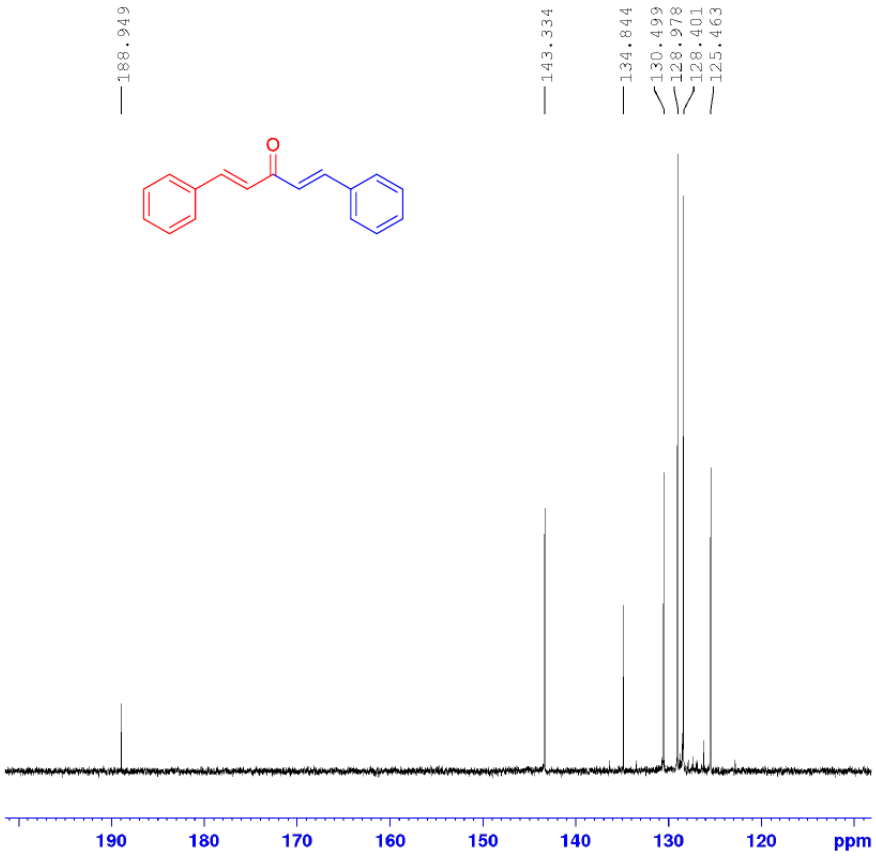
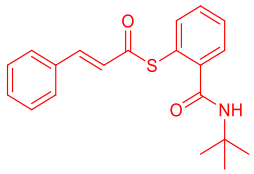
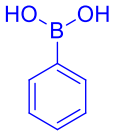
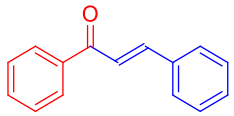
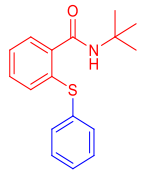
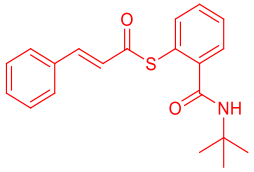
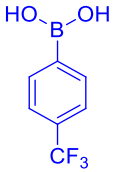
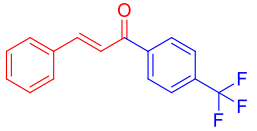
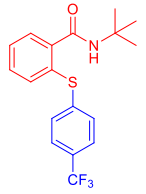
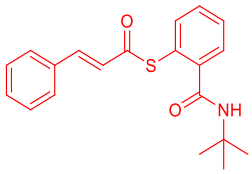
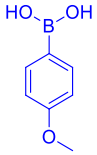
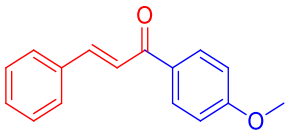
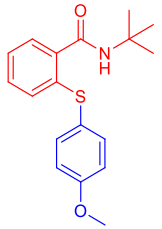
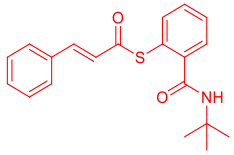
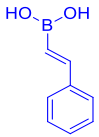
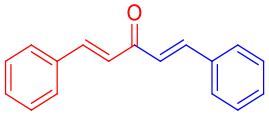
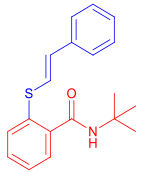
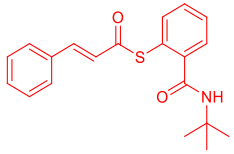
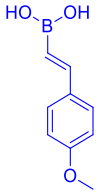
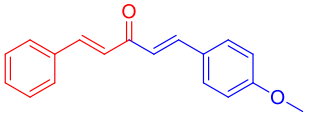
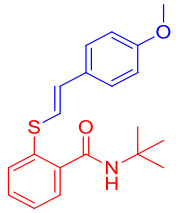
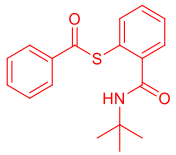
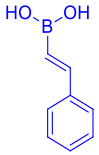
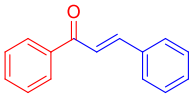
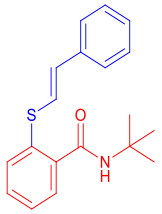
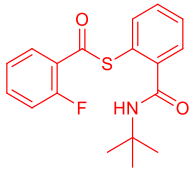
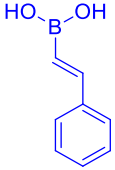
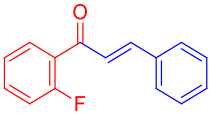
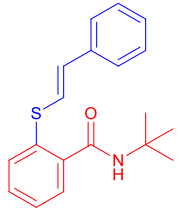
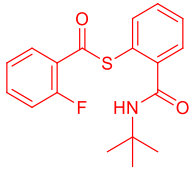
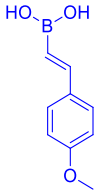
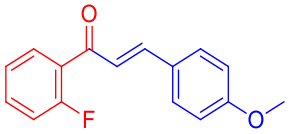
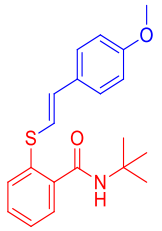


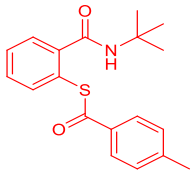
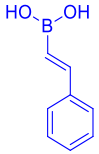
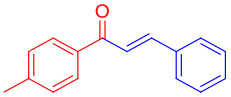
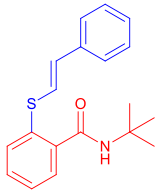
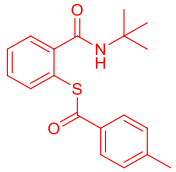
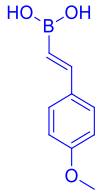
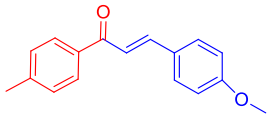
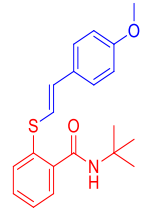
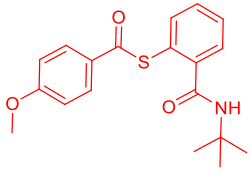
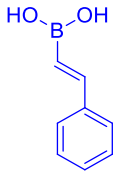
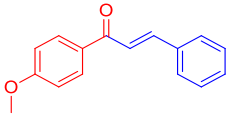
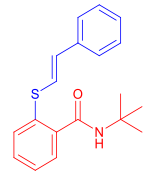
Figure 26: ^{13}C NMR spectrum for compound 80

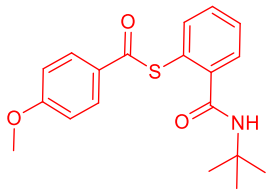
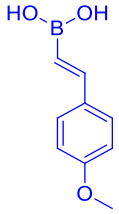
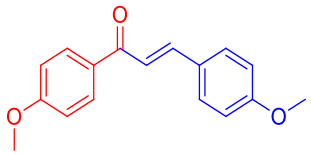
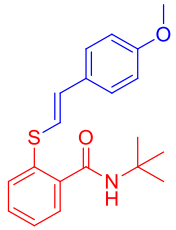
Table 3 : :Summary of Aerobic Copper-Catalysed synthesis of Chalcones

Entry	Thioester	Boronic acid	Products			
			Chalcone	Yield %	Thioether	Yield %
1	 **71**	 **26**	 **91**	53	 **73**	N.R
2	 **71**	 **74**	 **92**	32		N.R

					76	
3	 **71**	 **77**	 **93**	N.R	 **94**	N.R
4	 **71**	 **95**	 **96**	48	 **97**	N.R
5	 **71**	 **98**	 **99**	N.R	 **100**	N.R

6	 **68**	 **95**	 **91**	45	 **97**	32
7	 **69**	 **95**	 **101**	89	 **97**	46
8	 **69**	 **98**	 **102**	41		54

9	 **70**	 **95**	 **103**	46	**100**  **97**	58
10	 **70**	 **98**	 **104**	26	 **100**	32
11	 **72**	 **95**	 **105**	N.R		N.R

12	 **72**	 **98**	 **106**	N.R	**97**  **100**	N.R

[a]Reaction conditions : thioester (1mmol), boronic acid (2.5mmol), CuMeSal (5%mmol) , DMF (5 mL) , 50°C ,24hrs .[b , c] Isolated yields

The cross coupling reaction of phenyl boronic acid with vinyl thioester furnished the desired unsubstituted chalcone in 53% yield (**Table 3, entry 1**). The reactivity of the same vinyl thioester **(71)** was not as favoured when it was coupled with boronic acid substituted with a strongly electron withdrawing trifluoromethyl functional group as it generated the desired *para*-substituted chalcone in lower 32% yield **(Table 3, entry 2)**. The coupling reaction of boronic acid with *para*-substituted electron donating methoxy group **(77 and 98)** did not seem to favour the formation of the desired chalcones as both reactions did not initiate, only starting material were detected after 24 hours of stirring (**Table 3, entries 3 and 5).**

On the other hand, thioester *ortho*-substituted with fluoro-atom readily coupled with electron neutral as well as electron rich vinyl boronic acid **(95** and **98)** producing the desired chalcones in 89% and 41% yields, respectively (**Table 3, entries 7 and 8).** The corresponding thioether complementary products (**97** and **100)** were also isolated in 46% and 54% yields, respectively (**Table 3, entries 7 and 8)**. Tolyl thioester also managed to cross-coupled with electron-neutral as well as electron rich vinyl boronic acids giving the desired chalcones in 46% and poor 26% yields, respectively (**Table 3, entries 9 and 10)**. The corresponding thioether products were also isolated ((**Table 3, entries 9 and 10)**. Lastly the cross-coupling between thioester bearing an electron withdrawing group, methoxy, on the *para* position with either 2-transvinylphenylboronic acid **(94)** or *trans*-2-(4-Methoxyphenyl) vinylboronic **(97)** acid did not produce the desired product as only the starting materials were present after 24hrs **(Table 3 , entries 11 and 12).**

3.4 Conclusion

In conclusion, five thioesters were successfully synthesized and isolated, using previously reported methods, in poor to moderate yields (35-54%). With the thioesters at hand, thioester **68** was used in the optimization of the Liebeskind-Srogl cross-coupling reaction by expanding the scope using different thiophilic catalysts. The proposed thiophilic catalysts, namely: $Zn(OAc)_2$, $Cu(OAc)_2$ and Silver benzoate proved to be ineffective in this protocol as they did not promote the coupling reaction .

The optimized cross-coupling reaction conditions were used to successfully synthesize thirteen asymmetric ketones, bearing either electron-donating or withdrawing groups, in poor to moderate yield (20-65%) using various boronic acids as nucleophiles.

We also successfully synthesized eight chalcones in poor to excellent yields 26-89%. The significance of this specific study is that it reports on a novel synthesis of Chalcones using the aerobic, Cu^I -mediated Liebeskind-Srogl cross-coupling reaction, which to the best of our knowledge has never been reported before.

3.5 Future work

For future work, we would like to expand the scope of thiophilic carboxylate catalysts that can be used in aerobic Libeskind-Srogl cross coupling reaction to investigate if there could be a cheaper and more efficient alternative to the already well established CuMeSal catalyst. It is common knowledge that catalysts behave differently in various reaction conditions. We would like to investigate which reaction conditions would be better suited for transition metal complexes , Zinc acetate and Silver benzoate in order for them to become efficient catalysts in this protocol.

3.6 References

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Chapter 4: Experimental

4.1 Chemical and Instrumental Information

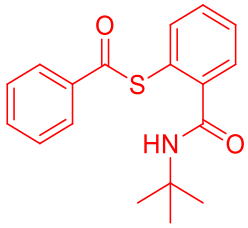
All experiments were conducted in oven-dried glassware containing a magnetic stirrer bar. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F (376.2 MHz) spectra were recorded on a Bruker Avance III NMR (9.4 T) spectrometer in normal glass NMR tubes. All the NMR spectra were recorded using solutions in specified deuterated solvents and are reported in parts per million (ppm) downfield from tetramethyl silane (TMS) as an internal standard. 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 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.

4.2 Synthesis of Thioesters

General procedure A

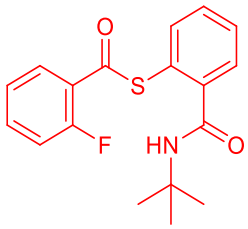
2,2-dithiodibenzoic acid (1 mmol) and excess thionyl chloride were added in a round bottom flask and refluxed for 4 hours resulting in 2,2'-disulfanediyldibenzoyl chloride. The excess thionyl chloride was removed from reaction mixture using rotary evaporator.2,2'-disulfanediyldibenzoyl chloride was dissolved in 15 mL of DCM and triethylamine (2.5 mmol) and tert-butylamine (2.2 mmol) were added slowly into the solution and the reaction was carried for 1 hour to form 2,2'-dithio-bis(*N*-*t*butyl) benzamide. After completion, the reaction mixture was washed 3 times with 20 mL of distilled water to remove HCl by-product. 2,2'-dithio-bis(*N*-*t*butyl) benzamide was placed in a dry 100 mL round-bottom flask and dissolved in methanol. Sodium borohydride ($NaBH_4$) was added at 0°C and reaction immediately began to bubble and turned orange. The reaction cooled to room temperature for 30 mins and gas evolution stopped, the reaction mixture was concentrated and dry THF was added. Triethylamine (2.5 mol) and benzoyl chloride were added at 0°C and allowed to warm to room temperature overnight. The reaction was quenched with H_2O and extracted with Ethyl acetate (20 mL) three times. The combined organic layers were and dried with $MgSO_4$, filtered and concentrated. Purification was achieved through column chromatography using hexane: ethyl acetate[1].

4.2.1 Synthesis of S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (68)



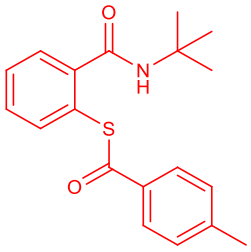
S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (68) : From general procedure A , **68** was obtained as a light-yellow crystalline powder (49%) :[1] H NMR ($CDCl_3$, 400MHz) : δppm 8.06 (d, *J* =7.32Hz, 2H) , 7.67 (t, *J* =7.44Hz, 1H) , 7.49-7.60 (m, 1H) , 7.55- 7.51 (m ,1H) , 7.49-7.45 (m ,4H) , 5.99 (br s , 1H) , 1.32 (s, 9H) . [13] C NMR ($CDCl_3$, 100MHz): δppm 192.7, 167.80, 144.16, 136.92, 136.26, 134.11, 130.52, 130.00, 128.95, 128.44, 127.63, 123.14, 51.79, 28.54. IR (neat, cm [1]): 3262 (w), 3060 (w), 1675 (s) ,1541 (m). LRMS (ESI) Calcd for $C_{18}H_{19}NO_2S$ [M+Na]: 336.11. Found: 336.05.

4.2.2 Synthesis of S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate (69)



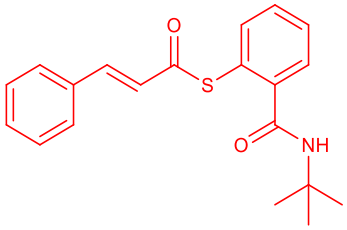
S-(2-(tert-butylcarbamoyl)phenyl) 2-fluorobenzothioate (69) : From general procedure A , **69** was obtained as white crystalline powder (54%) : [1]H NMR ($CDCl_3$, 400MHz) : δppm 7.97 (td , *J* =1.68Hz , 1H), 7.64-7.58 (m , 2H), 7.56-7.52 (m , 2H), 7.48 (td , *J*= 1.57 Hz , 1H) , 7.32 -7.21 (m , 3H), 5.96 (br s , 1H), 1.38 (s, 9H) . [13]C NMR ($CDCl_3$, 400MHz): δppm 188.85, 167.72, 161.79, 159.22, 143.97, 136.78, 135.14, 135.10, 130.62, 130.01, 128.38, 124.48, 123.45, 117.26, 117.10, 51.58, 28.57. [19]F NMR (376.2 MHz, CDCl3): δppm -109.41 (s). IR (neat, cm [1]): 3350 (w), 3002 (w), 1681 (s), 1541 (m). LRMS (ESI) calculated for $C_{18}H_{18}FNO_2S$ [M +Na] 355.10 Found: 355.60

4.2.3 Synthesis of S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate (70)



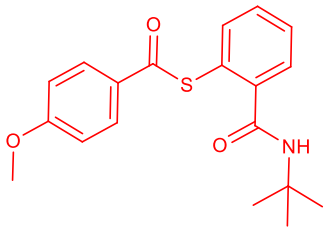
S-(2-(tert-butylcarbamoyl)phenyl) 4-methylbenzothioate (70) : From general procedure A ,**70** was obtained as white crystalline powder (35%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.97- 7.95 (m, 2H) , 7.62-7.60 (m, 1H) , 7.55-7.50 (m, 2H) , 7.48-7.46 (m ,1H) , 7.32 (d , *J* = 7.96Hz , 2H) , 6.04 (br s , 1H) , 2.46 (s, 3H) , 1.31 (s , 9H) . ^{13}C NMR ($CDCl_3$, 400MHz): δppm 191.85, 167.85, 145.20, 144. 22, 136.96, 133.71, 130.46, 129.95, 129.62, 128.45, 127.72, 123.51, 51.74, 28.53, 21.77. IR (neat, cm ^{1}): 3364 (w), 2960 (w), 1690 (s), 1526 (m). LRMS (ESI) calculated for $C_{19}H_{21}NO_2S$ [M+Na] 350.13 Found :350.30

4.2.4 Synthesis of (E)-S-(2-(tert-butylcarbamoyl) phenyl) 3-phenylprop-2-enethioate (71)



(E)-S-(2-(tert-butylcarbamoyl)phenyl) 3-phenylprop-2-enethioate (71) : From general procedure A , **71** was obtained as white crystalline powder (45%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.75 (s, 1H) , 7.71 (s, 1H) , 7.65-7.59 (m, 3H) , 7.53-7.51 (m ,2H) , 7.48-7.43 (m, 4H) , 6.89(s,1H) , 6.84 (s, 1H) , 6.02 (br s 1H) , 1.40 (s, 9H) . ^{13}C NMR ($CDCl_3$, 400MHz): δppm 189.86, 167.7, 143.83, 142.46, 136.63, 133.80, 131.60, 130.45, 129.96, 129.6, 128.65, 128.40, 123.84, 123.59, 51.84, 28.61. IR (neat, cm ^{1}): 3402 (w), 3059 (w), 1652 (s), 1527 (w). LRMS (ESI) calculated for $C_{20}H_{21}NO_2S$ [M+Na] 362.13 Found: 362.40

4.2.5 Synthesis of S-(2-(tert-butylcarbamoyl) phenyl) 4-methoxybenzothioate (72)



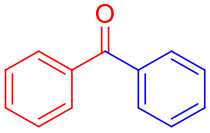
S-(2-(tert-butylcarbamoyl)phenyl) 4-methoxybenzothioate (72): From general procedure A , **72** was obtained as white crystalline powder (44%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 8.06-8.02 (m , 2H), 7.62- 7.59 (m , 1H), 7.54-7.50 (m , 2H), 7.47 -7.43 (m, 1H), 7.02-6.98 (m , 2H), 6.07(br s ,1H), 3.92 (s ,3H), 1.31 (s, 9H) . ^{13}C NMR ($CDCl_3$, 400MHz): δppm 190.73, 164. 40, 144.37, 137.02, 130.43, 129.46, 129.61, 128.45, 123.56, 114.13, 55.60, 51.71, 28.52. IR (neat, cm ^{1}): 3378 (w), 2967 (w), 1598 (s), 1571(w). LRMS (ESI) calculated for $C_{20}H_{21}NO_2S$ [M+Na] 362.13 Found: 362.20

4.3 Synthesis of Ketone

4.3.1 General procedure B

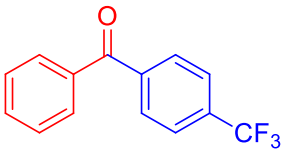
The corresponding thiol ester (1 mmol) , CuMeSal (5% mmol) and boronic acid (2.5 mmol) and dry DMF (4 mL) were placed in a 10mL round bottom flask with a magnetic stirrer and was heated at 50 ° C . After 24 hours, the reaction mixture was quenched with saturated NH_4Cl solution and washed three time with Et_2O (20 mL) and once with 100mL water. The combined organic layers were dried with $MgSO_4$, filtered and solvent removed under *vacuo*. The resulting residue was dissolved in DCM and purified using centrifugal preparative thin layer chromatography (chromatotron) using hexane: ethyl acetate (8:2) as an eluent[1].

4.3.2 Synthesis of Benzophenone (26)



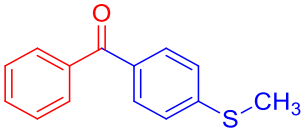
Benzophenone (26) Following general procedure B, S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1mmol , 50 mg) was coupled with phenylboronic acid (2.5mmol, 49 mg) to afford **26** as white crystalline powder (18 mg , 65%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.83 (d, *J* = 8.48Hz , 2H) , 7.61 (t , 8.94 , *J* = 8.94Hz , 1H) , 7.51 (d, *J* = 7.56 Hz , 2H) . ^{13}C NMR ($CDCl_3$, 100MHz): δppm 196.73, 137.64, 132.39, 130.05 and 128.27. MS (EI), m/z (%) : 51 (30%) , 77 (65%) ,105 (100%) , 182 (40%) ,182 [M^+] .IR: (C=O) 1678 cm^{-1}

4.3.3 Synthesis of phenyl(4-(trifluoromethyl)phenyl) methanone (75)



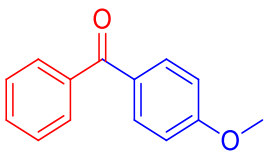
phenyl(4-(trifluoromethyl)phenyl)methanone (75) : Following general procedure B , **S**-(2-(tert-butylcarbamoyl) phenyl) benzothioate (1mmol, 70 mg) was coupled with 4-trifluoromethylphenylboronic acid (2.5mmol , 106 mg) to afford **75** as yellow crystalline powder (17 mg , 30%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.92 (d, *J* = 8 Hz , 2H) , 7.85-7.82 (m, 2H) , 7.78 (d, *J* =8 Hz , 2H), 7.67-7.63 (m , 1H), 7.55 - 7.51 (m , 2H). ^{13}C NMR ($CDCl_3$, 100MHz): 195.52, 140.76, 136.77, 133.07, 130.11, 128.53, 125.35. MS (EI), m/z (%) : 51 (13%, 77 (34%), 105 (100%), 145 (25%), 173 (23), 250 (40%), 250 [M^+] IR: (C=O) 1649 cm^{-1}

4.3.4 Synthesis of (4-(methylthio)phenyl) (phenyl)methanone (81)



(4-(methylthio)phenyl)(phenyl)methanone (81) : Following general procedure B , **S**-(2-(tert-butylcarbamoyl) phenyl) benzothioate (1 mmol , 50 mg) was coupled with 4-methylthiophenylboronic acid (2.5 mmol , 67 mg) to afford **81** as yellow powder (14 mg , 38%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.80- 7.76 9 (m, 1H), 7.62-7.58 (m, 1H), 7.50 (t, J= 8Hz , 1H), 7.33-7.29 (m, 1H), 2.56(s , 1H) . ^{13}C NMR ($CDCl_3$, 100MHz): 195.82, 145.29, 137.89, 133.70, 132.23, 130.65, 129.82, 128.26, 124.89 and 14.87. MS (EI), m/z (%) : 51 (15%), 77 (30%), 151 (100%), 227 (91%), 228[M^+]. IR: (C=O) 1655 cm^{-1}

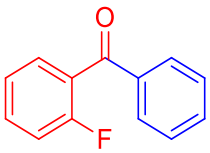
4.3.5 Synthesis of (4-methoxyphenyl) (phenyl)methanone (78)



(4-methoxyphenyl)(phenyl)methanone (78) : Following general procedure B, S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1 mmol, 70mg) was coupled with 4-

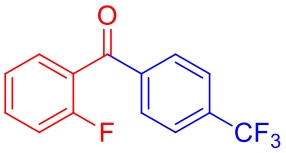
methoxyphenylboronic acid (2.5 mmol , 85 mg) to afford **78** as light pink crystalline powder (18 mg , 38%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.85 (dt , *J* = 4 , 1H) , 7.80-7.76 (m , 1H) , 7.58 (tt , *J* = 1.6Hz , 1H), 7.51-7.47 (m , 1H) , 7.00 (dt , *J* = 2.44Hz , 1H), 3.91 (s , 3H) ^{13}C NMR ($CDCl_3$, 100MHz) :195.55 , 163.24 , 138.32 , 132.55 , 131.57 , 130.21 , 129.72 , 128.18 , 113.57 and 55.49. MS (EI), m/z (%) : 51 (11%) , 77 (30%) , 92 (16%) , 105 (11%) , 135 (100%) , 212 (50) , 212 [M^+] . IR: (C=O) 1641 cm^{-1}

4.3.6 Synthesis (2-fluorophenyl) (phenyl)methanone (86)



(2-fluorophenyl)(phenyl)methanone (86) : Following general procedure B ,S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate (1mmol ,70 mg) was coupled with phenylboronic acid (2.5mmol , 65 mg) to afford **86** as yellow oil (11 mg , 26%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.78 (d , *J* = 8.28 Hz , 1H), 7.55-7.50 (m , 1H) , 7.49- 7.44 (m , 1H) , 7.43-7.38 (m, 1H) , 7.49- 7.44 (m, 1H), 7.43 -7.38 (m, 1H), 7.24 -7.17 (m , 1H) , 7.09 (t , *J* = 9.64 Hz , 1H) . ^{13}C NMR ($CDCl_3$, 100MHz): 192.43, 160.34, 136.42, 132.78, 132.05, 131.97, 129.73, 129.45, 128.78, 127.44, 123.25, 115.36 and 11.15. ^{19}F (376.2 MHz) : δppm -111.07 (s) . MS (EI), m/z (%) : 51 (21%) , 77 (61%) , 95 (32%) , 105 (100%) , 123 (78%) , 200 (50%) , 200 [M^+] . IR: (C=O) 1662 cm^{-1}

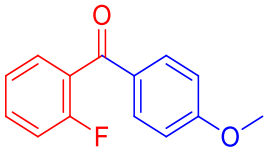
4.3.7 Synthesis (2-fluorophenyl) (4-(trifluoromethyl)phenyl) methanone (87)



(2-fluorophenyl)(4-(trifluoromethyl)phenyl)methanone (87) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate (1mmol , 70 mg) was coupled with 4-trifluoromethylphenylboronic acid (2.5mmol , 100mg) to afford **87** as yellow crystalline powder (33 mg , 58%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.97 (td , *J* = 1.69 Hz, 1H), 7.62-7.59 (m, 2H), 7.56 – 7.55 (m , 1H), 7.54 – 7.53 (m , 1H), 7.50 (d, *J* = 1.72 Hz, 1H) , 7.48(d, 1.8Hz , 1H), 7.36 -7.29 (m , 1H), 7.28 -7.27 (m , 2H), 7.26 -7.25 (m , 1H) , 7.25 – 7.22 (m , 1H), 7.16 – 7.14 (m , 1H), 2.49 (s , 1H) . ^{13}C NMR ($CDCl_3$, 100MHz) :192.40,

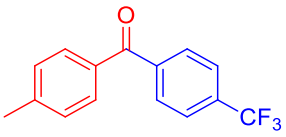
161.54, 159.02, 134.75, 133.93, 133.85, 130.95, 130.75, 129.33, 128.99, 128.61, 126.12, 125.5, 125.53, 125.49, 125.46, 124.59, 124.56, 116.59, 116.35 and 28.53. MS (EI), m/z (%): 95 (40%), 123 (100%) , 145 (20%) , 268 (58%) , 268 [M^+] . IR: (C=O) 1669 cm^{-1}

4.3.8 Synthesis of (2-fluorophenyl) (4-methoxyphenyl) methanone (88)



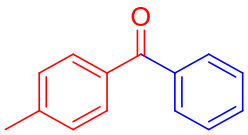
(2-fluorophenyl) (4-methoxyphenyl) methanone (88) : Following general procedure B, S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate (1mmol , 70 mg) was coupled with 4-methoxyphenylboronic acid (2.5mmol , 80 mg) to afford **26** as orange oil (20 mg , 41%): ^{1}H NMR ($CDCl_3$, 400MHz). 7.86 (dd, *J* = 1.12 , 1H), 7.55-7.49 (m, 1H), 7.30 -7.26 (M , 1H) , 7.20-7.15 (m, 1H), 7.20 -7.15 (m, 1H), 6.98- 6.95 (m , 1H), 3.90 (s, 2H) . ^{13}C NMR ($CDCl_3$, 100MHz): 191.96, 163.90, 158.52, 132.52, 132.47, 132.30, 130.44, 130.20, 124.24, 124.21, 116.26, 116.04, 113.76 and 55.52. MS (EI), m/z (%) : 77 (15%) , 92 (81%) , 107 (11%) , 135 (100%) , 228 [M^+] . IR: (C=O) 1653 cm^{-1}

4.3.9 Synthesis of p-tolyl(4-(trifluoromethyl)phenyl) methanone (84)



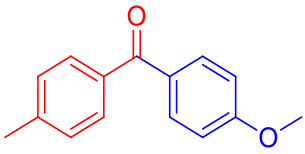
p-tolyl(4-(trifluoromethyl)phenyl)methanone (84): Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate (1mmol , 70 mg) was coupled with 4-trifluoromethylphenylboronic acid (2.5mmol , 102 mg) to afford **84** as white crystalline powder (11 mg , 20%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.89 (d, *J* = 8.6 Hz , 2H), 7.78 -7.73 (m, 4H), 7.33 (d, *J* = 8.4 , 2H), 2.48 (s , 3H) . ^{13}C NMR ($CDCl_3$, 100MHz). 195.25, 144.08, 141.15, 134.10, 130.33, 129.99, 129.22, 125.33, 125.30, 125.26, 125.22 and 21.69. ^{19}F (376.2 MHz) : δppm -63.00 (s) MS (EI), m/z (%) : 65 (11%) , 91 (24%) , 119 (100%) , 145 (19%) , 264 (33%) , 264 [M^+] . IR: (C=O)

4.3.10 Synthesis of phenyl(p-tolyl) methanone (83)



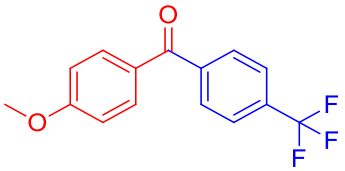
phenyl(p-tolyl)methanone(83): Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate (1mmol , 70 mg) was coupled with phenylboronic acid (2.5mmol , 65 mg) to afford **83** as orange oil (16 mg , 39%): ^{1}H NMR ($CDCl_3$, 400MHz): δppm 7.97-7.94 (m , 1H), 7.82-7.80 (m , 1H), 7.76-7.74 (m ,1H), 7.62-7.57(m , 1H), 7.55-7.73 (m ,1H) , 7.50-7.43 (m ,2H , 7.34 -7.29 (m ,3H), 2.47(s ,3H) . ^{13}C NMR ($CDCl_3$, 100MHz). 194.95, 138.00, 136.96, 135.51, 132.14, 130.46, 130.30, 129.93, 129.77, 129.62, 129.46, 129.40, 129.19, 129.05, 128.97, 128.44, 128.21, 127.72, 51.74 and 28.53. MS (EI), m/z (%) :51 (10%) , 65 (18%) , 77 (21%) , 91 (30%) , 105 (32%) , 119 (100%) , 196 [M^+] (62%) . IR: (C=O) 1652 cm^{-1}

4.3.11 Synthesis of (4-methoxyphenyl) (p-tolyl) methanone (85)



(4-methoxyphenyl)(p-tolyl)methanone (85) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate (1mmol ,70 mg) was coupled with 4-methoxyphenylboronic acid (2.5mmol , 81 mg) to afford **85** as light-yellow powder (17 mg ,35%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.76-7.73 (m , 2H), 7.60 (d , *J* = 8.76Hz , 2H), 6.88 (d , *J* = 8.84Hz , 2H), 3.81 (s , 3H), 2.36 (s , 3H) . ^{13}C NMR ($CDCl_3$, 100MHz) 195.35, 163.05, 142.59, 135.55, 132.42, 130.53, 129.99, 128.57, 113.50, 55.47 and 21.59. MS (EI), m/z (%) :39 (10%) , 96 (15%) , 151 (100 %) , 207 (12%) , 256 [M^+] . IR: (C=O) 1657 cm^{-1}

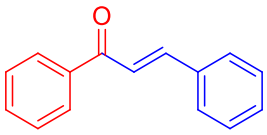
4.3.12 Synthesis of (4-methoxyphenyl) (4-(trifluoromethyl)phenyl) methanone (87)



(4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (87) : Following general procedure B , S-(2-(tert-butylcarbamoyl)phenyl) 4-methoxybenzothioate (1mmol , 70 mg) was coupled with 4-trifluoromethylphenylboronic acid (2.5mmol ,77 mg) to afford **87** as light-yellow powder (20 mg , 35%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.85 (t, *J* = 8.4 Hz , 1H) , 7.78 (d, *J* = 8.2Hz , 1H), 7.14 – 6.98 (m , 1H) . . ^{13}C NMR ($CDCl_3$, 100MHz). 189.52, 159.00, 136.80, 127.88, 125.03, 120.53, 120.49, 109.08 and 50.81. ^{19}F (376.2 MHz) : δppm -62.97 (s) .MS (EI), m/z (%) : 77 (15%), 107 (71%), 135 (100%), 280 [M^+] (35%) . IR: (C=O) 1648 cm^{-1}

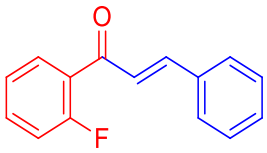
4.4 Synthesis of Chalcones

4.4.1 Synthesis of (E-) 1,3-Diphenyl-2-propen-1-one (91)



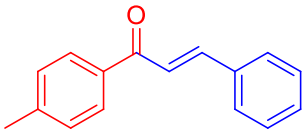
(E-)1,3-Diphenyl-2-propen-1-one: Following general procedure B, S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1mmol , 70 mg) was coupled with trans-2-phenylvinylboronic acid (2.5mmol ,82 mg) to afford **91** as yellow oil (19 mg ,45%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 8.06-8.04 (m, 1H), 7.85 (d , *J* =15.72 Hz , 1H) ,7.64-7.58 (m , 1H) , 7.56-7.52 (m , 1H), 7.45-7.44 (m , 2H) . ^{13}C NMR ($CDCl_3$, 100MHz): 190.63, 144.89, 138.25, 134.93, 132.79, 130.56, 128.98, 128.64, 128.52, 128.46 and 122.17. MS (EI), m/z (%) : 51 (11%), 77 (100%), 103 (52%), 131 (40%), 179 (21%), 208 [M^+] (83%) .

4.4.2 Synthesis of (E)-1-(2-fluorophenyl)-3-phenylprop-2-en-1-one (101)



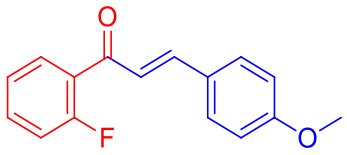
(E)-1-(2-fluorophenyl)-3-phenylprop-2-en-1-one (101) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate (1mmol ,70 mg) was coupled with trans-2-phenylvinylboronic acid (2.5mmol , 78 mg) to afford **101** as yellow oil (42 mg ,89%) : ^{1}H NMR ($CDCl_3$, 400MHz) . 7.84(td , *J* = 1.68Hz , 1H), 7.75(d , *J* = 1.68Hz , 1H), 7.66 – 7.64 (m , 2H) , 7.58 – 7.53 (m , 1H) , 7.40 (d, *J* = 2.81Hz , 1H), 7.37-7.31 (m , 3H), 7.22-7.17 (m , 2H) . ^{13}C NMR ($CDCl_3$, 100MHz): 189.12, 162.49, 159.98, 144.91, 134.74, 133.93, 133.84, 131.00, 130.97, 130.68, 128.96, 128.75, 128.61, 125.71, 125.64, 124.52 and 124.50. MS (EI), m/z (%): 51 (59%), 77 (100%), 95 (11%), 105(41%), 121 (21%), 149 (38%), 173 (10%), 197 (30%), 226 [M^+] (96%) . IR: (C=O) 1661.96 cm^{-1} (C=C) 1596 cm^{-1}

4.4.3 Synthesis of (E)-3-phenyl-1-(p-tolyl) prop-2-en-1-one (103)



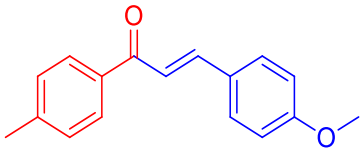
(E)-3-phenyl-1-(p-tolyl)prop-2-en-1-one (103) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate (1mmol ,70 mg) was coupled with trans-2-phenylvinylboronic acid (2.5mmol ,79 mg) to afford **103** as light yellow powder (22 mg , 46%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.98 – 7.96 (m , 2H) , 7.83 (d , *J* =15.72 Hz , 1H), 7.68 – 7.65 (m , 2H), 7.56 (d , *J* = 15.72 Hz , 1H), 7.45 – 7.43 (m , 3H), 7.33 (d , *J* = 7.98 , 3H) , 2.47 (s , 3H) . ^{13}C NMR ($CDCl_3$, 100MHz). 190.07, 144.41, 135.69, 135.26, 135.26, 135.07, 130.42, 129.34, 128.95, 128.67, 128.55, 128.48, 128.41, 127.31, 126.15 and 21.22. MS (EI), m/z (%) : 51 (10%), 65 (18%), 77 (22%), 91 (40%), 103 (25%), 119 (50%), 179 (18%) , 207 (25%) , 222 [M^+] (100%) . IR: (C=O) 1668 cm^{-1} , (C=C) 1592 cm^{-1}

4.4.4 Synthesis of (E)-1-(2-fluorophenyl)-3-(p-tolyl) prop-2-en-1-one (102)



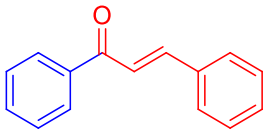
(E)-1-(2-fluorophenyl)-3-(p-tolyl)prop-2-en-1-one (102) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 2-fluorobenzothioate(1mmol ,70 mg) was coupled with trans-2-(4-methoxyphenyl)vinylboronic acid (2.5mmol ,80 mg) to afford **102** as yellow oil (22 mg , 41%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.87 – 7.79 (m , 1H), 7.75 (dd , *J* = 4, 1H) ,7.62- 7.58 (m, 2H), 7.32 – 7.26 (m , 2H), 7.20 – 7.16 (m , 1H), 6.96- 6.93 (m , 2H), 3.88 (s , 2H) . ^{13}C NMR ($CDCl_3$, 100MHz). 189.18, 189.15, 161.85, 144.85, 133.64, 133.54, 130.93, 130.90, 130.41, 127.67, 124.46, 124.42, 123.52, 123.46, 116.59, 116.36, 114.45 and 55.42. ^{19}F (376.2 MHz) : δppm -111.14 (s) MS (EI), m/z (%) : 95 (20%) , 108 (30%) , 123 (28%) , 161 (26%) , 213 (15%) , 241(18%) , 256 [M^+] (100%) . IR: (C=O) 1678 cm $^{-1}$, (C=C) 1582 cm $^{-1}$

4.4.5 Synthesis of (E)-3-(4-methoxyphenyl)-1-(p-tolyl) prop-2-en-1-one (104)



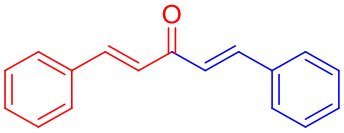
(E)-3-(4-methoxyphenyl)-1-(p-tolyl)prop-2-en-1-one (104) : Following general procedure B , S-(2-(tert-butylcarbamoyl) phenyl) 4-methylbenzothioate(1mmol ,70 mg) was coupled with trans-2-(4-methoxyphenyl)vinylboronic acid (2.5mmol ,95 mg) to afford **104** as light yellow powder (14 mg , 26%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.87 -7.85 (m, 2H), 7.80 (d , *J* =15.6 Hz ,1H), 7.73 (s , 1H), 7.69 (s, 1H), 7.69 (s , 1H), 7.54 -7.52 (m , 2H), 7.44 (dd, 15,6 Hz , 1H), 7.33 (s , 1H) , 7.23 (d , *J* =8.12Hz), 6.87 (d, *J* =8.82Hz , 2H), 3.79 (s , 2H) , 2.37 (s , 2H). ^{13}C NMR ($CDCl_3$, 100MHz) 161.61, 144.25, 143.35, 130.16, 129.62, 129.27, 128.57, 119.88, 114.42, 55.42 and 21.65. MS (EI), m/z (%) : 39 (10%), 96 (15%), 151 (100%) , 207 (12%), 256 [M^+]. IR: (C=O) 1672 cm $^{-1}$, (C=C) 1574 cm $^{-1}$

4.4.6 Synthesis of (E-) 1,3-Diphenyl-2-propen-1-one (91)



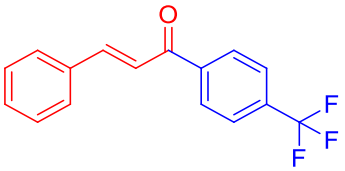
(E-) 1,3-Diphenyl-2-propen-1-one (91) Following general procedure B , (E)-S-(2-(tert-butylcarbamoyl) phenyl) 3-phenylprop-2-enethioate (1mmol, 70 mg) was coupled with phenylboronic acid (2.5mmol ,63 mg) to afford **91** as yellow crystalline powder (23 mg , 53%): ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 8.06-8.04 (m, 1H),7.84 (d , *J* =15.72Hz, 1H), 7.68 (dd, *J* = 2.85Hz , 1H), 7.62 (tt, *J* = 1.75Hz , 1H), 7.58 (s ,1H), 7.55 (s , 1H). 7.54 (d, *J* = 2.78Hz, 1H), 7.46- 7.44(m, 2H). ^{13}C NMR ($CDCl_3$, 100MHz): 188.95, 143.33, 134.84, 130.50, 128.98, 128.40 and 125.46. MS (EI), m/z (%) : 51 (11%) , 77 (100%) , 103 (52%) , 131 (40%) , 179 (21%) , 208 [M^+] (83%) . IR: (C=O) 1685 cm^{-1} , (C=C) 1628 cm^{-1}

4.4.7 Synthesis of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (96)



(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (96) : Following general procedure B , (E)-S-(2-(tert-butylcarbamoyl) phenyl) 3-phenylprop-2-enethioate(1mmol ,70 mg) was coupled with trans-2-phenylvinylboronic acid (2.5mmol ,76 mg) to afford **96** as yellow crystalline powder (23 mg , 48%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.77(d, *J* = 15.96 Hz 1H), 7.66-7.64 (m ,2H) ,7.45-7.44 (m , 3H) , 7.12 (d, *J* = 15.92 Hz , 1H). ^{13}C NMR ($CDCl_3$, 100MHz): 188.95, 143.33, 134.84, 130.50, 128.98, 128.40 and 125.46. MS (EI), m/z (%) : 51 (MS (EI), m/z (%) : 51 (19%) , 77 (45%) , 91 (25%) , 103 (60%) , 131 (35%) , 205 (15%) , 234 [M^+] (100%) . IR: (C=O) 1676 cm^{-1} (C=C) 1633 cm^{-1}

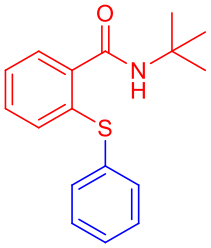
4.4.8 Synthesis of (E)-3-phenyl-1-(4-(trifluoromethyl) phenyl) prop-2-en-1-one (92)



(E)-3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (92) : Following general procedure B, (E)-S-(2-(tert-butylcarbamoyl) phenyl) 3-phenylprop-2-enethioate(1mmol , 70 mg) was coupled with phenylboronic acid (2.5mmol , 98 mg) to afford **92** as white crystalline powder (18 mg , 32%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 8.08 (s,1H) , 8.06(s,1H), 7.85(s, 1H), 7.81(s,1H), 7.68-7.67(m ,1H) , 7.66(d , *J* = 15.72 Hz ,1H), 7.46 (s, 1H) , 7.45(d, *J* = 1.96Hz, 1H), 7.43(d, *J* = 1.96Hz,1H) . ^{13}C NMR ($CDCl_3$, 100MHz): 206.88, 145.64, 143.97, 137.60, 135.25, 130.82, 130.32, 128.65, 128.54, 128.48, 128.43, 128.36 ,126.21 and 126.14. MS (EI), m/z (%) : 51 (8%) , 65 (8%) , 77 (12%) , 91 (43%) , 115 (100%) , 130 (22%) , 178 (35%) , 193 (95%), 208 (95%) , 276 [M^+]. IR: (C=O) 1659 , (C=C) 1589 cm^{-1}

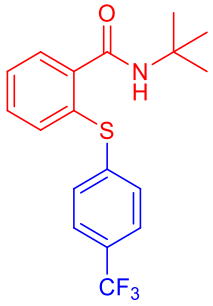
4.5 Synthesis of Thioether

4.5.1 Synthesis of N-(tert-butyl)-2-(phenylthio)benzamide (73)



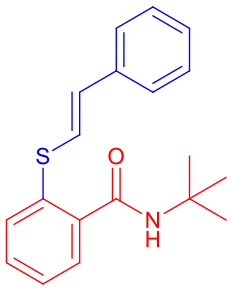
N-(tert-butyl)-2-(phenylthio)benzamide (73) : Following general procedure B , S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1mmol) was coupled with phenylboronic acid (2.5mmol) to afford **73** as white crystalline powder (43%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.69 -7.66 (m , 1H), 7.34 -7.31 (m , 6H), 7.30 -7.28 (m, 1H), 7.28-7.25 (m , 1H), 6.24 (br, 1H) , 1.38 (s, 9H) . ^{13}C NMR ($CDCl_3$, 100MHz): 166.94, 138.68, 135.39, 132.89, 132.39, 130.47, 129.46, 129.19, 127.60, 127.22, 51.92 and 28.60. LRMS (ESI) calculated for $C_{17}H_{19}NOS$ [M+Na] 308.12 Found: 308 . IR: (neat ,cm^{-1}) 3296 (w) , 2975 (s) , 1631 (s) ,1538 (s) .

4.5.2 Synthesis of N-(tert-butyl)-2-((4-(trifluoromethyl)phenyl) thio) benzamide (76)



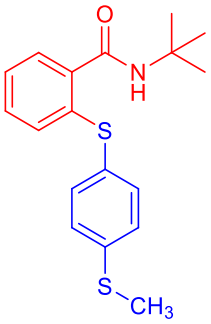
N-(tert-butyl)-2-((4-(trifluoromethyl)phenyl)thio)benzamide (76) : Following general procedure B , S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1 mmol) was coupled with 4-trifluoromethylphenylboronic acid (2.5 mmol) to afford **76** as light-yellow crystalline powder (22%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.71 – 7.69 (m , 1H), 7.54 (d , *J* = 8.32Hz , 2H), 7.44-7.41 (m , 3H), 7.30 (t ,*J* = 6 .7Hz , 3H), 6.06 (br , 1H) , 1.34 (s , 9H) . ^{13}C NMR ($CDCl_3$, 100MHz) :160.72, 141.82, 140.41, 134.74, 130.74, 129.64, 129.33, 128.98, 128.63, 126.11, 126.63, 126.11, 126.08, 51.99 and 28.54. LRMS (ESI) calculated for $C_{18}H_{18}F_3NOS$ [M+Na] 376.11 Found: 376 . IR (neat , cm $^{-1}$) 3311 (w) , 2974 (s) , 1643 (s) ,1403 (s) .

4.5.3 Synthesis of (E)-N-(tert-butyl)-2-(styrylthio)benzamide (97)



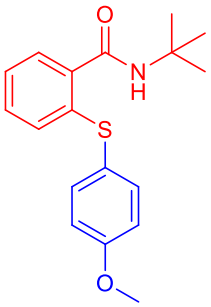
(E)-N-(tert-butyl)-2-(styrylthio)benzamide (97) Following general procedure B , S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1 mmol) was coupled with trans-2-phenylvinylboronic acid (2.5mmol) to afford **97** as light yellow crystalline powder (37%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.59(d, *J* = 7.6Hz , 1H), 7.47 (s, 1H), 7.45 (s, 1H) , 7.41 – 7.37 (m , 4H), 7.34 – 7.30 (m , 2H), 7.29(s, 1H) , 6.83 (d , *J* = 4.95Hz , 2H) , 6.09 (br s , 1H) , 1.49 (s, 9H) . ^{13}C NMR ($CDCl_3$, 100MHz): 167.28, 137.27, 136.30, 133.51, 133.45, 130.73, 130.47, 128.73, 128.53, 122.88, 126.93, 126.1, 122.74, 52.15 and 28.83. LRMS (ESI) calculated for $C_{19}H_{21}NOS$ [M +Na] 334.13 Found: 334.13 . IR (neat , cm^{-1}) 3300 (w) , 2969 (s) , 1634 (s) , 1446 (s) .

4.5.3 Synthesis of N-(tert-butyl)-2-((4-(methylthio)phenyl) thio) benzamide (82)



N-(tert-butyl)-2-((4-(methylthio)phenyl)thio)benzamide (82) Following general procedure B , S-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1 mmol) was coupled with 4-methylthiophenylboronic acid (2.5 mmol) to afford **82** as yellow oil (49%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.62 – 7.60 (m , 1H) , 7.56 -7.53 (m , 1H) , 7.28 (br s, 1H) , 7.24 (brs , 1H) , 7.23 -7.22 (m, 1H), 7.16 -7.15 (m, 1H), 6.16 (br s, 1H), 2.49 (s, 1H), 1.43 (s, 8H) . ^{13}C NMR ($CDCl_3$, 100MHz) :167.17, 155.01, 138.73, 137.70, 136.92, 133.91,132.24, 131.45 , 130.65, 130.58, 130.54, 130.44, 128.96, 128.80, 128.43, 127.62, 127.39, 126.95, 116.18 , 52.04, 28.70 and 15.71. LRMS (ESI) calculated for $C_{18}H_{21}NOS_2$ 354.11 Found: 354 . IR: (neat cm^{-1} 3300 (w) , 2969 (s) , 1634 (s) , 1446 (s).

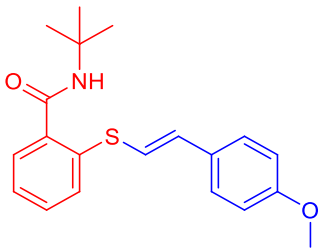
4. 5.4 Synthesis of N-(tert-butyl)-2-((4-methoxyphenyl) thio) benzamide (79)



Synthesis of N-(tert-butyl)-2-((4-methoxyphenyl)thio)benzamide (79) : Following general procedure B , **S**-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1mmol) was coupled with 4-methoxyphenylboronic acid (2.5mmol) to afford **79** as pink crystalline powder (53%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.56 (dd, *J* = 1.56Hz, 1H), 7.42 – 7.41 (m, 1H), 7.39 (s, 1H), 7.23 (d , *J* = 1.56Hz, 1H), 7.21 (d, *J* =1.72 Hz , 1H), 7.19 (br s, 1H), 6.98 (d, *J* = 1.36 Hz , 1H), 6.96 (d, *J* = 1.48Hz , 1H), 6.95 (s, 1H), 6.92 (s, 1H), 6.12 (br s, 1H) , 3.85 (s,

3H), 1.48 (s, 9H) . ^{13}C NMR ($CDCl_3$, 100MHz): 167.25, 135.26, 130.24, 129.38, 128.46, 125.81, 115.24, 55.38 and 28.81. LRMS (ESI) calculated for $C_{18}H_{21}NOS$ 338.13 Found: 338 . IR (neat ,cm^{-1} **)** 3303 (w) , 2967 (s) , 1633 (s) , 1496 (s).

4.5.5 Synthesis of (E)-N-(tert-butyl)-2-((4-methoxystyryl) thio) benzamide (100)

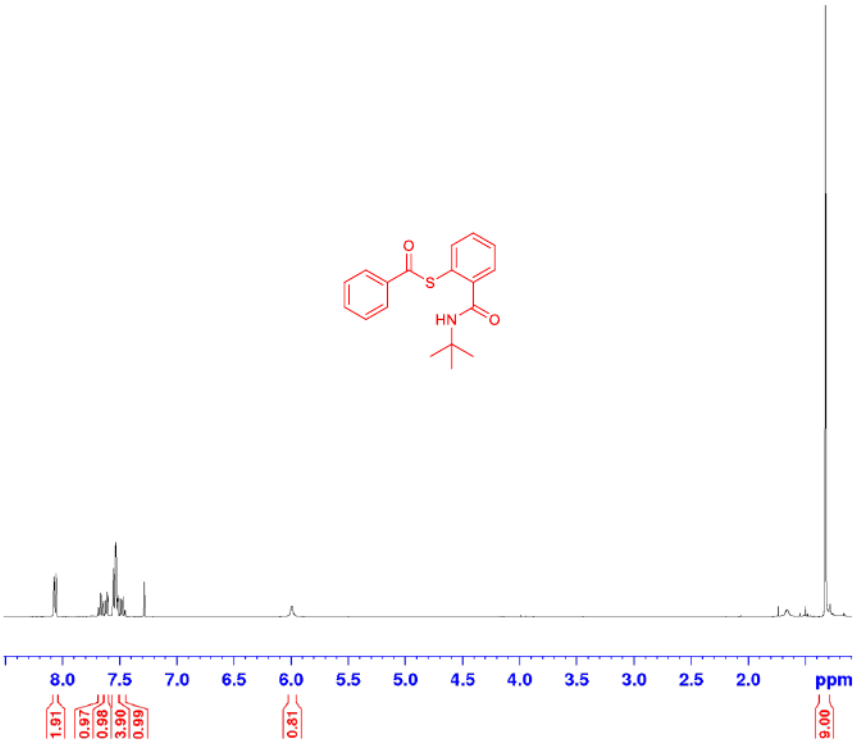


(E)-N-(tert-butyl)-2-((4-methoxystyryl)thio)benzamide (100) : Following general procedure B , **S**-(2- (tert-butylcarbamoyl) phenyl) benzothioate (1 mmol) was coupled with trans-2-(4-methoxyphenyl)vinylboronic acid (2.5 mmol) to afford **100** as white crystalline powder (54%) : ^{1}H NMR ($CDCl_3$, 400MHz) : δppm 7.97 (s, 1H) , 7.95 (s, 1H) , 7.63 -7.60 (m , 2H) , 7.54 (t , *J* = 1.84 Hz , 1H), 7.53 -7.52 (M, 1H), 7.48 (d ,*J* = 1.6Hz , 1H) , 7.46 (s , 1H), 7.33 (s, 2H), 7.31 (s, 2H), 6.95 (s, 1H), 6.89 (s, 1H), 6.57 (s , 1H), 6.04 (br s , 1H) , 3.83 (s, 1H) , 1.31 (s, 9H) . ^{13}C NMR ($CDCl_3$, 100MHz): 167.84, 144.28, 136.96, 134.24, 133.71, 130.46, 129.95, 129.62, 128.44, 127.72, 123.51, 119.54, 114.42, 114.17, 51.74, 28.53 and 21. 77. LRMS (ESI) calculated for $C_{20}H_{23}NO_2S$ 341 .14 Found: 341. IR:(neat, cm^{-1}) 3304 (w) , 2966 (s) , 1634 (s) ,1458 (s) .

4.6 References

(1) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. A New Paradigm for Carbon-Carbon Bond Formation: Aerobic, Copper-Templated Cross-Coupling. *J. Am. Chem. Soc.* **2007**, *129* (51), 15734–15735. https://doi.org/10.1021/ja074931n.

Appendix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S
HN
O
8.0
7.5
7.0
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
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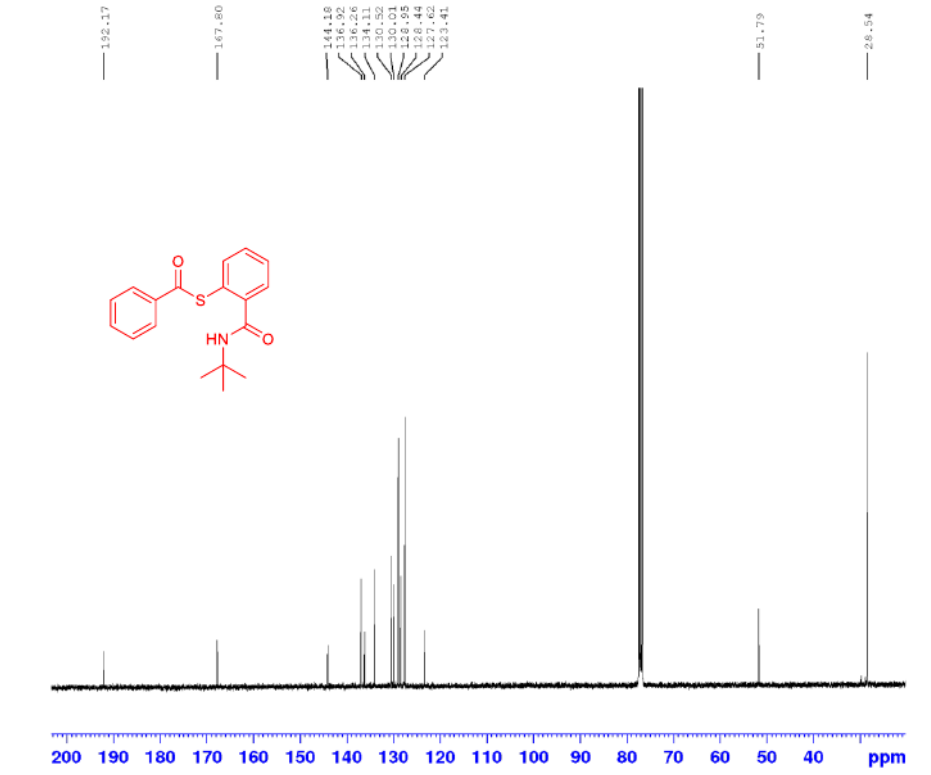
0.98
3.90
0.99
0.81
9.00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134.11
134.02
130.01
129.95
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123.41
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28.54
O
S
HN
O
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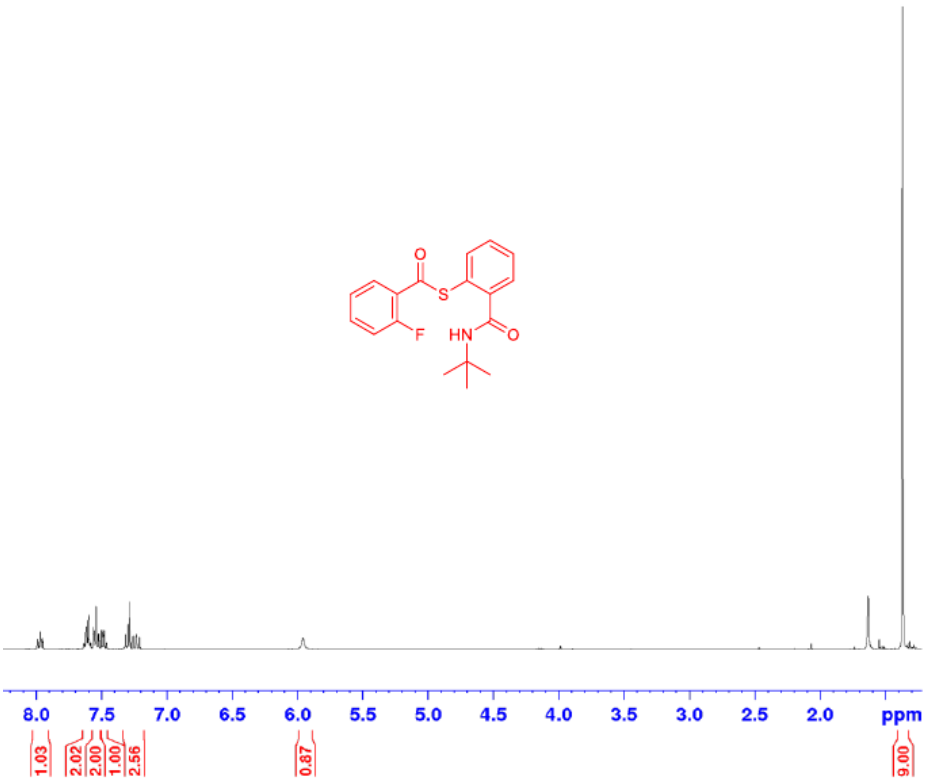
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S
F
HN
O
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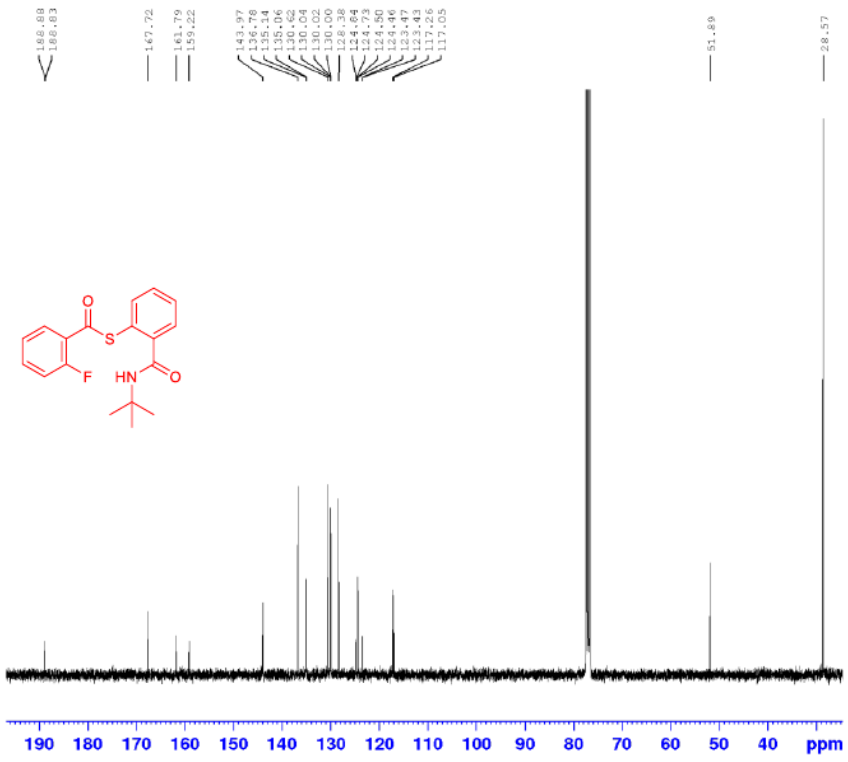
2.02
2.00
1.00
2.56
0.87
9.00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186.83
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159.22
143.97
136.78
135.14
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130.62
130.04
130.02
130.00
128.38
124.64
124.73
124.50
124.46
123.47
123.43
117.26
117.05
51.89
28.57
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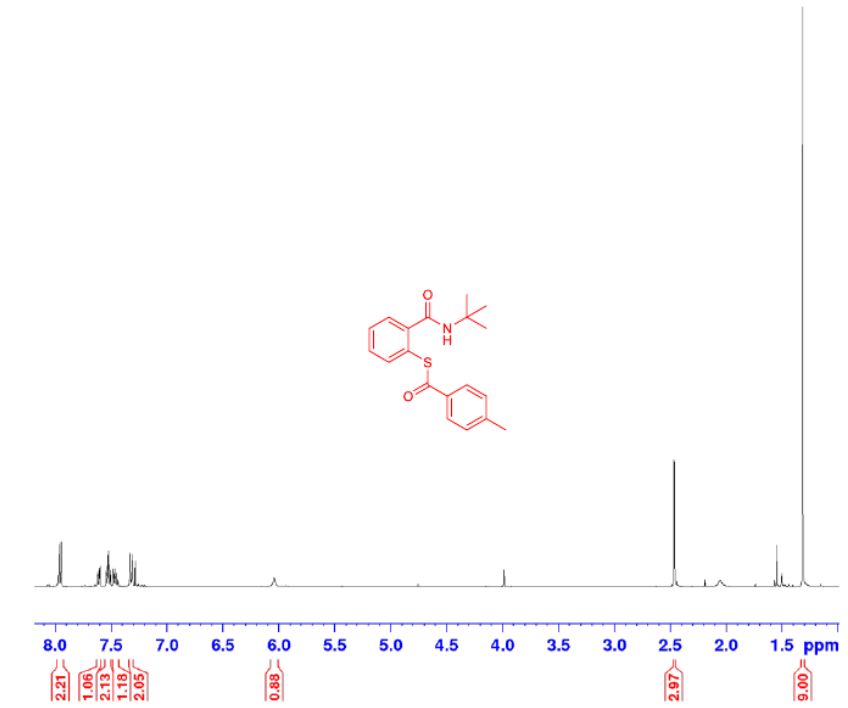
S
F
HN
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm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N
H
S
O
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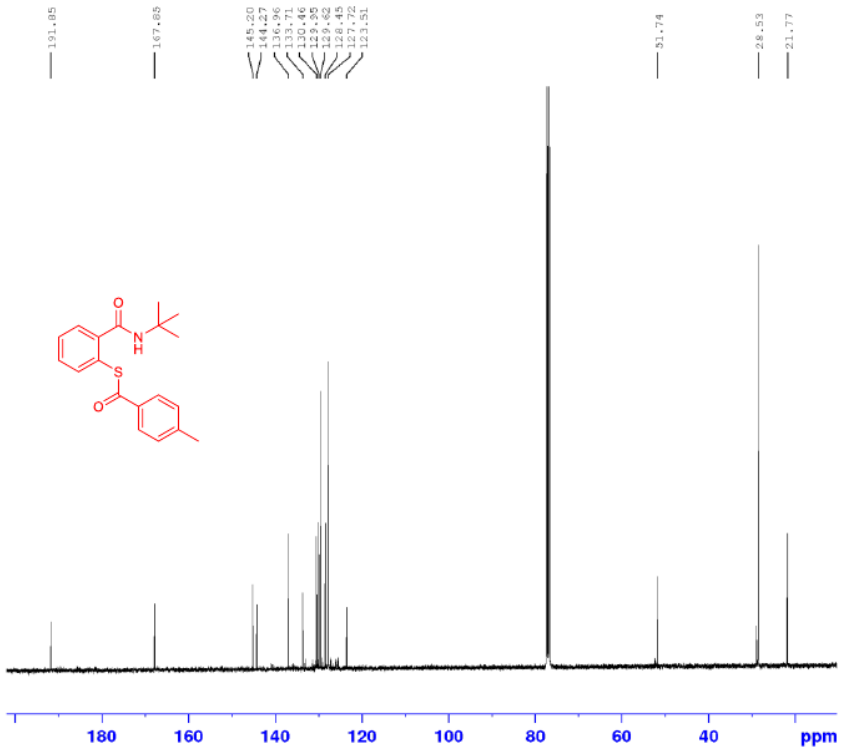
1.18
2.05
0.88
2.97
9.00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145.20
144.27
136.96
133.71
130.46
129.95
129.62
128.45
127.72
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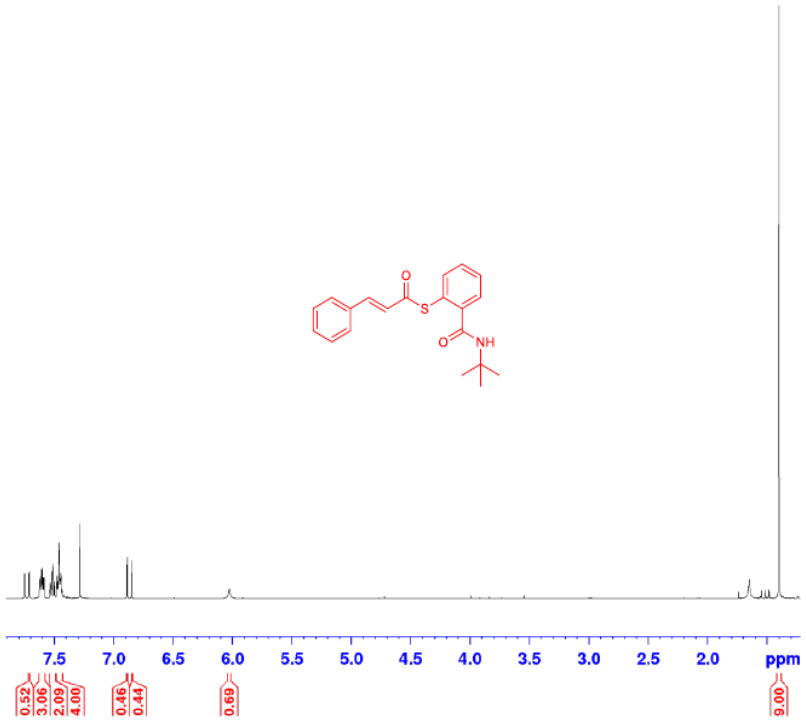
51.74
28.53
21.77
O
N
H
S
O
180
160
140
120
100
80
60
40
ppm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4.5
4.0
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2.0
ppm
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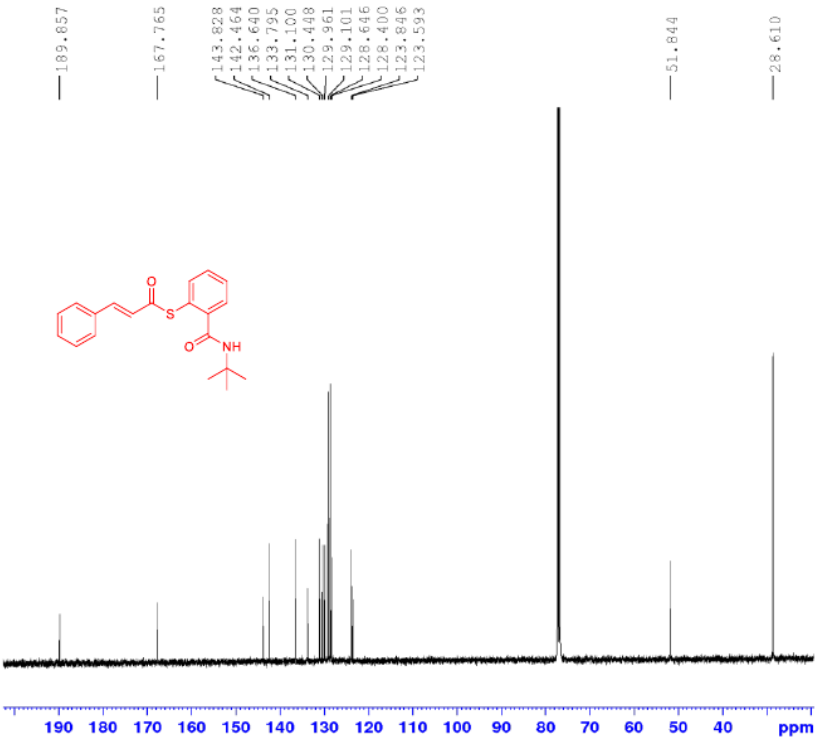
9.00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123.593
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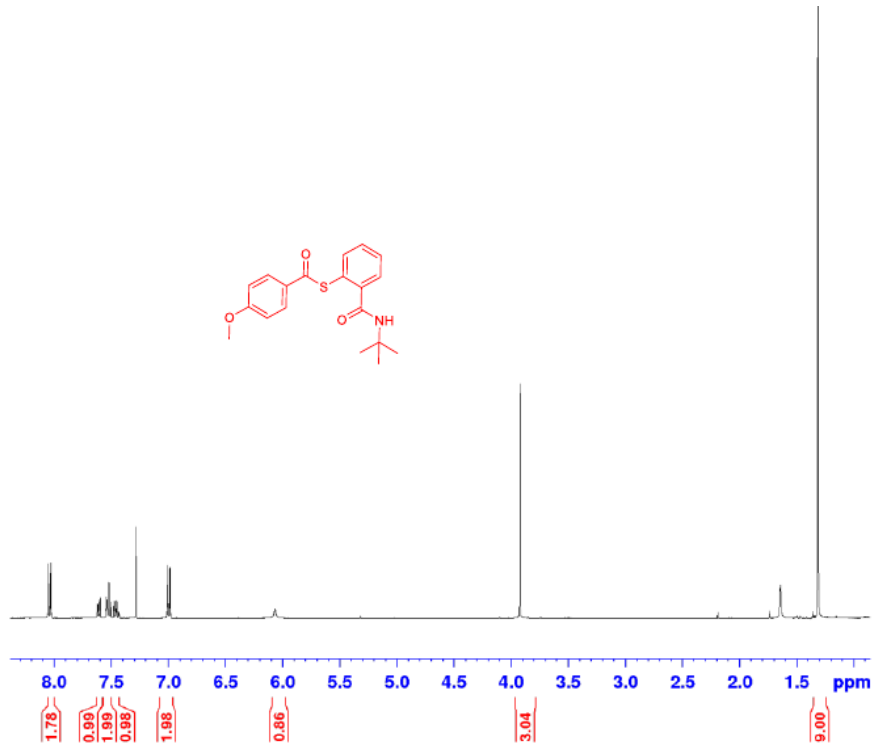
28.610
O
S
O
NH
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm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O
NH
O
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6.0
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4.5
4.0
3.5
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0.98
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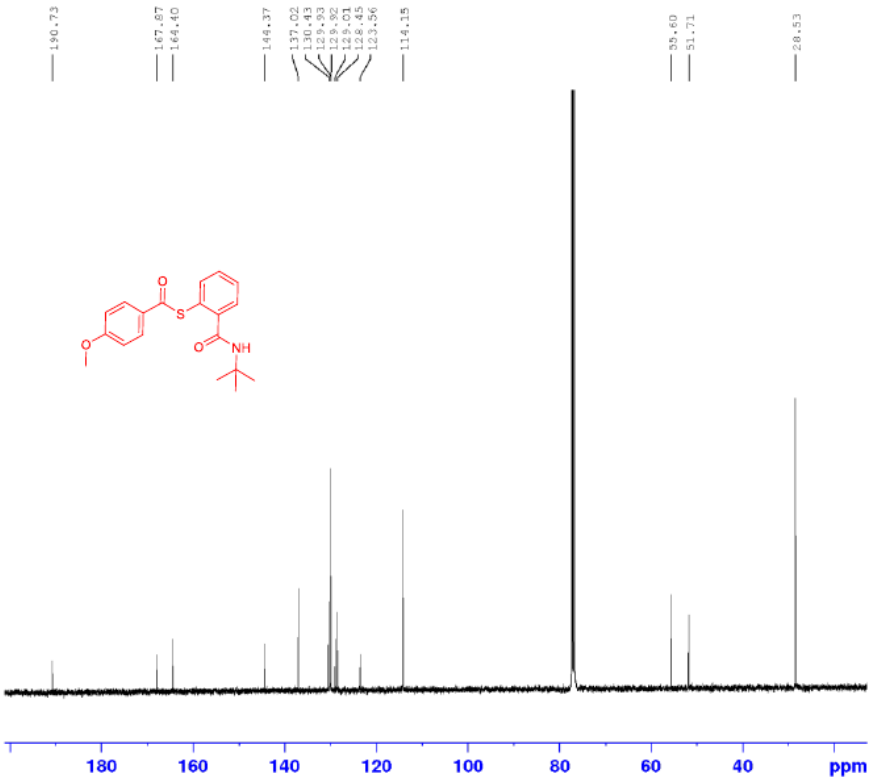
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144.37
137.02
130.43
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129.92
129.01
128.45
123.56
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55.60
51.71
28.53
O
S
O
NH
O
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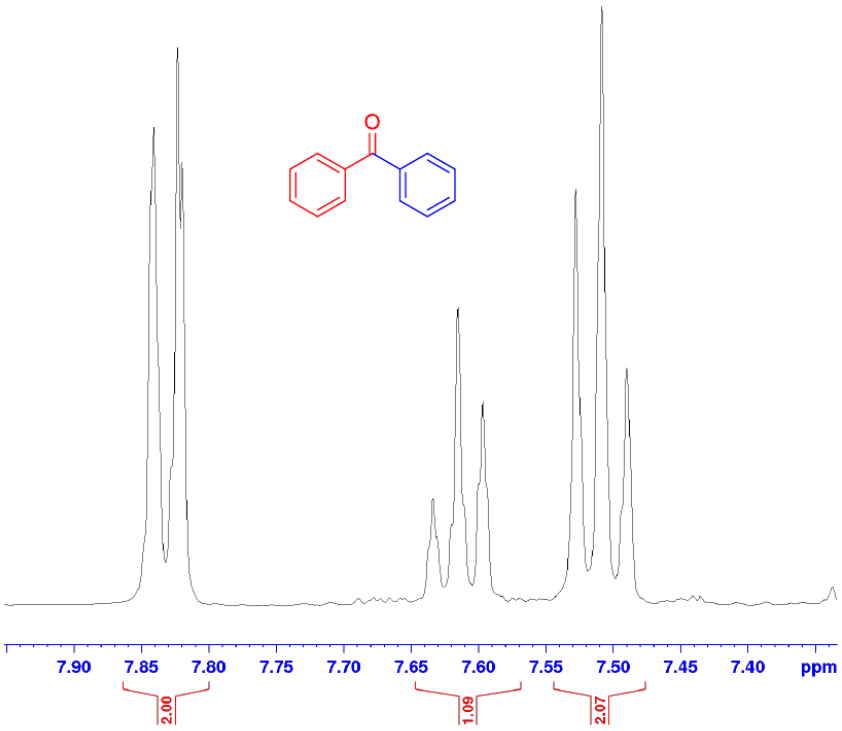
160
140
120
100
80
60
40
ppm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7.55
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7.45
7.40
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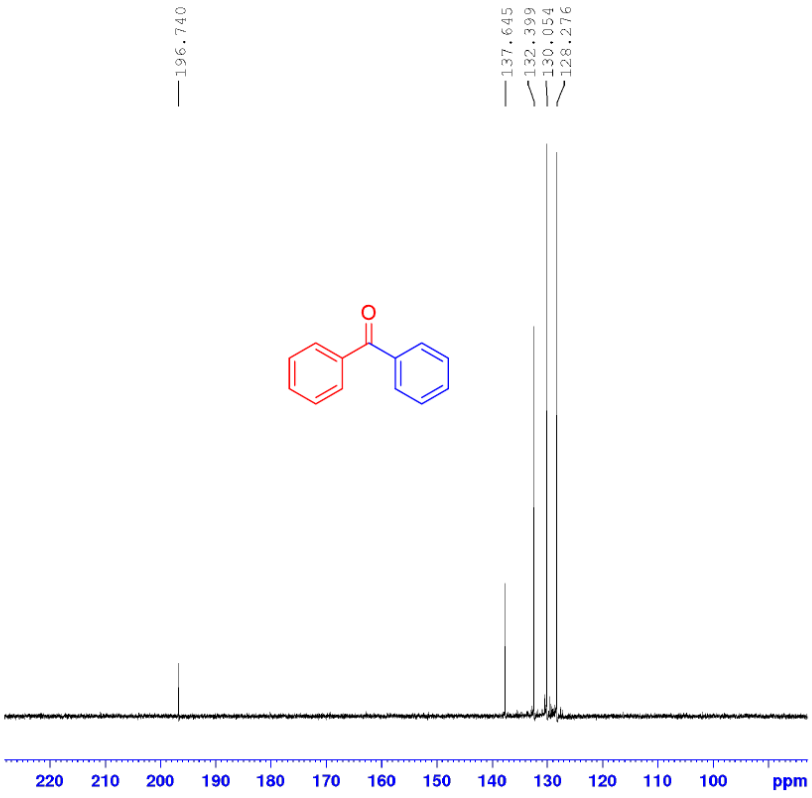
1.09
2.07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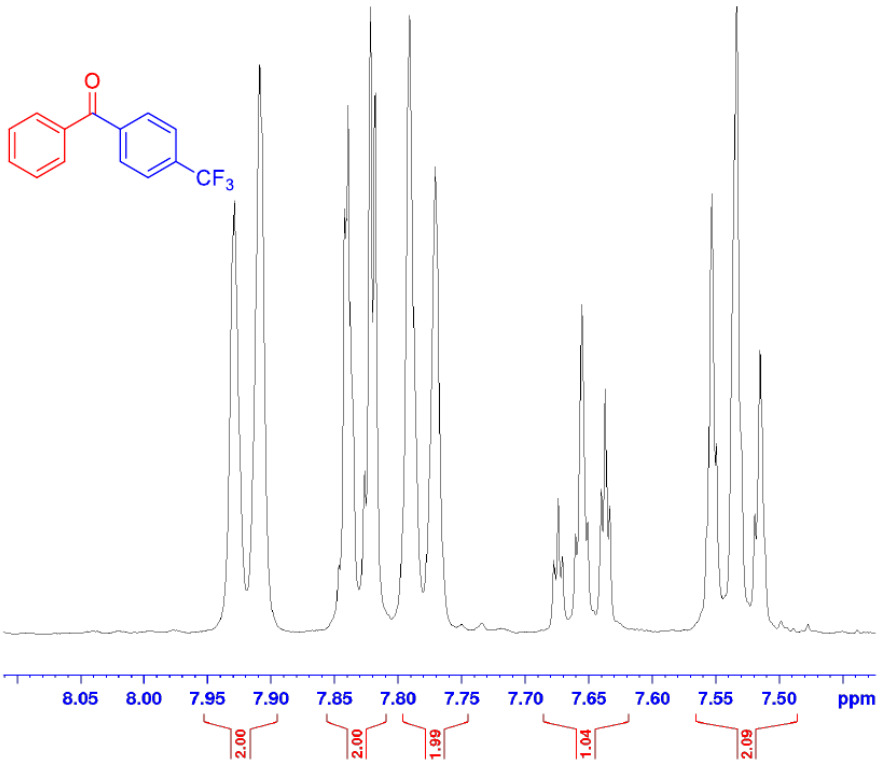
120
110
100
ppm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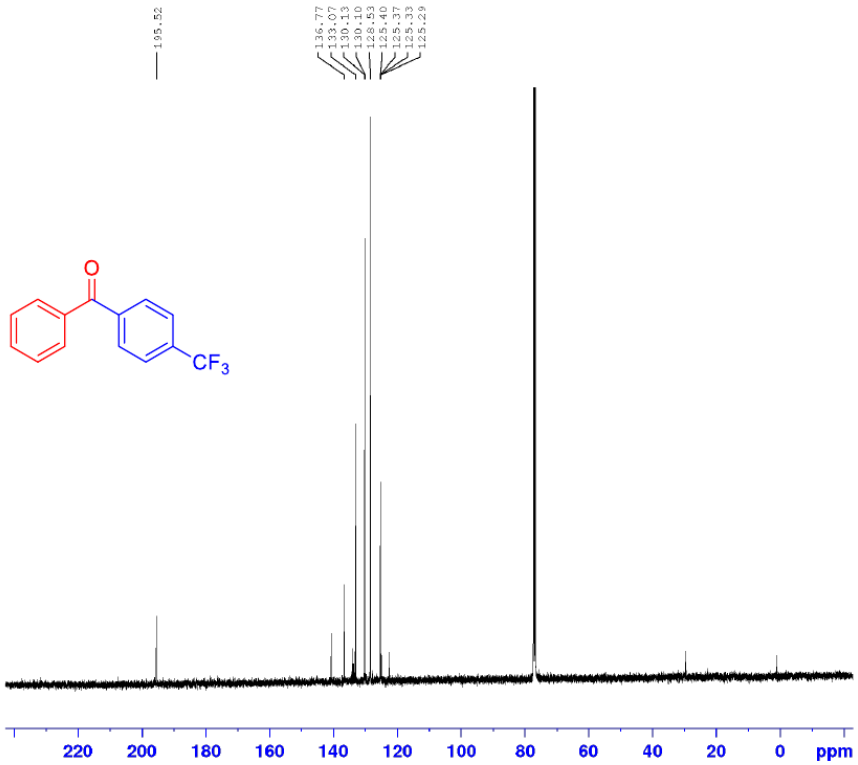
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120
100
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60
40
20
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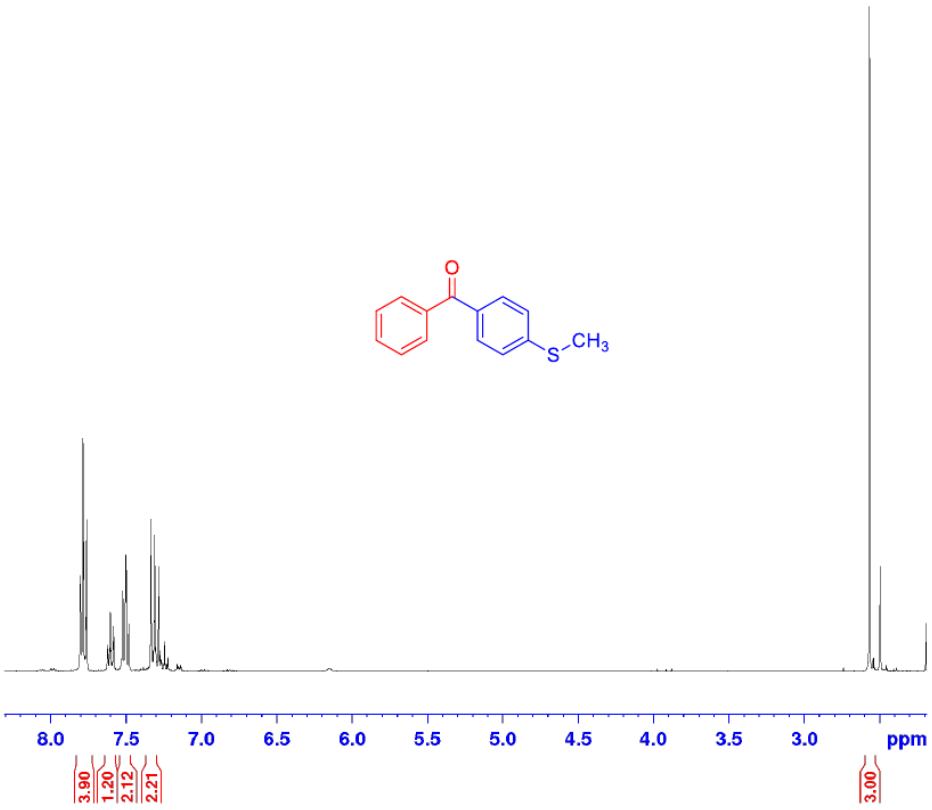
ppm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6.0
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4.5
4.0
3.5
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ppm
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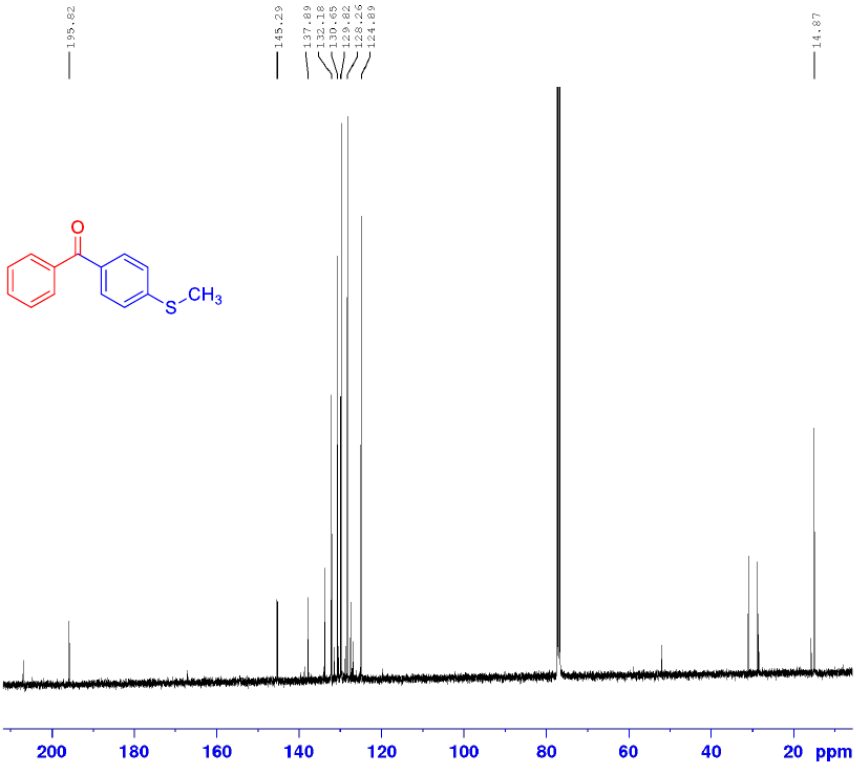
2.12
2.21
3.00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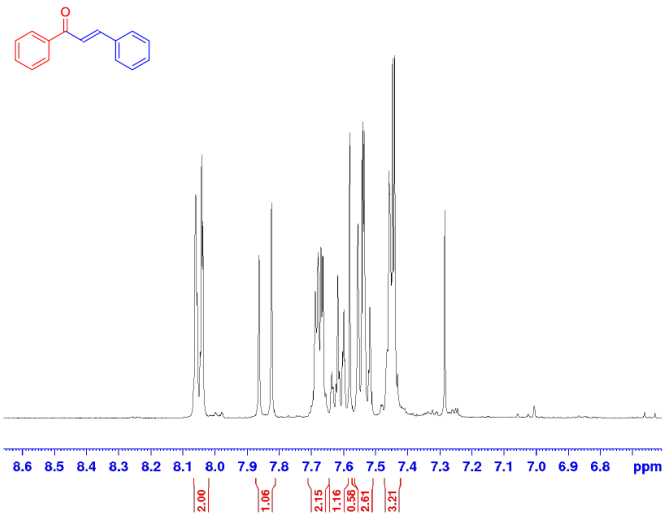
140
120
100
80
60
40
20
ppm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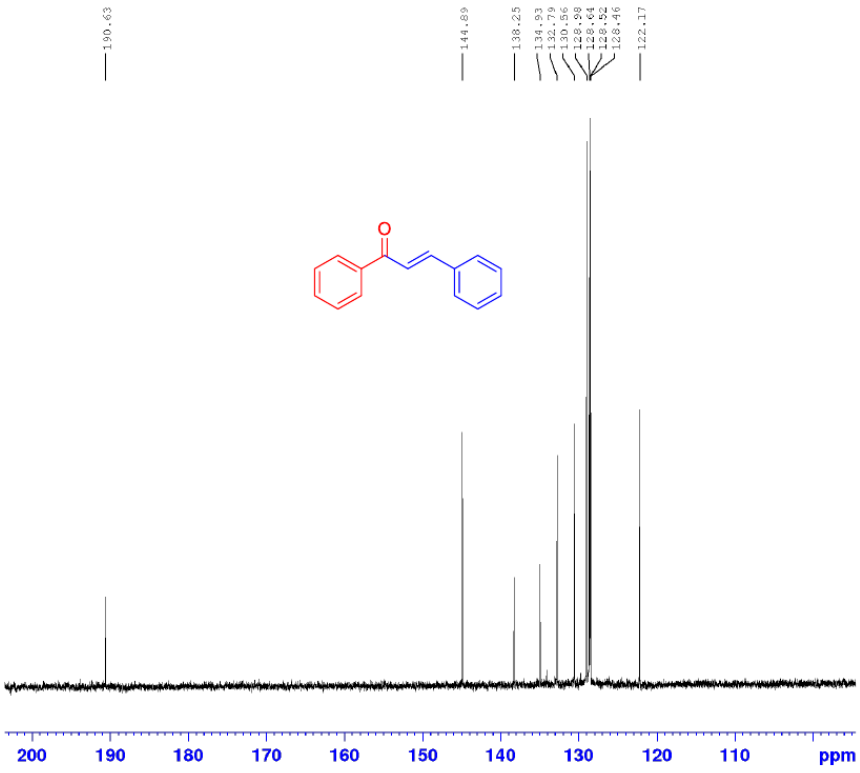
1.06
2.15
1.16
0.58
2.61
3.21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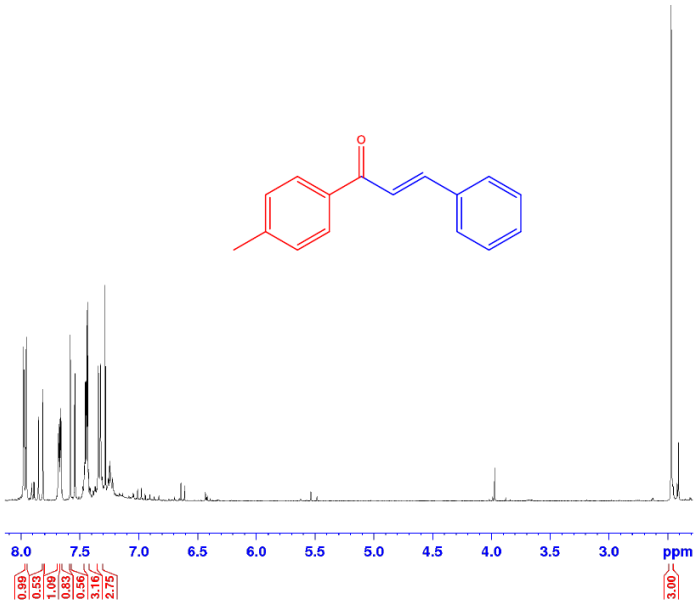
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6.5
6.0
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5.0
4.5
4.0
3.5
3.0
ppm
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0.83
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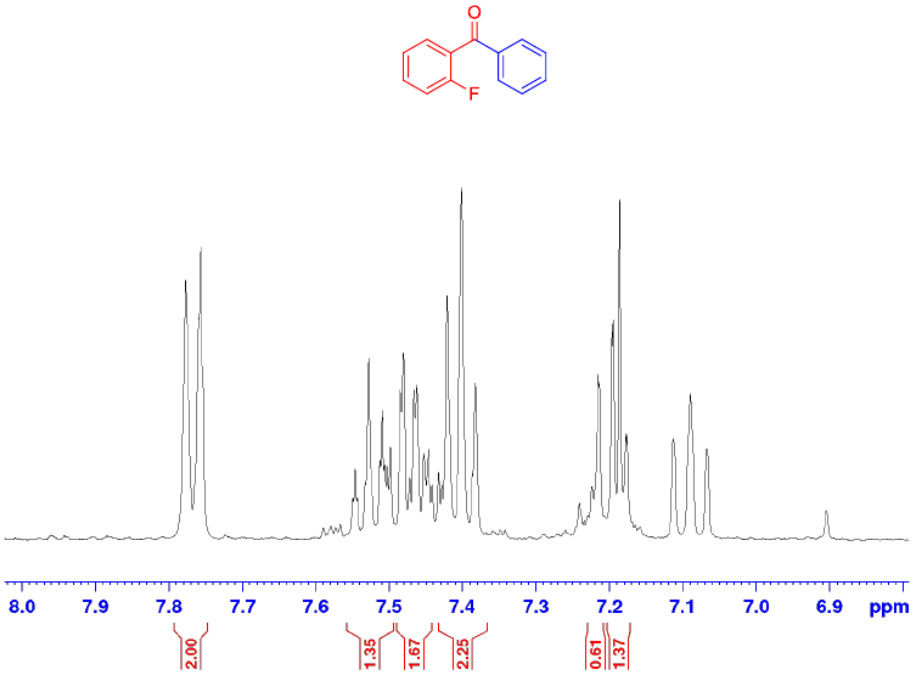
3.00


O
F
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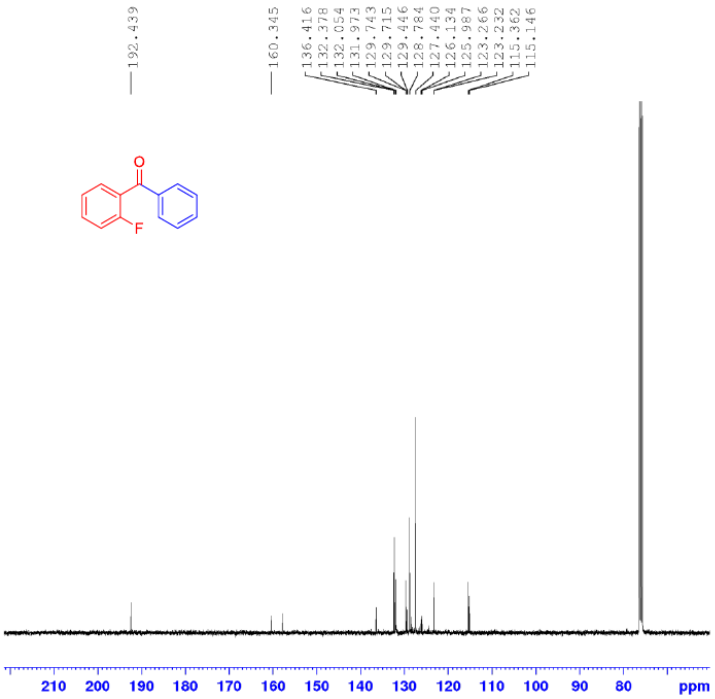
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
2.00
1.35
1.67
2.25
0.61
1.37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129.715
129.446
128.784
127.440
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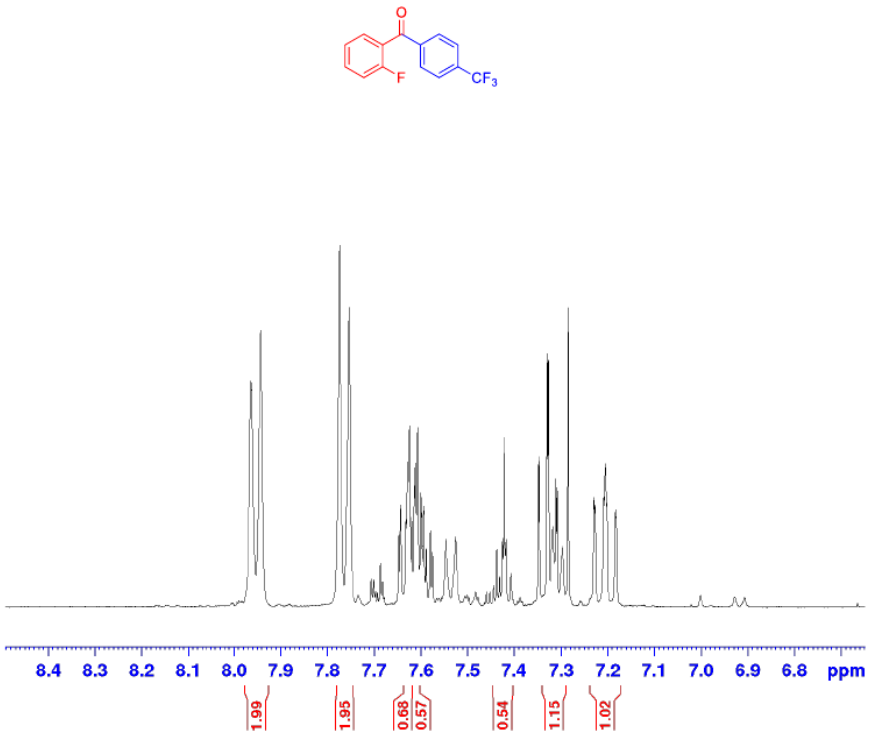
125.987
123.266
123.232
115.362
115.146
O
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 ppm


O
F
CF3
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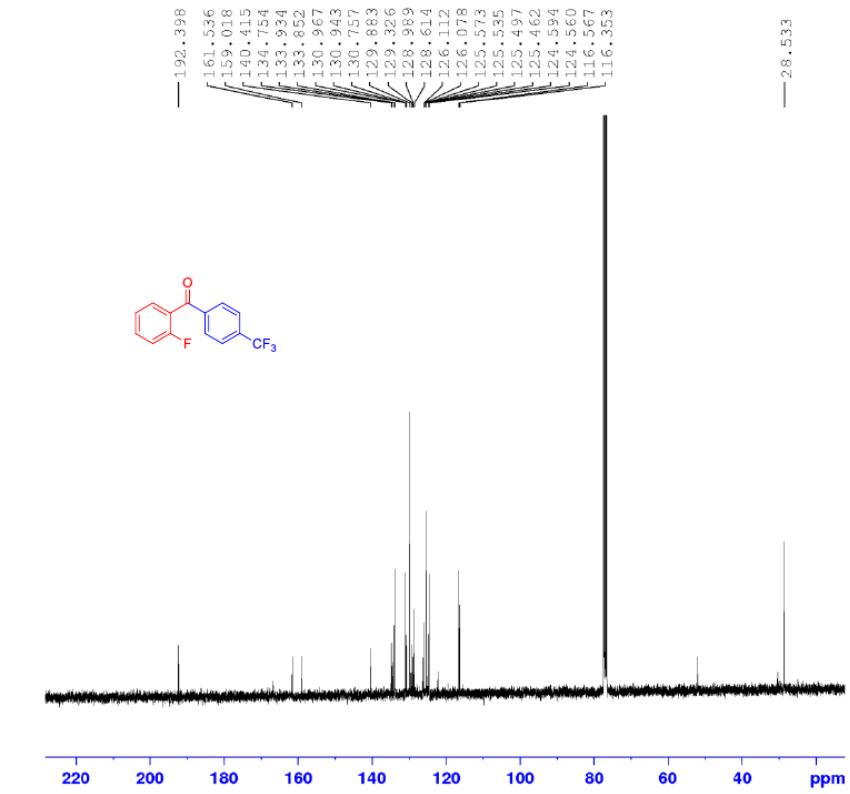
1.99
1.95
0.68
0.57
0.54
1.15
1.02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129.883
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128.614
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160
140
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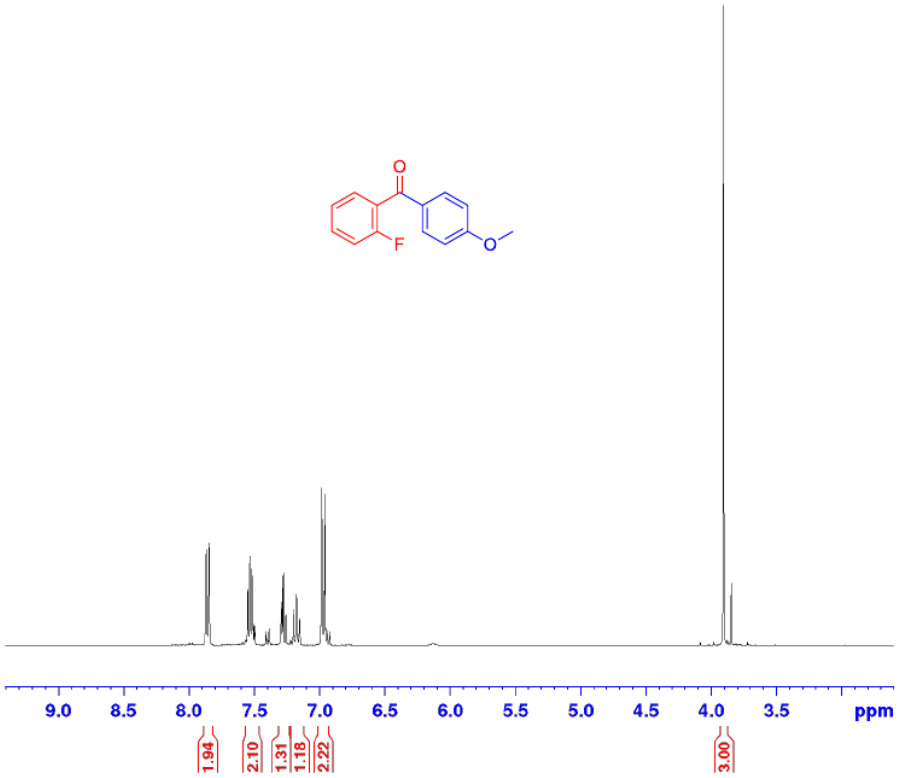
80
60
40
ppm


O
F
O
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8.0
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7.0
6.5
6.0
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ppm
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2.10
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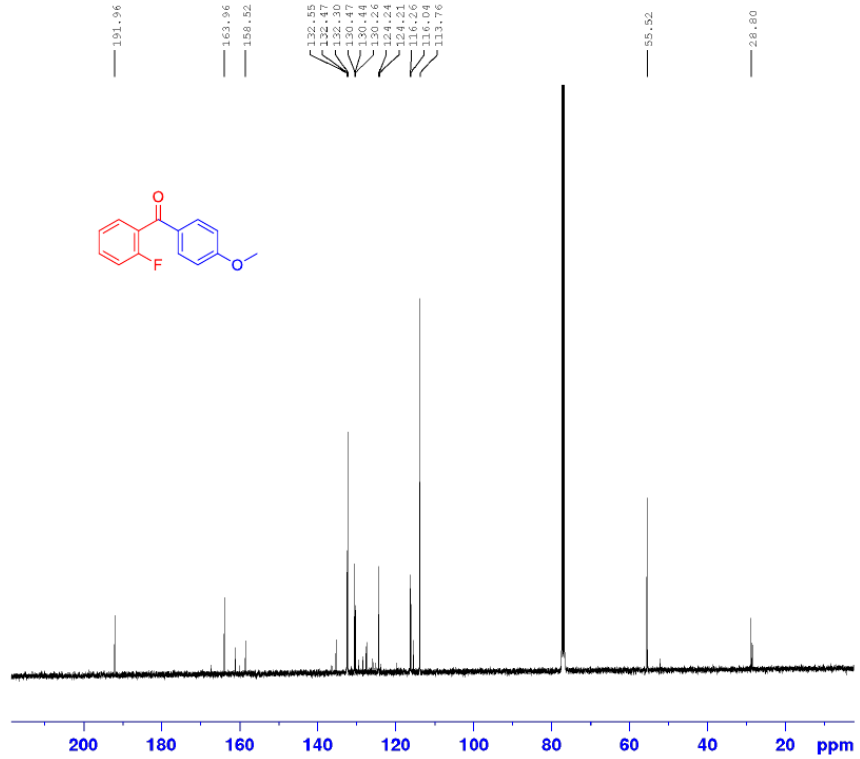
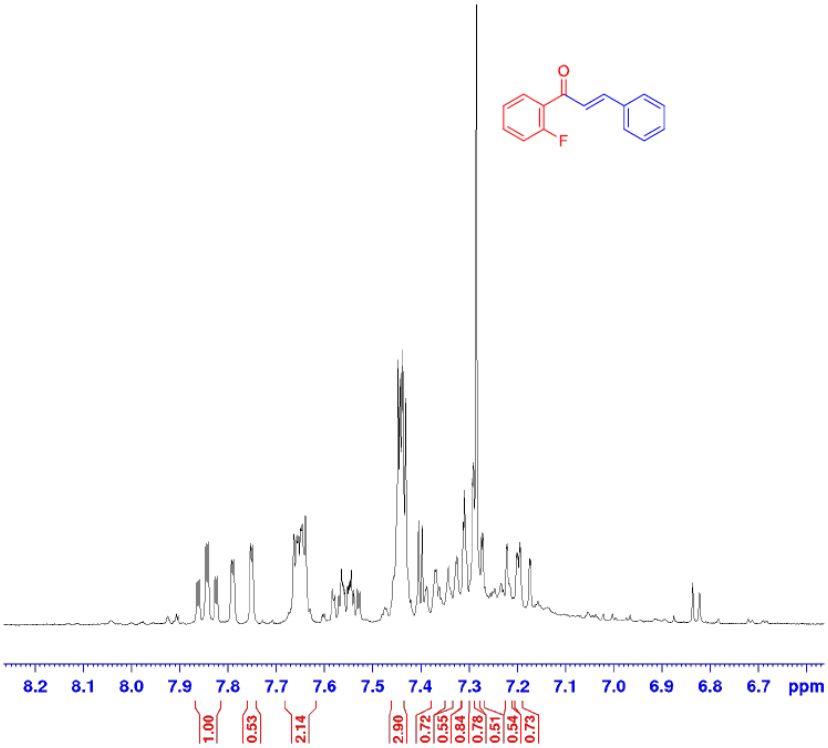
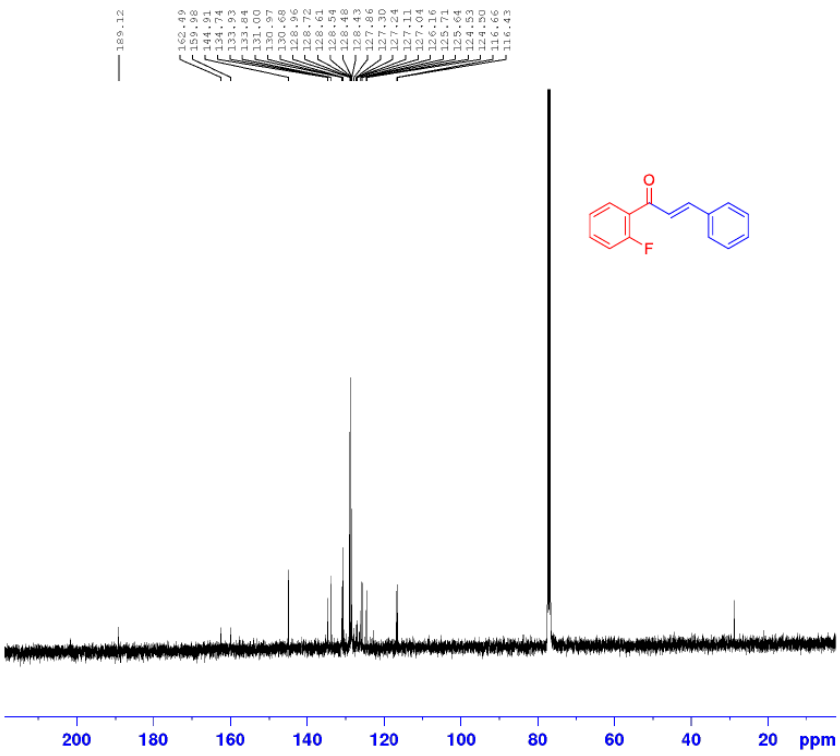

191.96
163.96
158.52
132.55
132.47
132.30
130.47
130.44
130.26
124.24
124.21
116.26
116.04
113.76
55.52
28.80
O
F
O
200
180
160
140
120
100
80
60
40
20
ppm


O
F
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
ppm
1.00
0.53
2.14
2.90
0.72
0.55
0.84
0.78
0.51
0.54
0.73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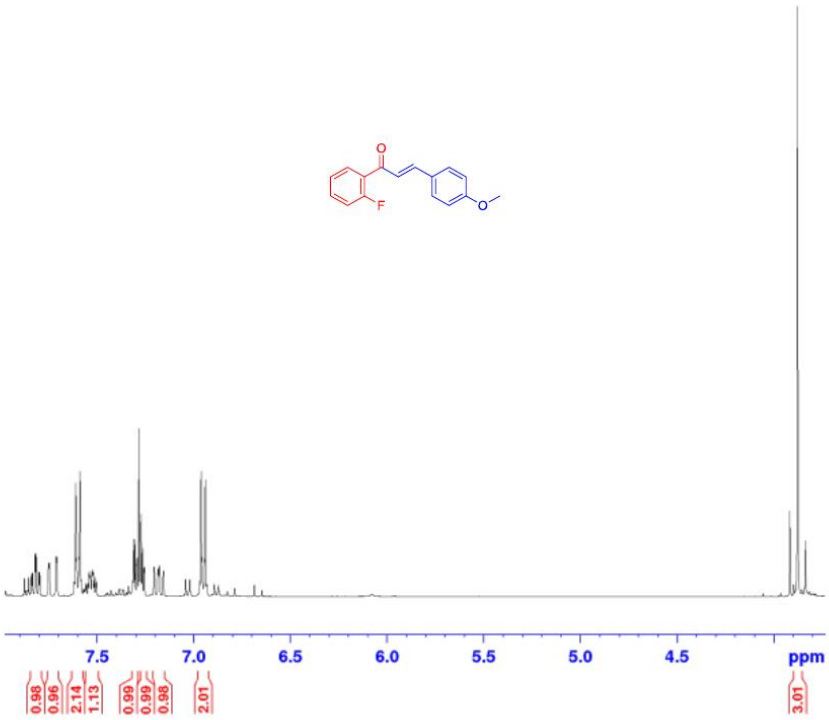
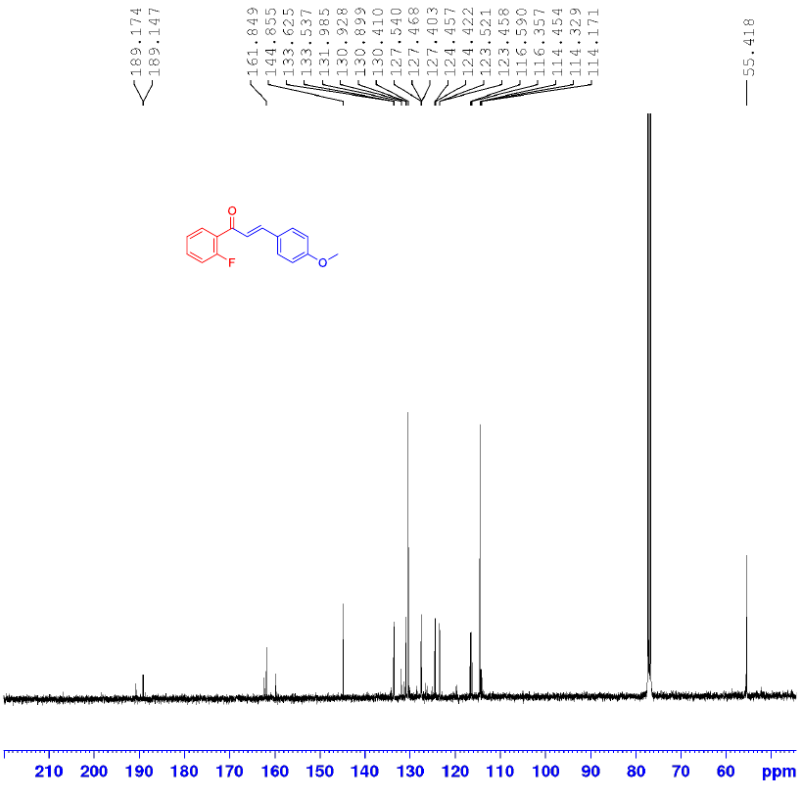
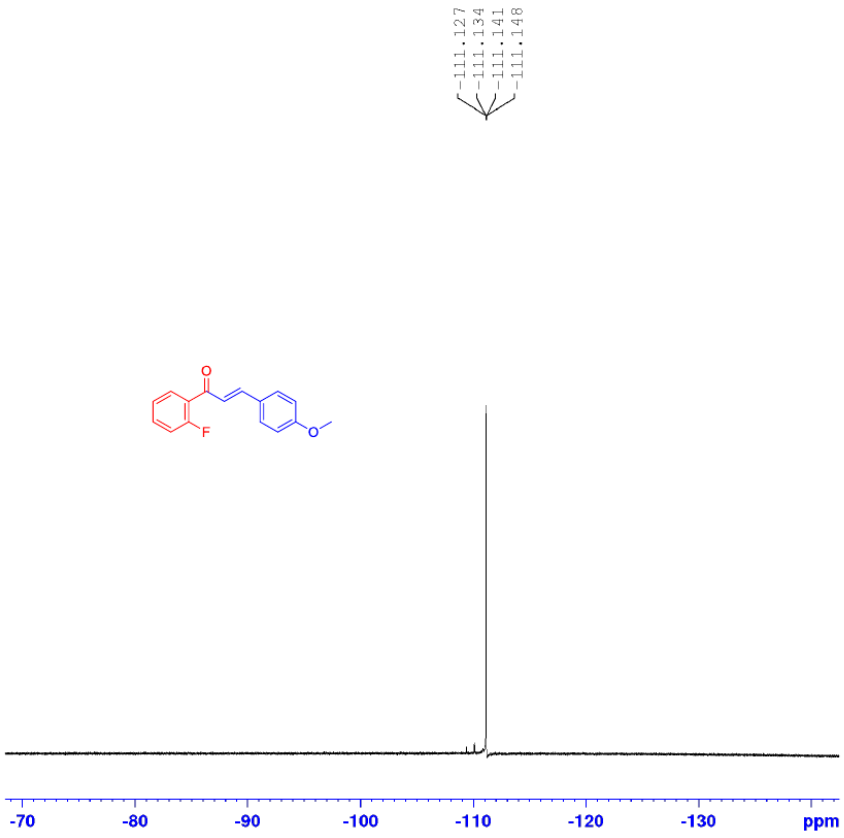
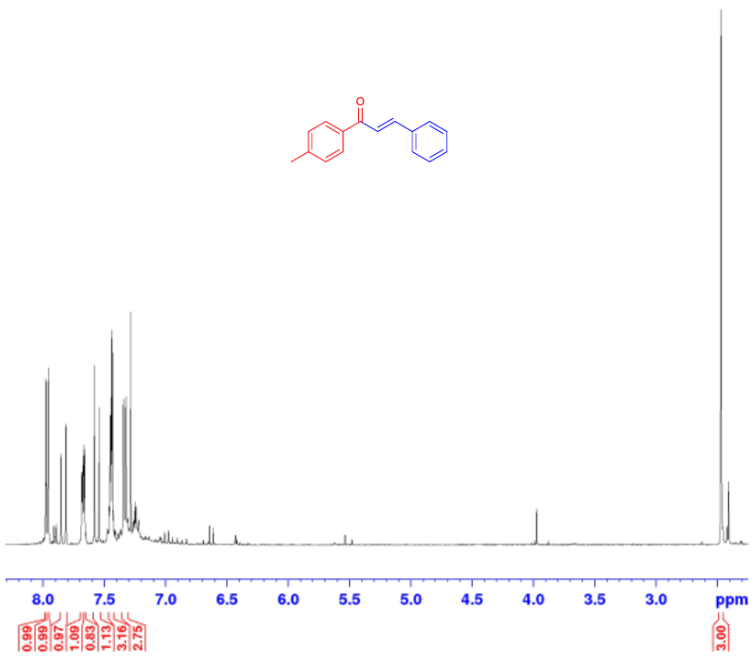
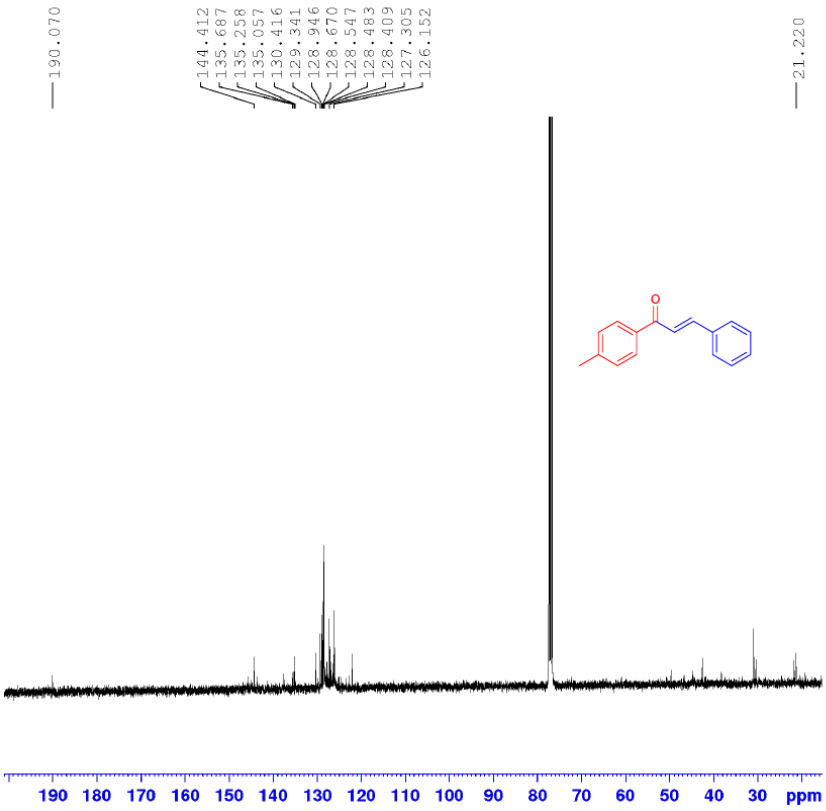
162.49
159.98
144.91
134.74
133.93
133.84
131.00
130.97
130.68
128.96
128.72
128.61
128.54
128.48
128.43
127.86
127.30
127.24
127.11
127.04
126.16
125.71
125.64
124.53
124.50
116.66
116.43
O
F
200
180
160
140
120
100
80
60
40
20
ppm

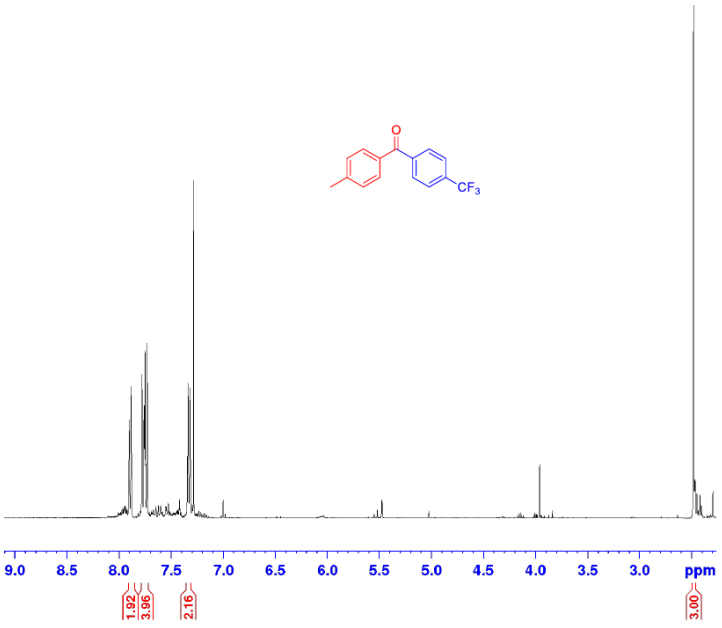

O
F
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
0.98
0.96
2.14
1.13
0.99
0.99
0.98
2.01
3.01

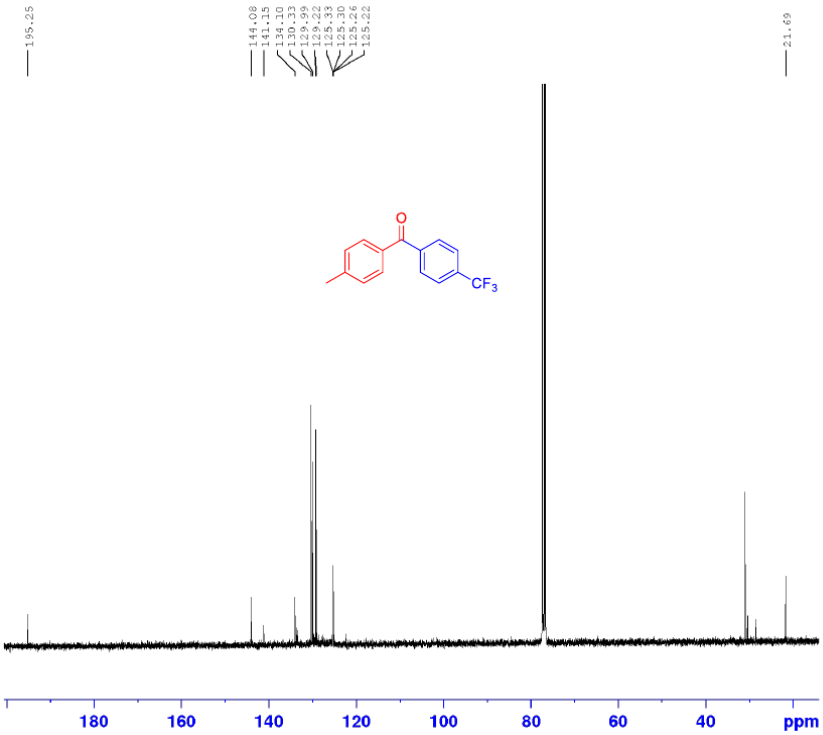

189.174
189.147
161.849
144.855
133.625
133.537
131.985
130.928
130.899
130.410
127.540
127.468
127.403
124.457
124.422
123.521
123.458
116.590
116.357
114.454
114.329
114.171
55.418
O
F
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

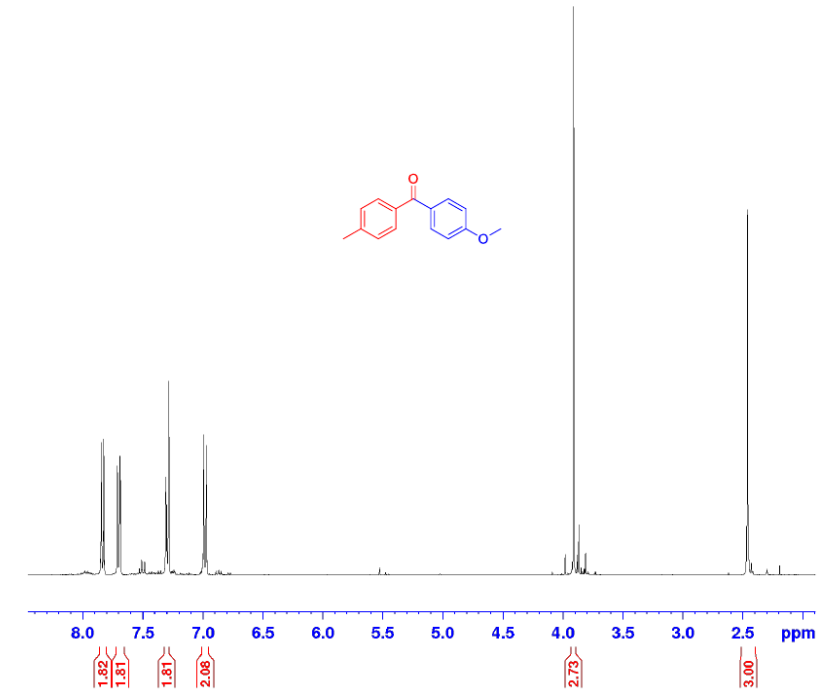

-111.127
-111.134
-111.141
-111.148
O
F
O
-70
-80
-90
-100
-110
-120
-130
ppm

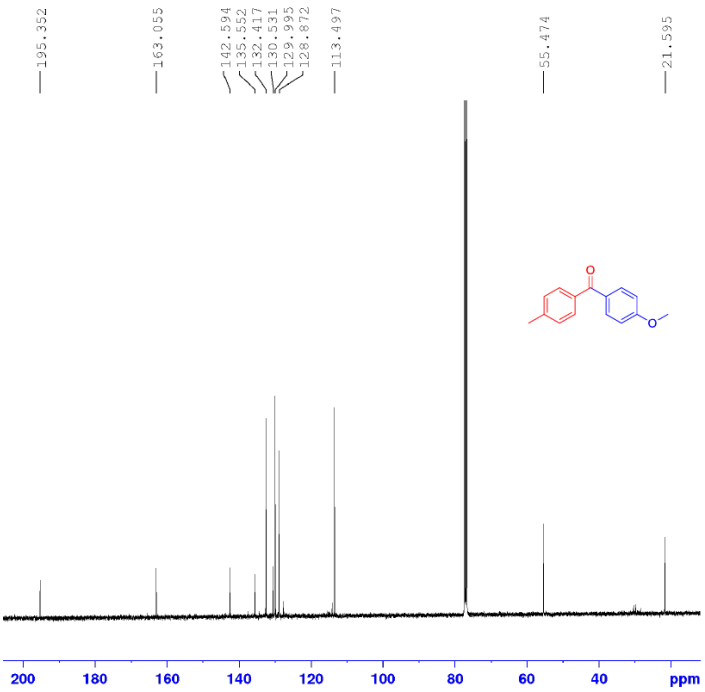

O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.99
0.99
0.97
1.09
0.83
1.13
3.16
2.75
3.00

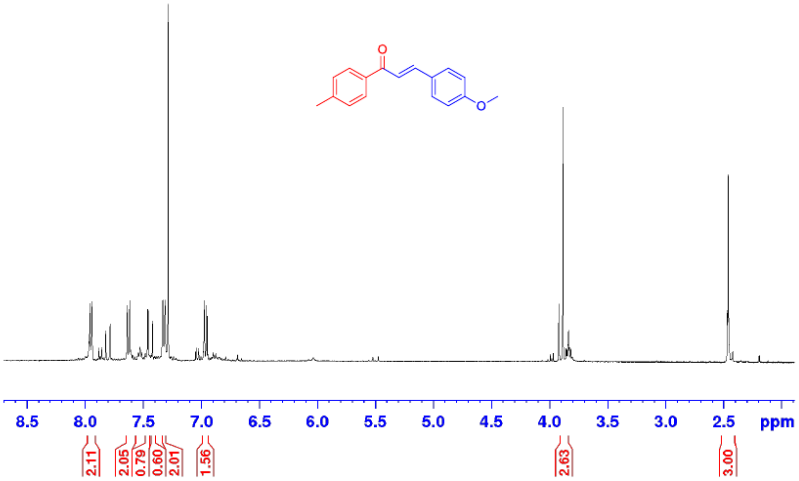

190.070
144.412
135.687
135.258
135.057
130.416
129.341
128.946
128.670
128.547
128.483
128.409
127.305
126.152
21.220
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

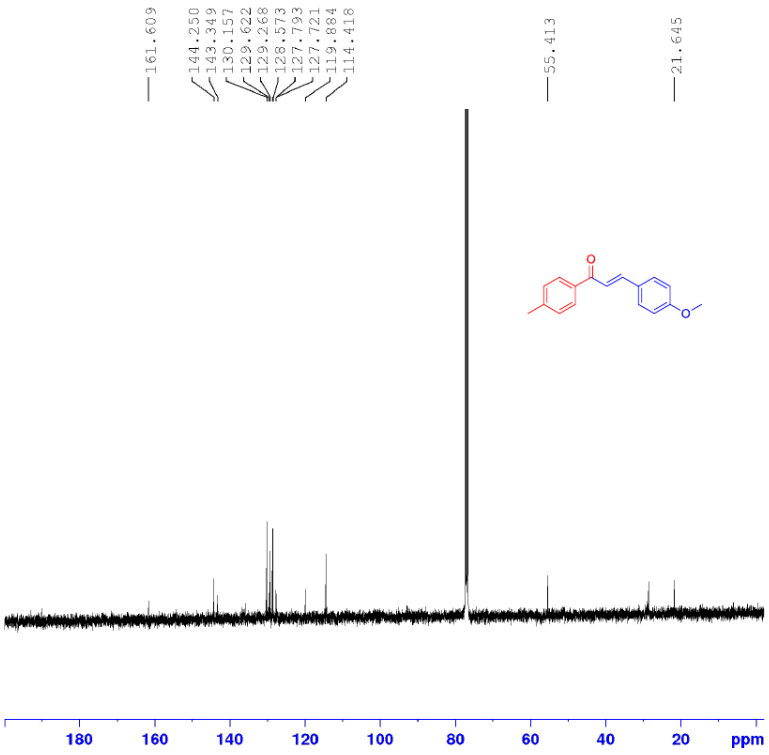

O
CF3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 ppm
1.92
3.96
2.16
3.00

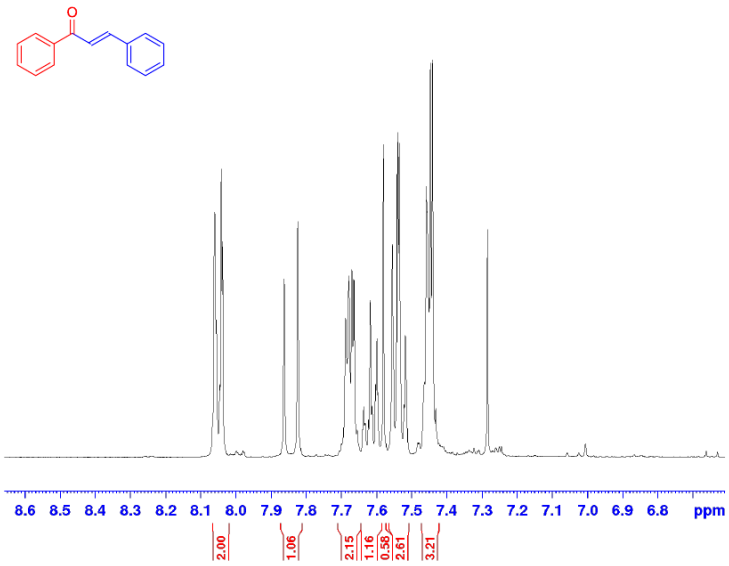

195.25
144.08
141.15
134.10
130.33
129.99
129.22
125.38
125.30
125.26
125.22
21.69
O
CF3
180
160
140
120
100
80
60
40
ppm

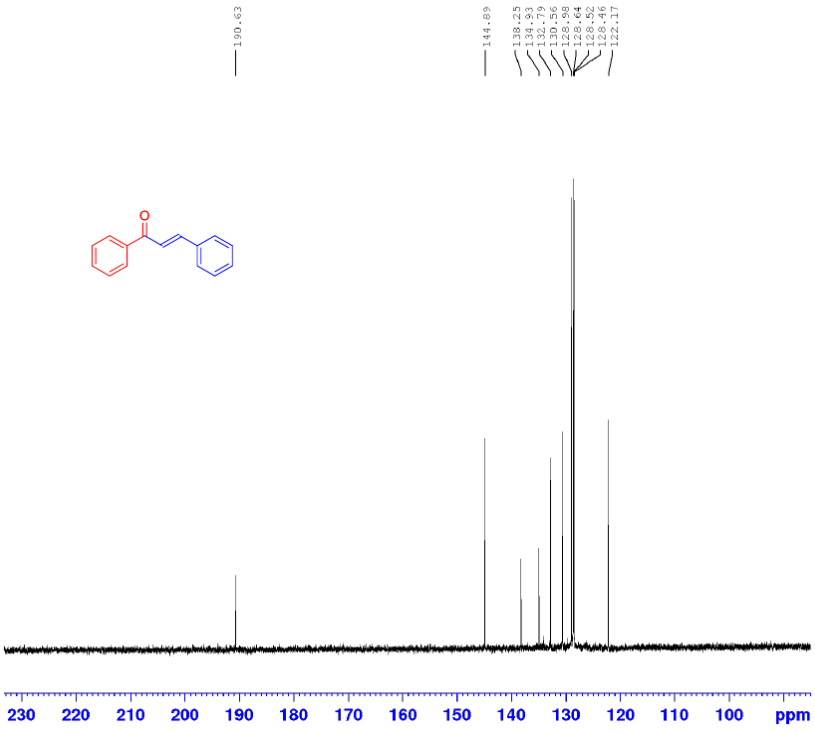

O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.82
1.81
1.81
2.08
2.73
3.00

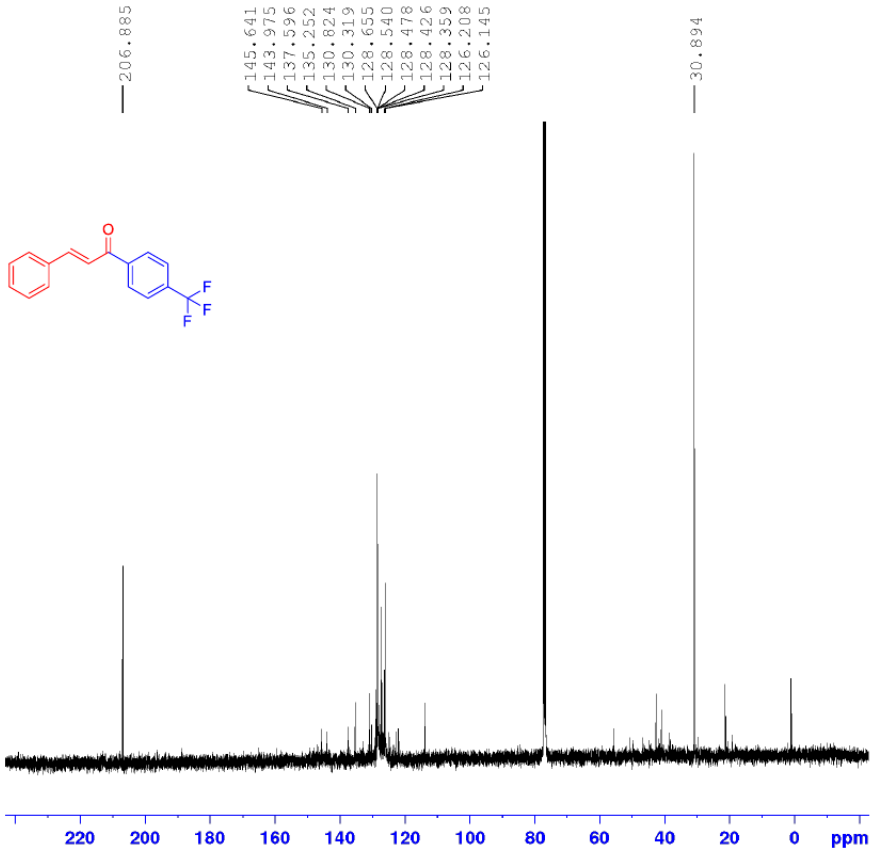

195.352
163.055
142.594
135.552
132.417
130.531
129.995
128.872
113.497
55.474
21.595
O
O
200
180
160
140
120
100
80
60
40
ppm

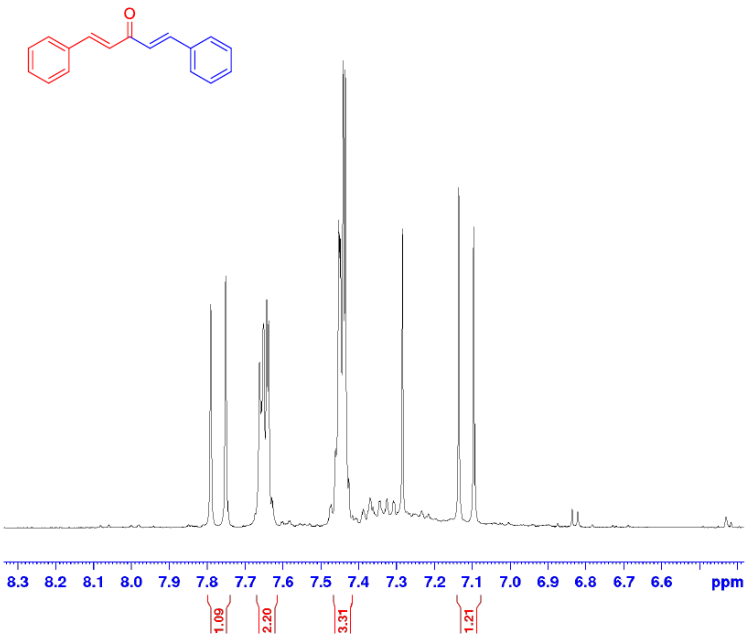

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
2.11
2.05
0.79
0.60
2.01
1.56
2.63
3.00

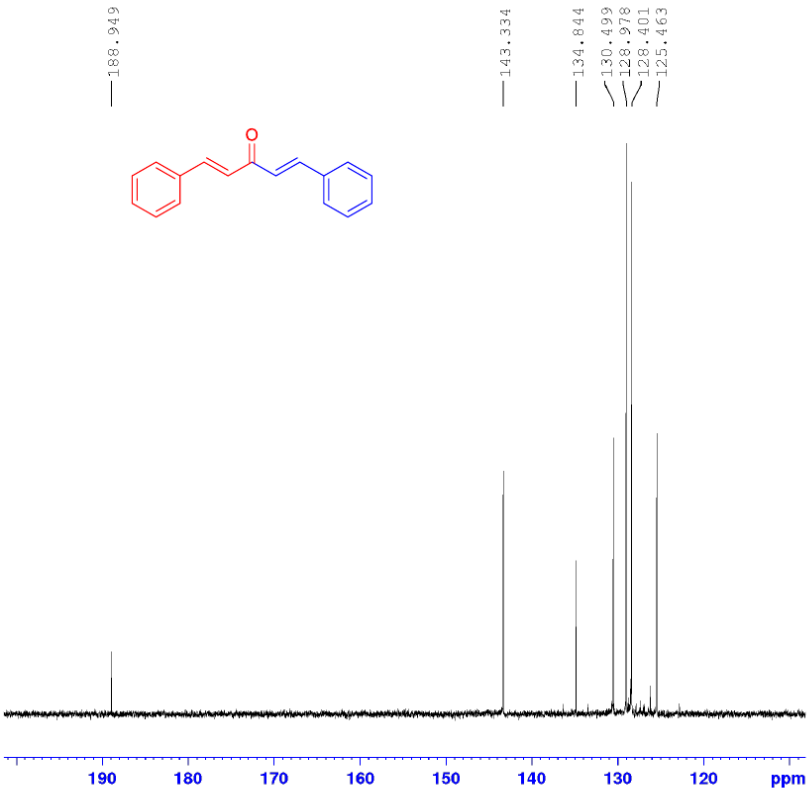

161.609
144.250
143.349
130.157
129.622
129.268
128.573
127.793
127.721
113.884
114.418
55.413
21.645
180
160
140
120
100
80
60
40
20
ppm

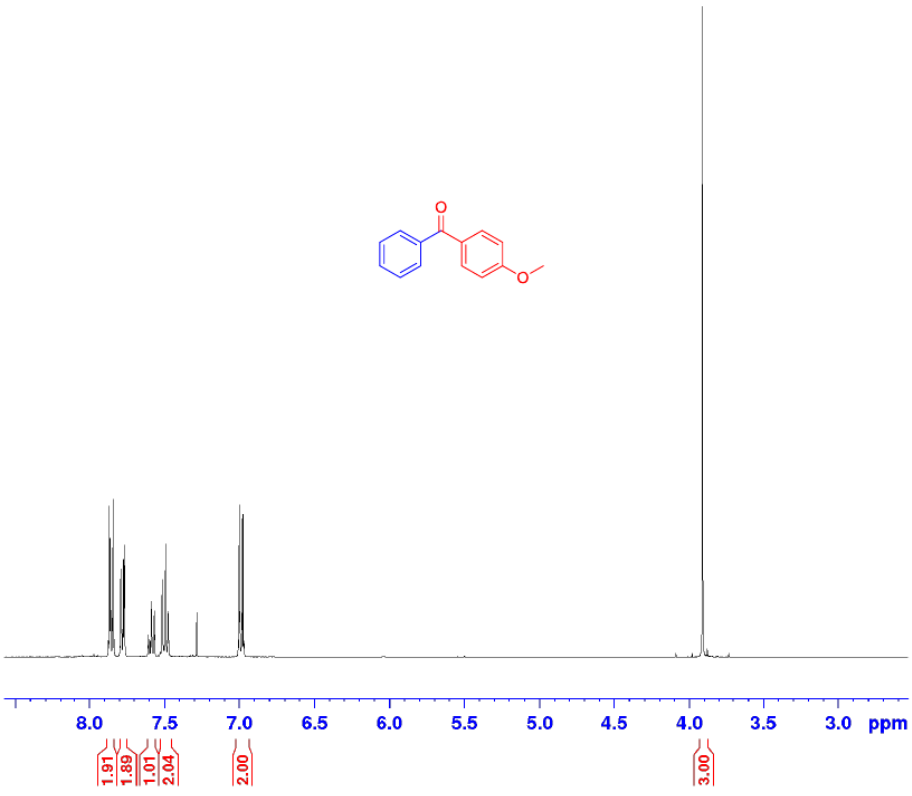

8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
2.00
1.06
2.15
1.16
0.58
2.61
3.21

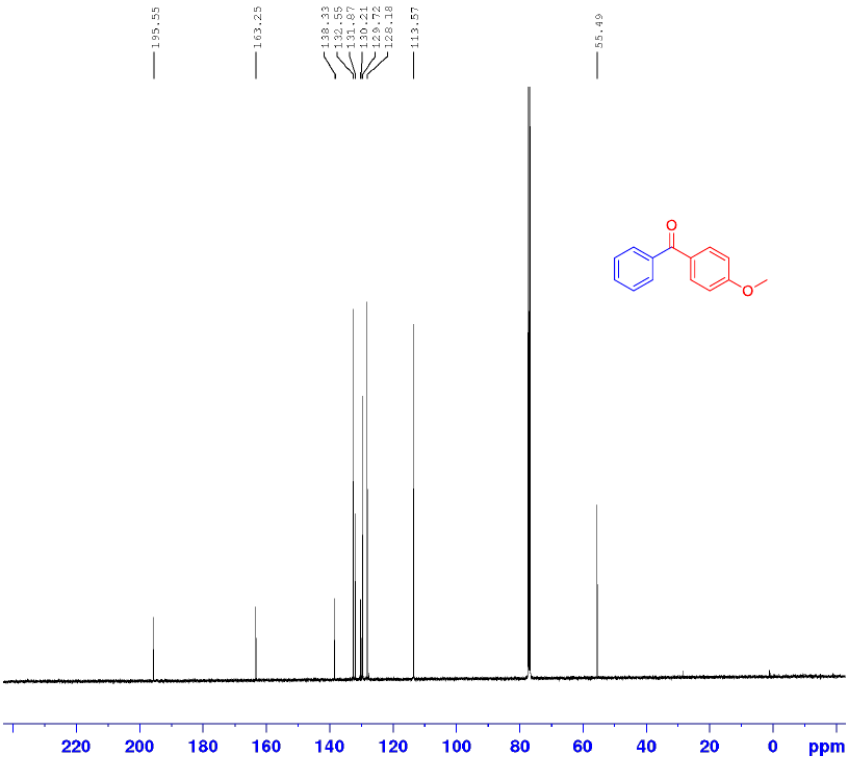

190.63
144.89
138.25
134.93
132.79
130.56
128.98
128.64
128.52
128.46
122.17
230 220 210 200 190 180 170 160 150 140 130 120 110 100 ppm

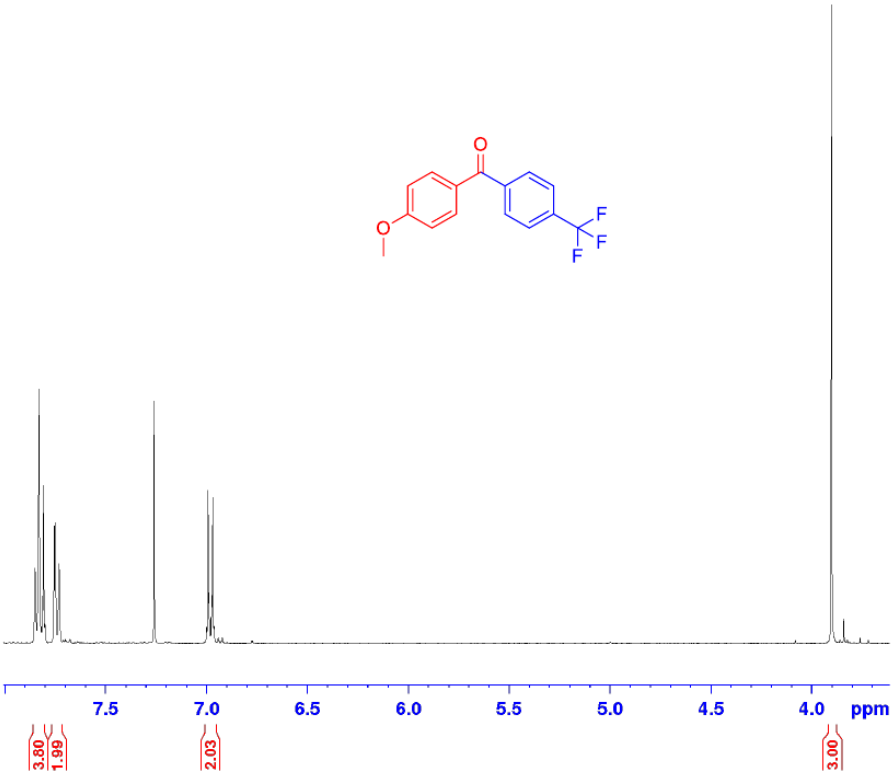

206.885
145.641
143.975
137.596
135.252
130.824
130.319
128.655
128.540
128.478
128.426
128.359
126.208
126.145
30.894
O
F
F
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

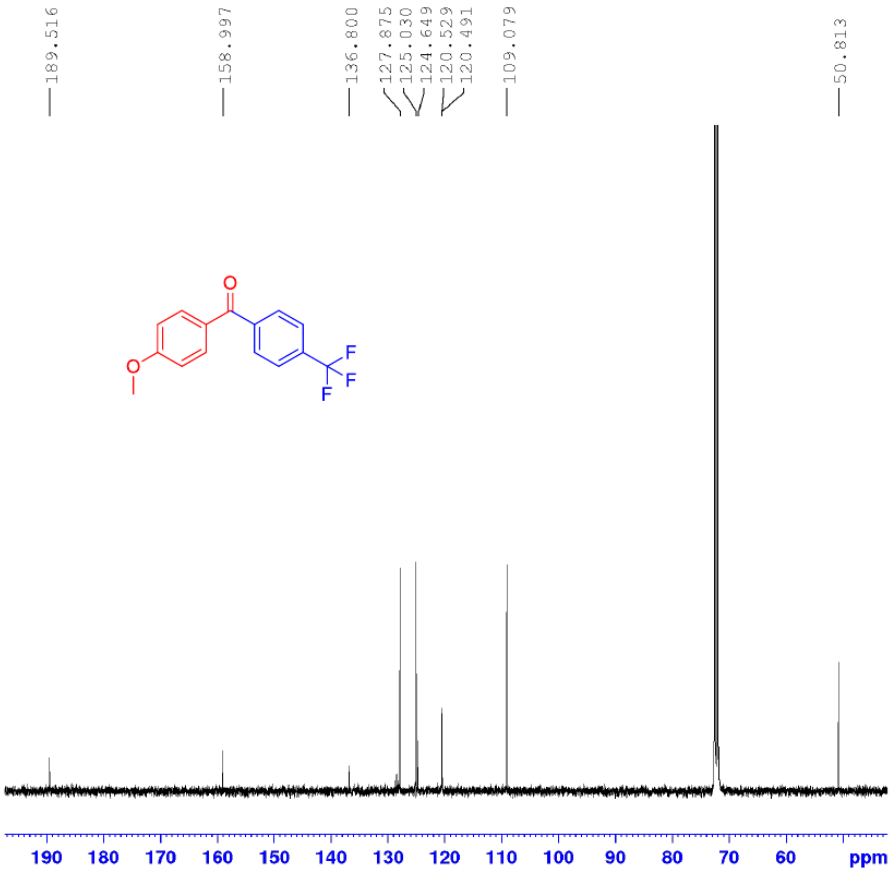

O
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm
1.09
2.20
3.31
1.21

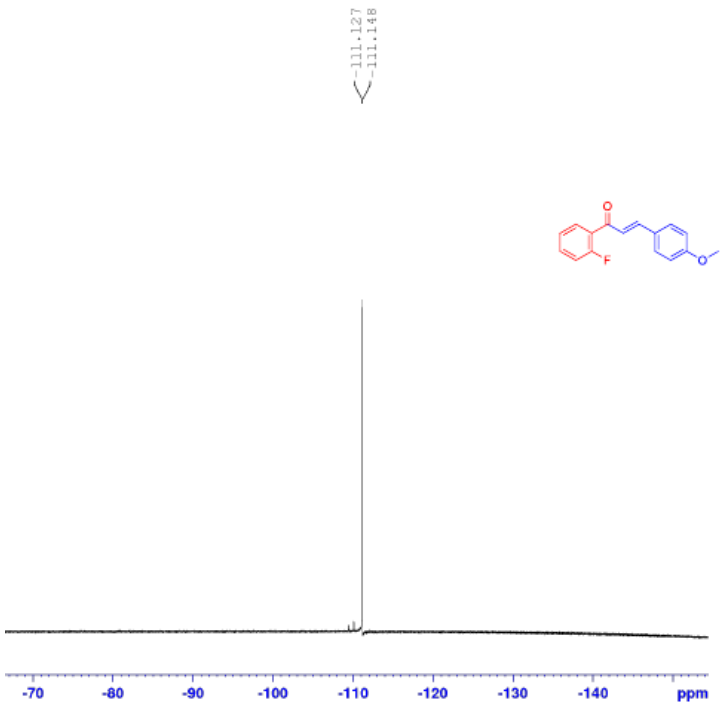

188.949
143.334
134.844
130.499
128.978
128.401
125.463
O
190
180
170
160
150
140
130
120
ppm

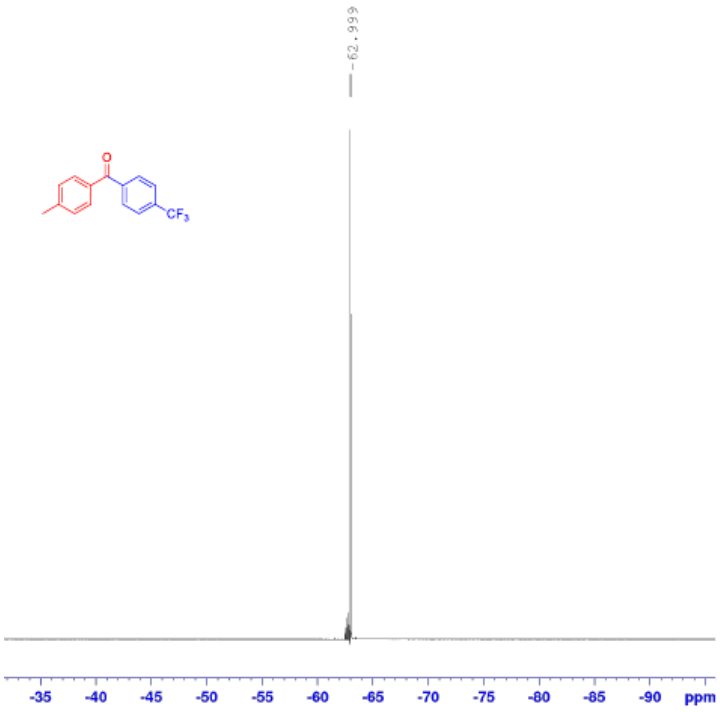

O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.91
1.89
1.01
2.04
2.00
3.00

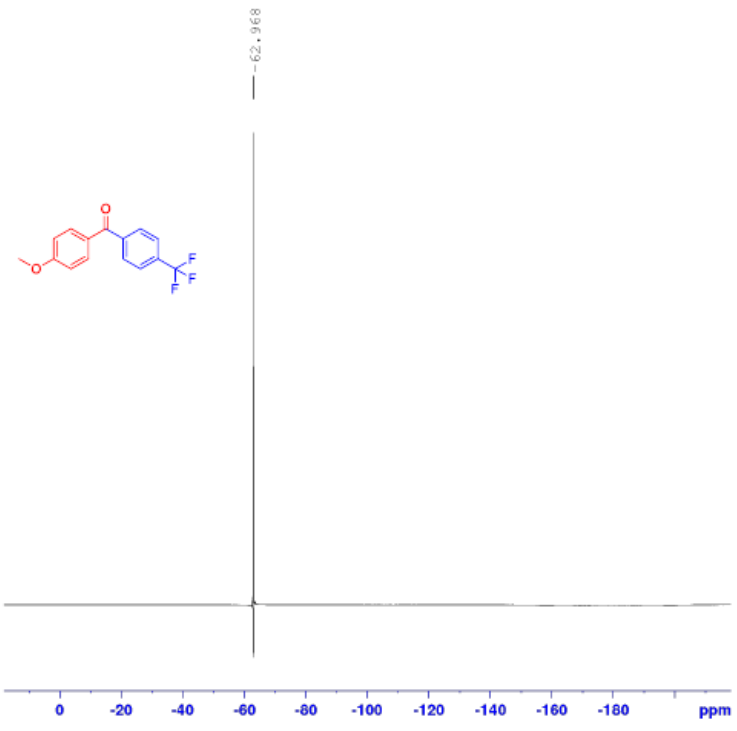

195.55
163.25
138.33
132.55
131.07
130.21
129.72
128.18
113.57
55.49
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

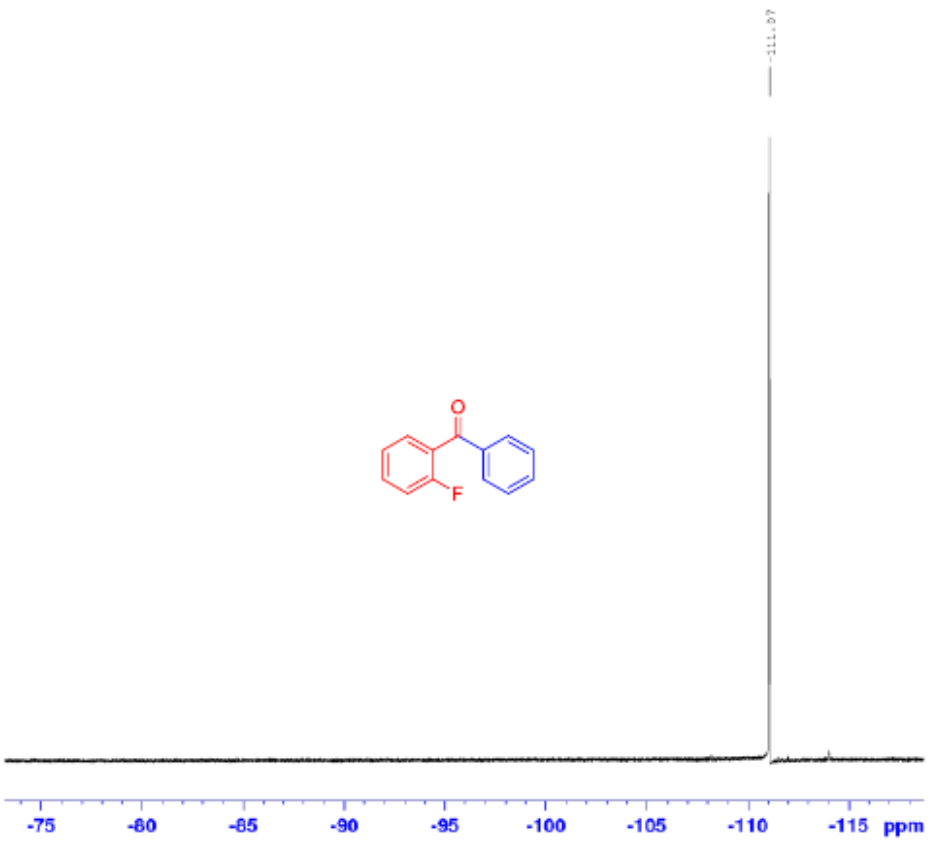

O
O
F
F
F
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
3.80
1.99
2.03
3.00

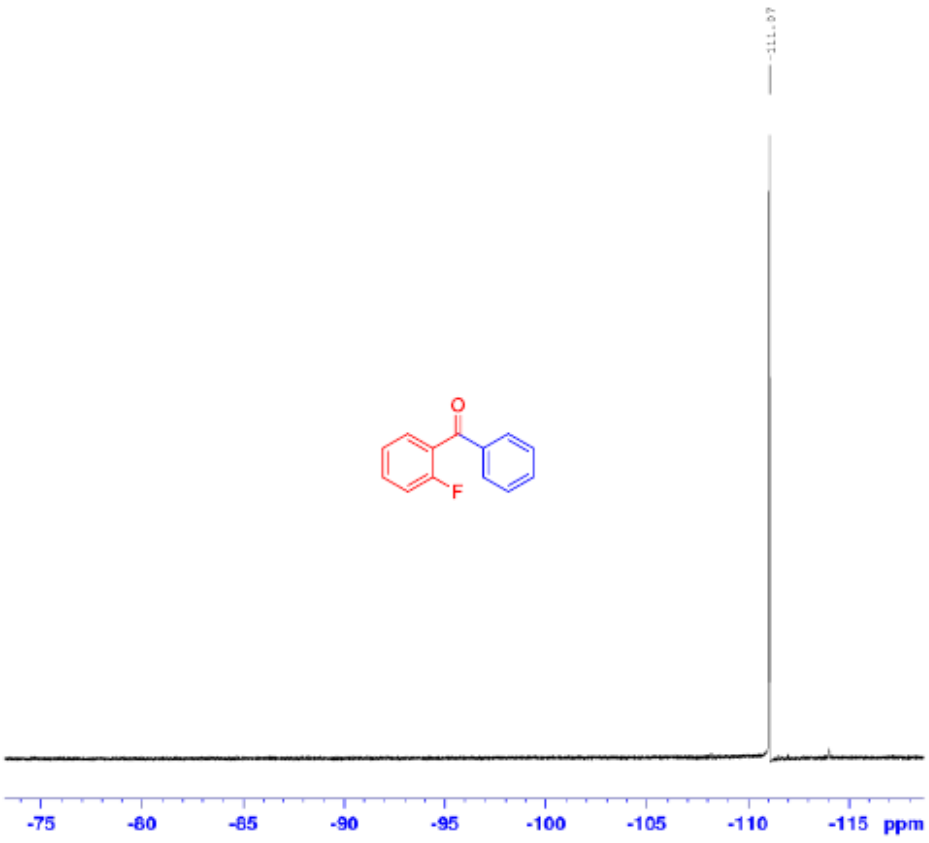

189.516
158.997
136.800
127.875
125.030
124.649
120.529
120.491
109.079
50.813
O
O
F
F
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 ppm


-111.127
-111.148
O
F
O
-70 -80 -90 -100 -110 -120 -130 -140 ppm


-62.999
O
CF3
-35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 ppm


-62.968
O
O
F
F
F
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm


O
F
-75
-80
-85
-90
-95
-100
-105
-110
-115
ppm


O
F
-75
-80
-85
-90
-95
-100
-105
-110
-115
ppm