Kumada and Liebeskind-Srogl Coupling of Aryl Thiosulfonates As Electrophilic Coupling Partners in The Synthesis of Biaryls

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DISSERTATION DECLARATION

The experimental work described in this dissertation was carried out in the school of chemistry and physics, University of Kwa-Zulu 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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Date 12-04-2021

ABSTRACT

The need and desire for versatility and diversity in cross-coupling reactions was the drive for the studies conducted in this thesis. Traditionally, transition-metal catalyzed cross-coupling reactions have heavily relied on organohalides and pseudo-halides as electrophilic-coupling partners. As a result, alternative compounds such as organosulfur compounds, which are potential electrophilic-coupling partners, have often been overlooked and subsequently understudied. Hence, this study was aimed at exploring the reactivity of S-phenylarylthiosulfonates as electrophilic-coupling partners in the transition metal-catalyzed cross-coupling such as Liebeskind-Srogl and Kumada-Corriu cross-coupling reactions towards the synthesis of biaryls.

In this study, disulfides were synthesized from the economical, time-efficient and catalyst-free oxidation of thiols in good to excellent yields (70-83%). The disulfides were in-turn reacted with sodium arylthiosulfonates to produce the desired symmetrical and unsymmetrical *S*-arylthiosulfonates in 69-73% yields.

With different *S*-arylthiosulfonates in hand, we investigated their reactivity as electrophilic coupling partners in transition metal catalyzed C-C bond forming cross-coupling reactions, namely: Kumada-Corriu and Liebeskind-Srogl in an attempt to expand the scope of electrophilic coupling partners in organic synthesis portal.

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ABBREVIATIONS

rt	Room temperature
Me	Methyl
OMe	Methoxy
NBS	*N*-Bromosuccinimide
Me_3SiCl	Trimethylchlorosilane
$Br_2C_2H_2$	Dibromoethane
$CDCl_3$	Deuterated Chloroform
DCM	Dichloromethane
MeCN	Acetonitrile
THF	Tetrahydrofuran
EtOAc	Ethyl acetate
NMP	N-Methyl-2-pyrrolidone
HMPA	Hexamethylphosphoramide
CuTC	Copper(I)-thiophene-2-carboxylate
Cu(I)MeSal	Copper(I)-3-methylsalicylate
$Cu(OAc)_2$	Copper(II) acetate
$PdCl_2$	Palladium(II) chloride
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)

$Ni(acac)_2$	Nickel(II) acetylacetone
$NiCl_2(dppf)$	[1-1'-Bis(diphenylphosphino)ferrocene]dichloronickel(II)
TFP	Tri(2-furyl)phosphine
CsF	Cesium fluoride
PPh_3	Triphenylphosphine
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppe	1,2-Bis(diphenylphosphino)ethane
IMes	N-heterocyclic carbene
s	singlet
d	doublet
t	triplet
dd	doublet of doublet
ddd	doublet of doublet of double

LIST OF TABLES

Table 3.1. : Oxidation of Differently Substituted Thiols to Furnish Disufides……41

Table 3.2. : Synthesis of Unsymmetrical Arylthiosulfonates……...49

Table 3.3. : Attempted Synthesis of 4-methyl-1,1'-bephenyl……...59

Table 3.4. : Optimization Studies……63

Table 3.5. : Ni-Catalyzed Cross-Coupling of Phenylthiosulfonate with Phenylmagnesium Bromide……..71

Table 3.6. : Optimized Cross-Coupling of Phenylthiosulfonates with Grignard Reagents……..72

LIST OF FIGURES

Figure 1.1. : Arenesulfonate compounds (S – O bond cleavage)….....3

Figure 1.2. : Sulfonylhydrazines (S – N bond cleavage)……3

Figure 1.3. : Unsymmetrical benzenethiosulfonates……..……4

Figure 1.4. : Symmetrical benzenethiosulfonates……..…4

Figure 1.5. : Biaryls to be synthesized……....5

Figure 2.1. : Electrophilic partners and their bond cleavages……8

Figure 2.2. : Arenesulfonate compounds (S – O bond cleavage)……...30

Figure 2.3. : Sulfonylhydrazines (S – N bond cleavage)…….....30

Figure 2.4. : symmetrical and Unsymmetrical benzenethiosulfonates..……31

Figure 2.6. : Biaryls…….....33

Figure 3.1. : Organosulfur compounds……..36

Figure 3.2. : Arylthiosulfonates ……..36

Figure 3.3. : ^{1}H NMR spectrum of bis(4-chlorophenyl) disulfide……39

Figure 3.4. : ^{13}C NMR spectrum of bis(4-chlorophenyl) disulfide……..40

Figure 3.5. : ^{1}H NMR spectrum of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate……...47

Figure 3.6. : ^{13}C NMR spectrum of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate……...48

Figure 3.7. : ^{1}H NMR spectrum of *S*-*p*--tolyl-4-methylbenzenesulfonothioate….53

Figure 3.8. : ^{13}C NMR spectrum of *S*-*p*--tolyl-4-methylbenzenesulfonothioate…54

Figure 3.9. : ^{1}H NMR spectrum of *S*-phenylbenzenethiosulfonate……56

Figure 3.10. : ^{13}C NMR spectrum of *S*-phenylbenzenethiosulfonate……...57

Figure 3.11. : ^{1}H NMR spectrum of 4-methyl-1,1'-biphenyl…….....64

Figure 3.12. : ^{13}C NMR spectrum of 4-methyl-1,1'-biphenyl……65

Figure 3.13. : ^{1}H NMR spectrum of 1,1'-biphenyl……69

Figure 3.14. : ^{13}C NMR spectrum of 1,1'-biphenyl……..70

Figure 3.15. : Disulfides synthesized……75

Figure 3.16. : Synthesized benzenethiosulfonates……76

Figure 3.17. : Phenylthiosulfonates to be synthesized ……...78

LIST OF SCHEMES

Scheme 2.1. : First reported Suzuki-Miyaura cross-coupling reactions……....11

Scheme 2.2. : Reactions of organohalides with ortganoboranes reported in 1986……..12

Scheme 2.3. : Synthesis of biaryls through coupling of arylchorides with phenylboronic acids……13

Scheme 2.4. : Nickel-catalyzed reactions of magnesium bromides and organochlorides……..13

Scheme 2.5. : Coupling of phenylboronic acid with dichlorobenzene compounds…....14

Scheme 2.6. : Synthesis of biaryls through the coupling of meta-substituted electrophilic coupling partners……14

Scheme 2.7. : First reported Nickel-catalyzed $C_{(sp3)} – C_{(sp3)}$ coupling reactions…….....15

Scheme 2.8. : Reactions of alkylfluorides under nickel/butadiene catalytic system……16

Scheme 2.9. : Reactions of vinyltriflates with alkylbromides……17

Scheme 2.10.: Reactions of alkylmagnesium bromides demonstrating the effects of the ligands' bite angles on product formation……18

Scheme 2.11.: Reactions between aryltosylates/mesylates with arylboronic acids…....19

Scheme 2.12.: Sequential reactions aryldiazonium salts with arylboronic acid……20

Scheme 2.13.: Reactions of aryldiazonium salts reported by Feplin in 2009……21

Scheme 2.14.: Ni-catalyzed reactions between p-butyl-trimethylammonium benzenetriflate and phenylboronic acid……...22

Scheme 2.15.: Palladium catalyzed coupling between arylsulfonyl chlorides and boronic acids……23

Scheme 2.16.: Hiyama-type coupling reaction of sodium aryltriflate and arylsiloxanes.....24

Scheme 2.17.: Pd-catalysed reactions of sodium arylsulfinates and srylboronic acids…….25

Scheme 2.18.: Reactions of arylsulfonyl hydrazines with arylboronic acids……...26

Scheme 2.19.: Cross-coupling reactions of arylsulfonyl hydrazines and arylsilanes…..27

Scheme 2.20.: Reactions of neopentyl arenesulfonate with differently substituted Grignard reagents……...28

Scheme 2.21.: Reactions showing the competition between the C-S and C-O bond cleavages…….29

Scheme 2.22.: Reactions showing selective coupling for the reactions of sulfonates.....29

Scheme 3.1. : General scheme for the synthesis of arylthiosulfo……..37

Scheme 3.2. : General scheme for the synthesis of disulfides……..38

Scheme 3.3. : Synthesis of bis(4-chlorophenyl) disulfide……...38

Scheme 3.4. : Synthesis of disulfides……41

Scheme 3.5. : Oxidation of disulfides towards the synthesis of thiosulfonates……..43

Scheme 3.6. : Direct oxidation of thiols towards the synthesis of thiosulfonates……...44

Scheme 3.7. : General scheme for the synthesis of arylthiosulfonates from disulfides……44

Scheme 3.8. : Mechanism for the sulfenylation of sulfinic acids……..45

Scheme 3.9. : Synthesis of S-4-chlorophenyl-4-methylbenzenesulfonothioate…….46

Scheme 3.10.: Mechanism explaining the reduction of sulfonyl chloride……51

Scheme 3.11.: Synthesis of S-p-tolyl-4-methylbenzenesulfonothioate……52

Scheme 3.12.: Synthesis of S-phenyl benzenesulfonothioate……..55

Scheme 3.13.: $PdCl_2$ catalyzed attempted synthesis of 4-methyl-1-1'-biphenyl……...58

Scheme 3.14.: First reported Liebeskind-Srogl cross-coupling reactions……..60

Scheme 3.15.: Liebeskind-Srogl mechanism……....61

Scheme 3.16.: Cu(I)Iodide-mediated attempted synthesis of 4-methyl-1,1'-biphenyl…….62

Scheme 3.17.: Mechanism for the base-free coupling reactions of thiosulfonates and boronic acids……66

Scheme 3.18.: synthesis of 1,1'-biphenyl……68

Scheme 3.19.: Mechanism for the coupling of thiosulfonates through Kumada-type coupling to synthesize biaryls……...79

TABLE OF CONTENTS

1. CHAPTER ONE……...1
1.1. Introduction…….....1
1.2. Problem Statement……..…….…….....2
1.3. Dissertation statement……..……..2
1.4. Aims of The Project…….....3
1.4.1. Objectives……..…….…….4
1.5. Significance of Study……..……..5
1.6. References…….…….7

2. **CHAPTER TWO……...8**
2.1. Introduction……..…….....8
2.2. Electrophilic Coupling Partners in Transition-Metal Catalyzed Cross-Coupling Reactions……...…10
2.2.1. Traditional Electrophilic Coupling Partners…..……10
2.2.1.1. C-X (X = Halide atom) Bond Cleavage……....10
2.2.1.2. C-X (X = Pseudo-halide) Bond Cleavage……..……...16
2.2.2. Non-Traditional Electrophilic Coupling Partners……...19
2.2.2.1. Non-Sulfur Containing Electrophiles……19
2.2.2.1.1. Aryldiazonium Salts……..……20
2.2.2.1.2. Ammonium Triflates…….....21
2.2.2.2. Sulfur-Based Electrophiles……22
2.2.2.2.1. Arylsulfonyl Chlorides…….....23
2.2.2.2.2. Sodium Arylsulfinates……..……...24
2.2.2.2.3. Sulfonyl Hydrazines…….....25
2.2.2.2.4. Aryl Arenesulfinates…….....27
2.3. Aims of The Project……..……..30
2.3.1. Objectives……..……..31
2.4. References……...……..32

3. CHAPTER THREE……..……35
3.1. Synthesis of Starting Materials……37
3.1.1. Synthesis of Disulfide……37
3.1.1.1. Synthesis of *bis*-(4-chlorophenyl) Disulfide…….……38
3.1.1.2. Synthesis of Differently Substituted Disulfides…….....41
3.1.2. Synthesis of Phenyl Thiosulfonates…….....43
3.1.2.1. Synthesis of Unsymmetrical Phenyl Thiosulfonates…….....44
3.1.2.1.1. Synthesis of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate……46
3.1.2.2. Synthesis of Symmetrical Phenyl Thiosulfonates……..……50
3.1.2.2.1. Synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothioate…….....52
3.1.2.2.2. Synthesis of *S*-phenyl benzenesulfonothioate……..……..54
3.2. Synthesis of Biaryls……..……..57

3.2.1. Synthesis of Biaryls Through Coupling of Thiosulfonates and Boronic Acids……....58
3.2.1.1. Attempted Synthesis of 4-methyl-1,1'-biphenyl……..……..58
3.2.1.2. Cu(I)Iodide – Mediated Synthesis of 4-methyl-1,1'-biphenyl…….…….....61
3.2.1.3. Cu(I)TC / Cu(I)MeSal – Mediated Synthesis of 4-methyl-1-1'-biphenyl..….....62
3.2.2. Synthesis of Biaryls through Kumada-Corriu Cross-Coupling……..……67
3.2.2.1. Synthesis of 1,1'-biphenyl……..……67
3.3. Conclusion……67
3.4. Recommendation for Future Work……...78
3.5. References……..……89

4. CHAPTER FOUR……..……81
4.1. Chemicals and Instrumentation…….....81
4.2. Synthesis of Disulfides……..……81
4.2.1. General Experimental Procedure A…….....81
4.2.2. Synthesis of *bis*-(4-chlorophenyl) disulfide……..……..82
4.2.3. Synthesis of *bis*-(4-methylphenyl) disulfide……..……82
4.2.4. Synthesis of *bis*-(4-nitrophenyl) disulfide……..……83
4.2.5. Synthesis of *bis*-(4-methoxyphenyl) disulfide…….…….....83
4.2.6. Synthesis 1,2-diphenyldisulfane……..……..……84
4.3. Syntheis of Unsymmetrical Thiosulfonates……84
4.3.1. General Experimental Procedure B……84
4.3.2. Synthesis of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate……..……85
4.3.3. Synthesis of *S*-4-chlorophenylbenzenesulfonothioate…….....85
4.3.4. Synthesis of *S*-phenyl-4-methoxybenzenesulfonothioate…….....86
4.3.5. Synthesis of *S*-phenyl-4-methylbenzenesulfonothioate……..87
4.4. Synthesis of Symmetrical Thiosulfonates……..87
4.4.1. General Experimental Procedure C……87
4.4.2. Synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothioate……88
4.4.3. Synthesis of *S*-phenylbenzenesulfonothioate…….....88
4.5. Liebeskind – Srogl Synthesis of 4-methyl-1,1'-biphenyl……..89
4.6. Kumada-Corriu Syntheis of 1,1'-biphenyl……..……91
4.7. References……92

CHAPTER ONE

1.1. INTRODUCTION

Transition-metal cross-coupling reactions are of importance and are used for new carbon-carbon bond construction.[1] They are vital as they are employed in a variety of synthetic procedures; from the synthesis of fine chemicals, pharmaceuticals to natural products.[2] Their vast employment and success in synthetic organic chemistry stems from their high functional group tolerance, mild reaction conditions and their use of easily available reagents.[3]

Transition-metal catalyzed reactions see the coupling of nucleophilic partners with electrophilic partners (activated or inactivated).[4] Generally, they employ organohalide and pseudohalide compounds as electrophilic coupling partners. The nucleophilic partners are often organometallic, and these include Grignard reagents and organostannanes, to mention a few. They often employ palladium catalysts but due to their high cost and that of their supporting ligands, numerous efforts have been made into developing other transition-metal catalysts suitable for cross-coupling reactions.[5,6,7]

Since transition-metal catalyzed cross-coupling reactions have heavily relied on organohalides and pseudohalides as electrophilic coupling partners, over the years, developments seeking to utilize alternative electrophilic partners have risen. However, though this is the case, desulfitative reactions have often been overlooked and understudied. In recent developments, desulfitative reactions have been found as attractive alternatives to the traditional, in the coupling of organometallic species.[8] For desulfitative reactions, research has manly focused on arylsulfonyl chlorides as electrophilic coupling partners as they are inexpensive and readily available. Recent research has also reported on other electrophilic partners such as arylsulfonyl hydrazides (S-N bond) which are also readily available, stable in air, amongst others.[9]

1.2. PROBLEM STATEMENT

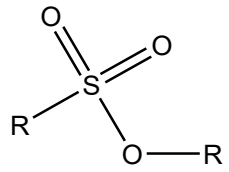
For cross-coupling reactions employed either in research or in the industry, there has always been a need to conduct these reactions under optimum conditions and this includes finding the most suitable electrophilic partners. Suitable electrophilic partners are those that are easily available, air and moisture stable, and having reactions at moderate to low temperatures. Although other electrophilic partners are known, transition-metal catalyzed reactions often employ organohalides (alkyl- and aryl-halides) as well as pseudo-halides (tosylates and mesylates). Reactions of these traditional electrophiles occur at elevated temperatures and lengthened reaction times. The use of organosulfur compounds in transition-metal cross-coupling reactions is very limited however, their use in the pharmaceutical industry due to their high stability makes them great candidates as alternative electrophilic partners in cross-coupling reactions.

1.3. DISSERTATION STATEMENT

With a deficiency of research utilizing organosulfur compounds as electrophilic partners in transition-metal catalyzed reactions an interest was sprung as organosulfur compounds are easily available and are known to be moisture and air stable. On this dissertation, as electrophilic partners to Grignard and organoboron reagents, organosulfur compounds (phenylthiosulfonates) are expected to partake in a coupling under mild reactions conditions, enhancing selectivity and stability to synthesize biaryls.

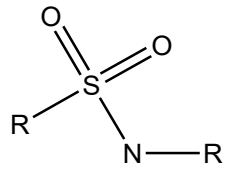
1.4. AIMS OF THE PROJECT

With research having explored only the S-O (Figure 1.1.) and the S-N (Figure 1.2.) bond cleavages in transition-metal catalyzed reactions, to our knowledge the S-S bond cleavage has not been explored for any electrophilic coupling partners. Therefore, the overarching aim of this study is to develop procedures that provide the formation of new C-C bonds by taking advantage of the S-S bond of thiosulfonates. Thiosulfonates will be our electrophilic coupling partners in the cross-coupling reactions coupled with Grignard and organoboron reagents as nucleophilic partners. Thiosulfonates are expected to react under optimum conditions to produce biaryls with minimum production of byproducts.



R = Alkyl, Aryl

Figure 1.1. Arenesulfonate compounds (S-O bond cleavage)

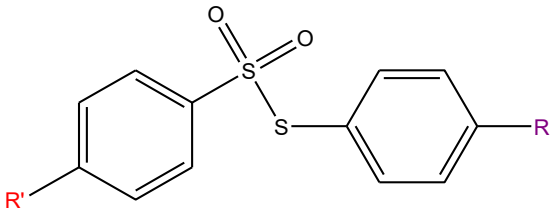


R = Alkyl, Aryl

Figure 1.2. Sulfonylhydrazines (S-N bond cleavage)

1.4.1. Objectives

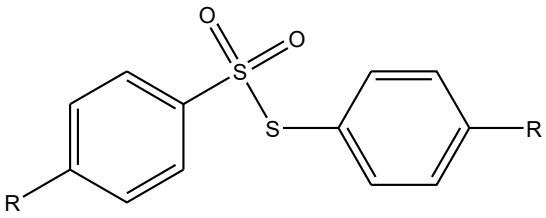
I) The first study of this project will see the synthesis of differently substituted, unsymmetrical benzene thiousulfonates (Figure 1.3.) from disulfides. Symmetrical benzene thiosulfonates (Figure 1.4.) will also be synthesized through direct reduction. Product confirmation will be done through the analysis of ^{1}H NMR, ^{13}C NMR, MS and melting point technique.



R = H, CH_3, Cl, NO_2

R' = H, CH_3

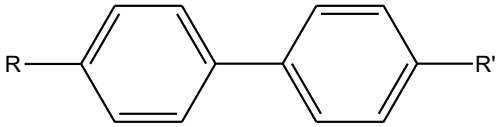
Figure 1.3. Unsymmetrical Benzene Thiosulfonate



R = H, CH_3

Figure 1.4. Symmetrical Benzene Thiosulfonates

2. The second part of the project will first see the synthesis of differently substituted biaryls (Figure 1.5.) through the cross-coupling of symmetrical and unsymmetrical benzene thiosulfonates with Grignard reagents and boronic acids.



R = H, CH_3, Cl, NO_2
R' = H, CH_3, Cl, OCH_3

Figure 1.5. Biaryls to be synthesized

The compounds synthesized will be fully characterized using ^{1}H NMR, ^{13}C NMR, IR, melting point and GC-MS.

1.5. SIGNIFICANCE OF THE STUDY

Most everyday substances are organic in nature and are obtained mainly through synthesis. This is a field in organic chemistry that has played an important role; from design to analysis, to construction in both research and industry. The field has had a great impact in all that's living. For example, the discovery of new drugs is highly reliant on synthesis, the production of plastics and fuels are also dependent on synthesis.

Although synthetic organic chemistry has enabled the ease in production of the desired products over the years, this has come with a price, not only to the environment but to humans as well. Certain synthetic procedures employ reagents that are toxic, some synthetic reactions lead to the formation of side products which bring harm to the environment. As a result of this poor lab safety, there has been a breakout of many diseases which in turn ends up negatively affecting many other socio-economic aspects.[8]

For these reasons, there is a need to develop methodologies that will lead to synthetic reactions being performed under optimum conditions, reactions producing minimal

byproducts that wouldn’t be compromising to the environment as well as human health. Such methodologies would allow a broader scale of products to be produced, ensuring full advantage is taken when it comes to synthesis.

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CHAPTER TWO

LITERATURE REVIEW

2.1. INTRODUCTION

Transition-metal catalyzed cross-coupling reactions afford the coupling of organometallic nucleophilic partners (Grignard, organoboron, organostannane reagents, etc) with electrophilic partners (activated or inactivated)[1,2] to construct new C-C and C-heteroatom bonds.[3,4] Traditionally, organohalides (alkyl/aryl) and pseudo-halides (tosylate/ mesylates) were used as electrophilic coupling partners with their reactions proceeding *via* the C-X (X = halide, pseudo-halide atom) bond cleavage.[5] However, over the years, developments employing alternative electrophilic partners have been made (Figure 2.1.).[5,6]

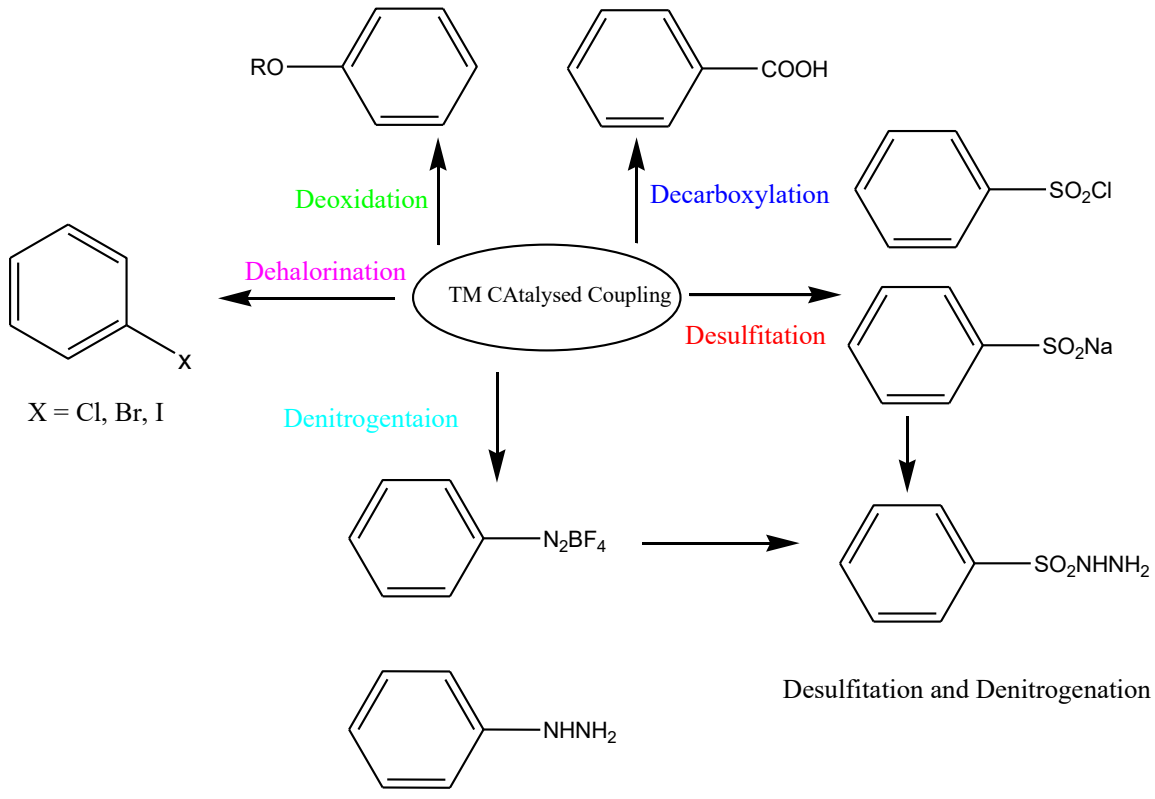


Figure 2.1. Electrophilic partners and their bond cleavages.

Transition-metal catalyzed cross-coupling reactions have heavily relied and focused on the development of palladium as a catalyst and their ligand systems for the couplings, especially in the Suzuki-Miyaura type reactions. The success of palladium catalysts can be attributed to their high catalytic activities as well as their reaction turn over, plus their tolerance to a pool of functional groups. Due to the expense of palladium catalysts and their supporting ligand systems, the use of palladium-based catalytic systems has been restricted.[7] Since then, other transition metals such as Cu(I)[5], Ni(0)[8] , Co(II)[9], Fe(II and III)[10] are slowly being discovered as catalysts in many cross-coupling reactions especially the nickel catalytic system which has shown great stability and activity, low cost, applicability even without a supporting ligand.[11]

With the progression of years, transition-metal catalyzed cross-coupling reactions (such as Suzuki-Miyaura, Kumada-Corriu, Hiyama, *etc*), have become the most powerful and dominant methodologies in organic synthesis to synthesize new C-C bonds.[3] They are of vital importance in organic synthesis as they are employed in a variety of synthetic procedures for the synthesis of biaryls, fine chemicals, pharmaceuticals and biologically active natural products.[12] Their vast employment and success in synthetic organic chemistry can be attributed to their high functional group tolerance, mild reaction conditions and their use of easily available reagents.[13]

There is a constant need to develop and improve cross-coupling reactions that yield biaryls and their homologues since biaryls are the backbone of a variety of organic compounds such as polymers, ligands and pharmaceutical drugs.[14,15] However, some of the cross-coupling reactions such as Negishi and Stille have been associated with challenges such as; difficulty in preparation, high cost, toxicity and instability.[3,16] In light of these challenges, studies have evolved to find reaction conditions that are mild, green, low-cost while employing non-toxic electrophilic coupling partners possible.

2.2. ELECTROPHILIC COUPLING PARTNERS IN TRANSITION-METAL CATALYSED CROSS-COUPLING REACTIONS

Electrophilic coupling partners are generally defined as electron poor reagents which when coupled with electron rich fragments, new C-C or C-heteroatom bonds are formed. Due to constant developments in transition-metal catalyzed coupling reactions, there are numerous electrophilic coupling partners that have been reported in literature to date.

2.2.1. Traditional Electrophilic Coupling Partners

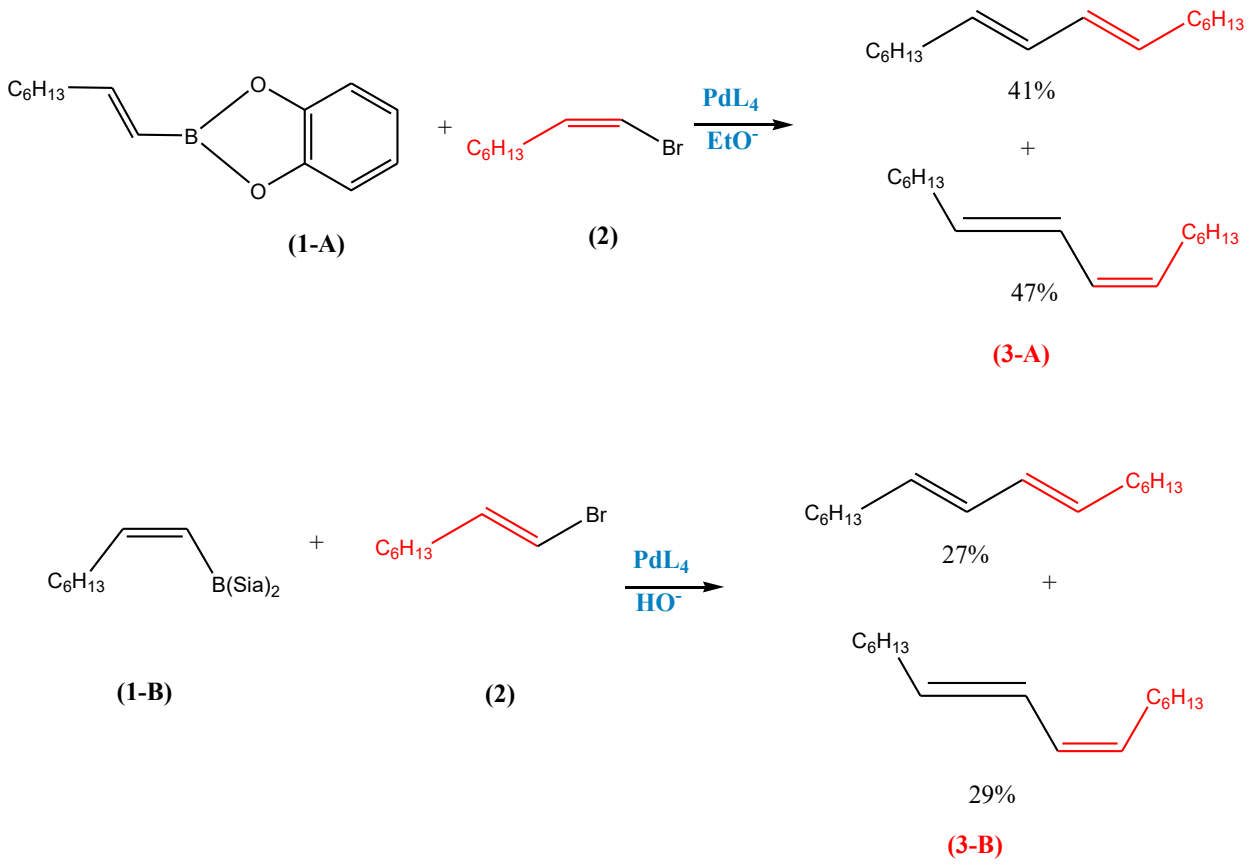
2.2.1.1. C-X (X-halide) Bond Cleavage

Traditionally, transition-metal catalyzed cross-coupling reactions have heavily relied and made use of electrophilic coupling partners that follow dehalogenation to promote the construction of new C-C or C-heteroatom bonds.[17] Aryl iodides and bromides are good examples in this case as they have received a lot of attention in the past as electrophilic coupling partners in most transition-metal catalyzed cross coupling reactions due to their relatively higher reactivity and stability.[18] While both aryl bromides and aryl iodides are more costly than the corresponding aryl chlorides, the inexpensive aryl chlorides are less reactive requiring special and novel ligand systems to lower the higher energy required in the oxidative insertion step of the C-Cl bond into the metal centre.[19,20]

There are several cross-coupling reactions that make use of aryl halides as electrophilic coupling partners and these include but not limited to Suzuki-Miyaura cross-coupling, Kumada cross-coupling, Heck cross-coupling etc.

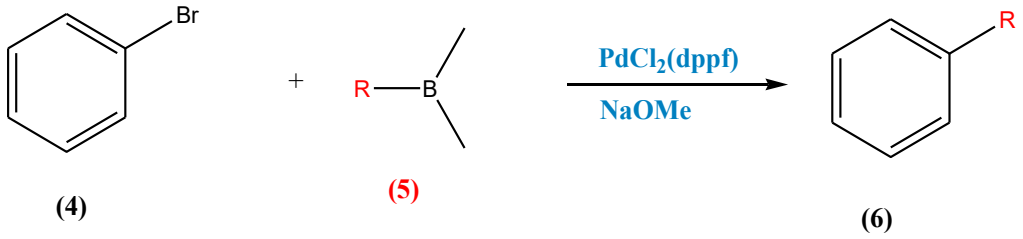
The Suzuki-Miyaura cross-coupling reaction dates to 1979 when Miyaura and Yamaha discovered that organoboranes (1) could be coupled to alkyl halides in the presence of a palladium catalyst. The first attempt to carry out this reaction using alkenylborane (2)

under a palladium complex catalyst failed and it was then that the authors discovered that the addition of a base was essential in improving the rate of the reaction and product yields (Scheme 2.1.).[21]



Scheme 2.1. First reported Suzuki-Miyaura Cross-Coupling reactions

To further expand the scope and the application of the Suzuki-Miyaura cross-coupling in organic synthesis, in 1986 Suzuki and Miyaura investigated the influence of the basicity strength towards the synthesis of symmetrical and asymmetrical biaryls (6). Aryl iodides and aryl bromides (4) were coupled with different organoboranes (5) in the presence of a base and a palladium catalyst. For the reactions, the presence of strong bases led to the production of the desired products in high yields without the formation of by-products whereas, the use of a weak base such as sodium acetate led to a low product yield (Scheme 2.2.).[22]



(4) (5) (6)

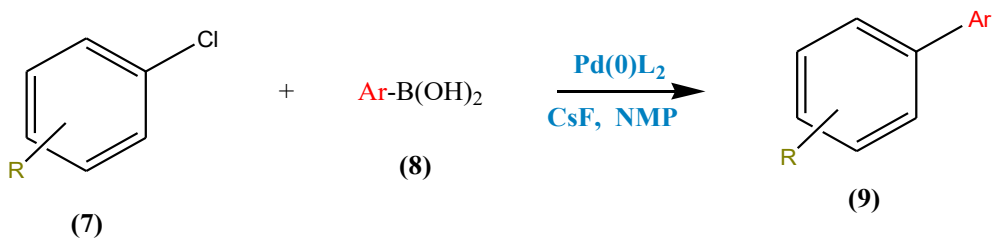
R = Aryl, alkyl

78% - 98%

Scheme 2.2. Reactions of organohalides with organoboranes reported in 1986.

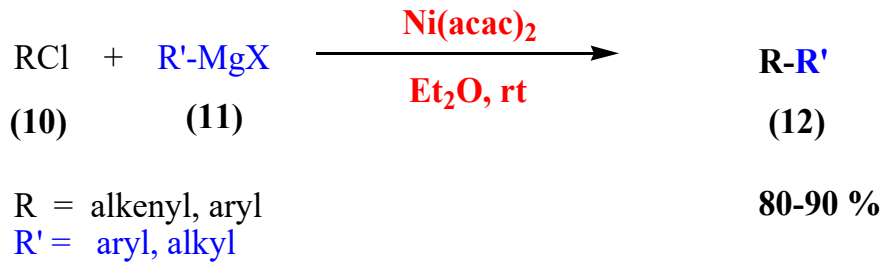
The mild reaction conditions and the tolerance of different functional groups as well as the efficiency of Suzuki Miyaura cross-coupling reaction popularized this methodology finding application in the synthesis of biologically active natural products and pharmaceutical drugs.[20]

The success of the Suzuki-Miyaura cross-coupling reaction was however limited to the use of aryl/alkyl/ and alkenyl bromides or iodides as electrophilic coupling partners. Organochlorides were not reactive until Shen and co-workers devised a procedure that could accommodate inexpensive organochlorides. In 1997, Shen and co-workers reported the coupling of arylchlorides (7) with phenyl boronic acids (8) to synthesize biaryls (9) in a Pd-catalytic system (Scheme 2.3.). The biaryls were produced in yields ranging from poor to excellent. In this study, Shen discovered that the combination of a highly active Pd/ligand catalyitic system with arylchlorides which possessed electron-withdrawing groups led to a more reactive and efficient system, more especially those arylchlorides that were *para* and *ortho* substituted. This is because of the electron-withdrawing effect of the substituents which leaves arylchlorides more electron-deficient, hence more susceptible to nucleophilic attack and in turn enhancing their reactivity.[20]



Scheme 2.3. Synthesis of biaryls through coupling of aryl chlorides with phenyl boronic acid

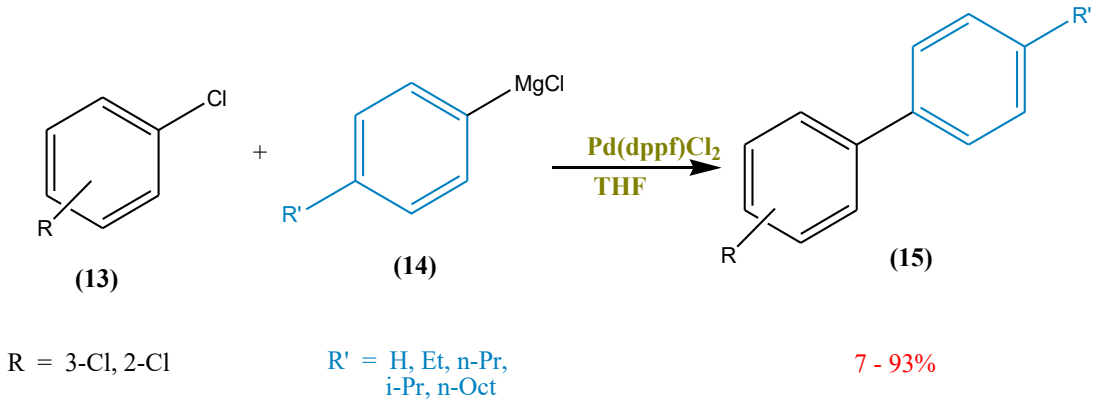
Another transition-metal catalyzed cross-coupling reaction which relies on organohalides as electrophilic coupling partners was discovered by Kumada in 1972.[23] Kumada, *et al*. discovered that aryl- and vinyl chlorides (10) could couple with alkyl- and arylmagnesium bromide (11) under catalytic amounts of $Ni(dppe)Cl_2$ to produce the desired hydrocarbons (12) in good to excellent yields (Scheme 2.4.). Similar to the Suzuki-Miyaura cross-coupling reaction, organochlorides react sluggishly in Kumada cross-coupling reaction compared to organobromides and iodides. However, Kumada revealed that the presence of bidentate supporting ligands accelerated the cross-coupling between organochlorides and Grignard reagents to produce the desired products in reasonable yields.[24,25]



Scheme 2.4. Nickel-catalysed reactions of magnesium bromides and organochlorides

Following the breakthrough made by Kumada in 1972 overcoming the low reactivity of organochlorides in the Kumada cross-coupling reactions, Katayama and Umeno went on to perform coupling reactions of arylchlorides. In 1991, Katayama and co-workers reported the coupling reactions between phenylmagnesium chlorides (14) and

arylchlorides (13) using $Pd(dppf)Cl_2$ as a catalyst to produce biaryls (15) (Scheme 2.5.). For these reactions, the authors successfully demonstrated selective replacement of one halogen in an environment where there are two identical halogens.[26]

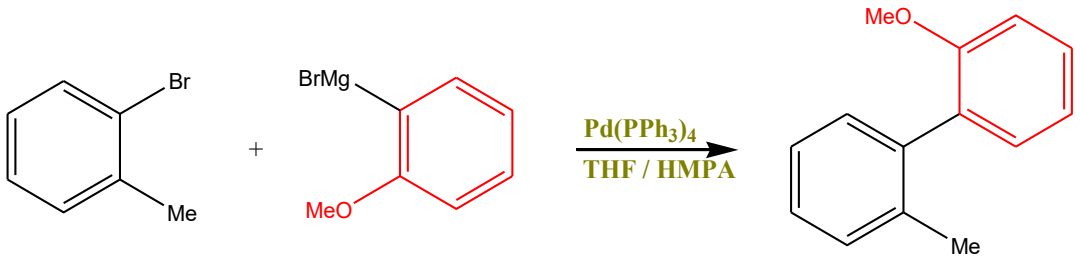


(13) **(14)** **(15)**

R = 3-Cl, 2-Cl R' = H, Et, n-Pr, i-Pr, n-Oct 7 - 93%

Scheme 2.5. Coupling of phenylboronic acid with dichlorobenzene compounds.

Expanding the scope of the kumada cross-coupling reactions by investigating the influence of substituents on the reactivity of coupling substrates. In 1986, Widdowson and Zhang reported the coupling reaction between 2-bromotoluene (16) and 2-methoxy phenylmagnesium bromide (17) using $Pd(PPh_3)_4$ as a catalyst towards the synthesis of biaryls (18) (Scheme 2.6). The biaryls (18) were synthesized in poor yields and Zhang discovered that when both coupling partners possess substituents on the *ortho* positions, the yields of the coupled products were low.[27]

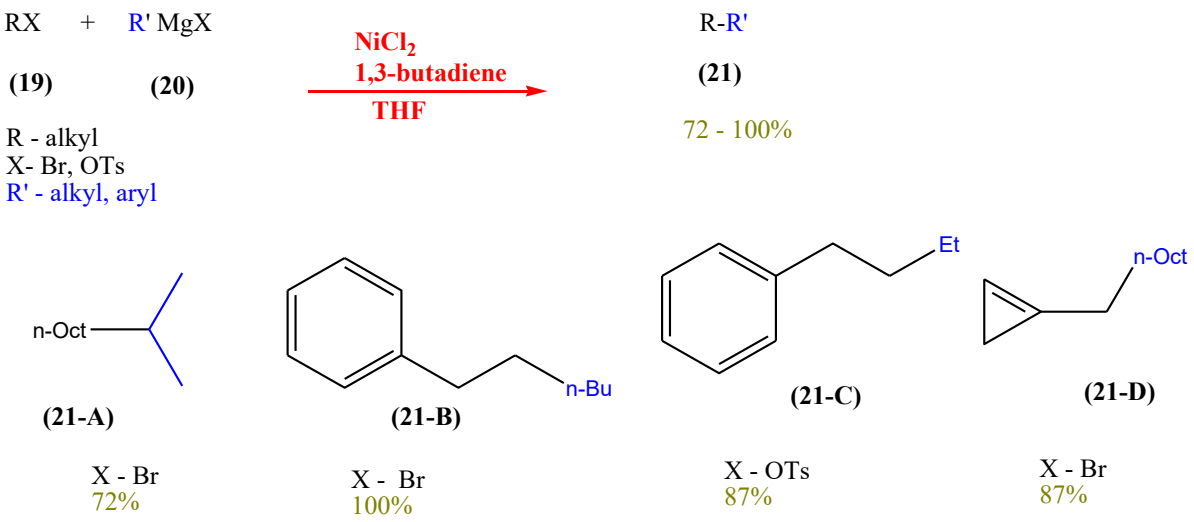


(16) **(17)** **(18)**

8%

Scheme 2.6. Synthesis of biaryls through the coupling of meta-substituted electrophilic coupling partners

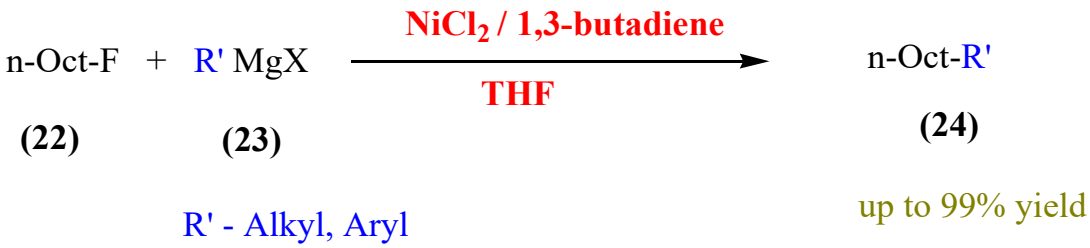
Noting that the reactions of palladium as a catalyst had been studied extensively and given the high price of palladium and its ligands, Kambe, *et al*. brought the attention to nickel as a catalyst in transition-metal catalyzed reactions. Kambe reported the first successful Ni-catalysed $C_{(sp3)}$-$C_{(sp3)}$ Kumada-type cross-coupling reaction in 2002, approximately 30 years after the first nickel-reported Kumada-Corriu type cross-coupling reactions since the reactions of nickel posed many challenges. The team demonstrated the coupling between alkylmagnesium bromide (20) with organobromides and tosylates (19) under an optimized system consisting of $NiCl_2$/butadiene catalyst-ligand support system. The coupled-products (21) were synthesized in yields ranging from moderate to excellent (Scheme 2.7.).[28]



Scheme 2.7. First reported Nickel-catalyzed $C_{(sp3)}$-$C_{(sp3)}$ coupling reactions.

In 2003, Kambe et al., extended on the work they had done in 2002 where they utilized the nickel/butadiene catalytst/ligand system, only this time employing different electrophilic coupling partners. Alkylflourides (22) were coupled with organomagnesium bromides (23) with the coupled products (24) synthesized in excellent yields (Scheme

2.8.).[29] The reactivity of the alkyl halides was found to increase in the following order; Cl < F < Br.[23]



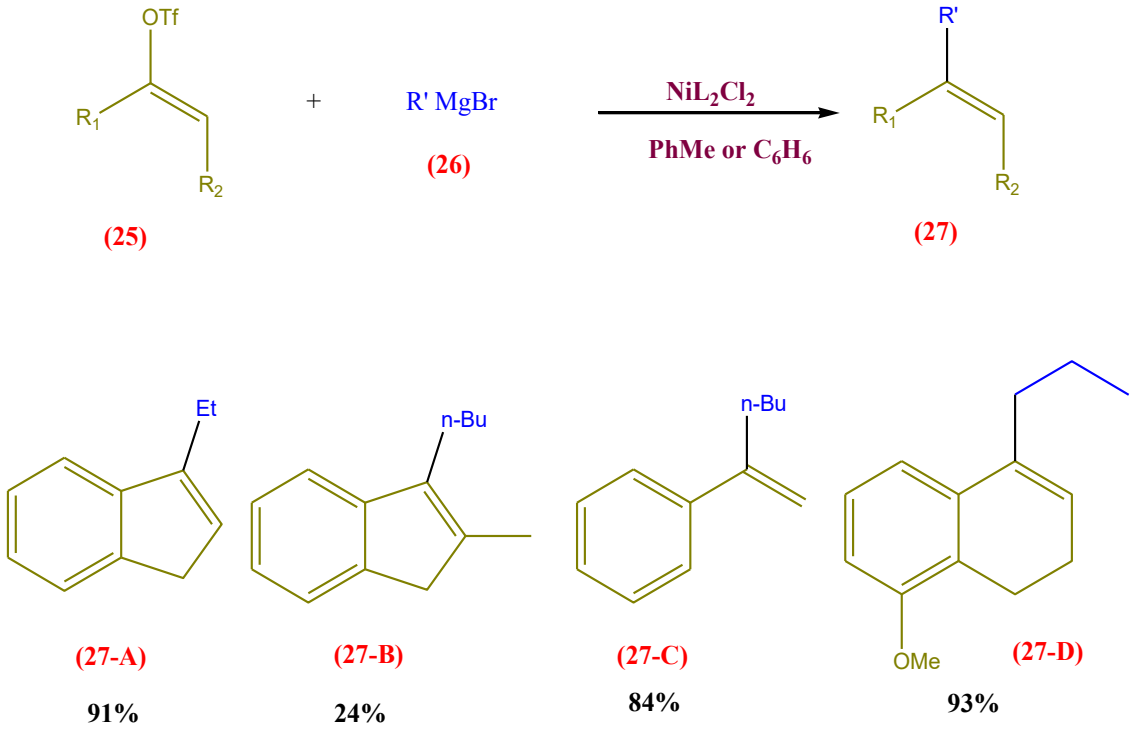
Scheme 2.8. Reactions of alkylflourides under Nickel/butadiene catalytic system.

2.2.1.2. C-X (X: pseudo-halide) bond cleavage

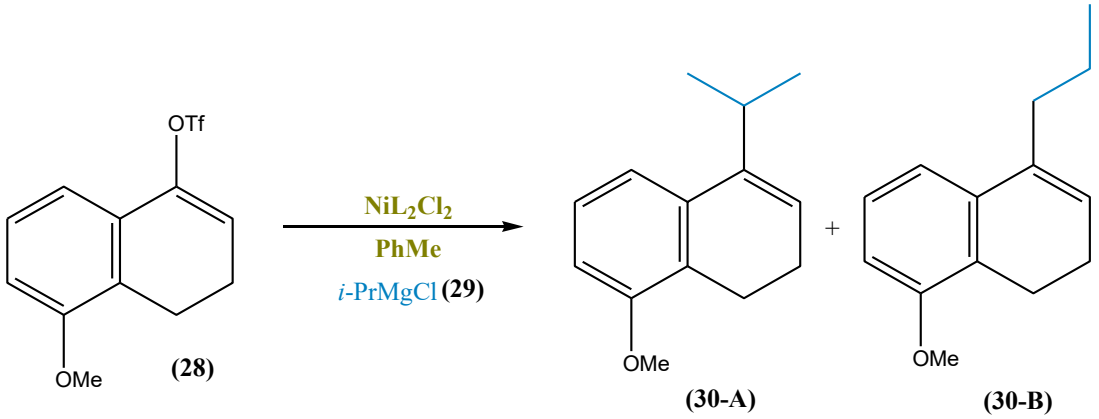
Despite their high reactivity and popularity as electrophilic coupling partners in many transition-metal catalyzed reactions, organohalides are generally not environmentally friendly and their use as coupling partners produces toxic halide byproducts.[30] Pseudo-halides are alternative electrophilic coupling partners that are more environmentally friendly than organohalides with their reactions having been well documented.[31]

Tosylates, mesylates and triflates are the most popular and well-studied pseudohalides,[31] owing to their properties i.e. high stability, low cost and vast availability being similar to that of organohalides making them equivalents to aryl halides in synthesis.[15] However, their low reactivity has forced the need to develop and the use of highly active catalysts which in turn leaves pseudo-halides less desirable. The cross-coupling reactions of pseudo-halides reactions proceeds *via* deoxidation (C-O bond cleavage) making their oxygenated organic byproducts less harsh to the environment.[17,18]

The participation of pseudo-halides as electrophilic coupling partners was demonstrated by Fiaschisi, and co-workers in 1999 where they reacted vinyl triflates (25) with alkylmagnesium bromide (26) to furnish structurally diverse products (27) under a catalytic Nickel complex (Scheme 2.9.). For the reactions, the authors observed the impact of the Ligands' bite angles on the overall catalytic system. They discovered that the impact of the ligand's bite angle was more prominent on the secondary alkylmagnesium bromide than on the primary alkylmagnesium bromide (29). The reactions of secondary alkylmagnesium bromides led to the formation of side product and to overcome such, ligands with a smaller bite angle such as dppp and dppe (Scheme 2.10.) were employed.[32]



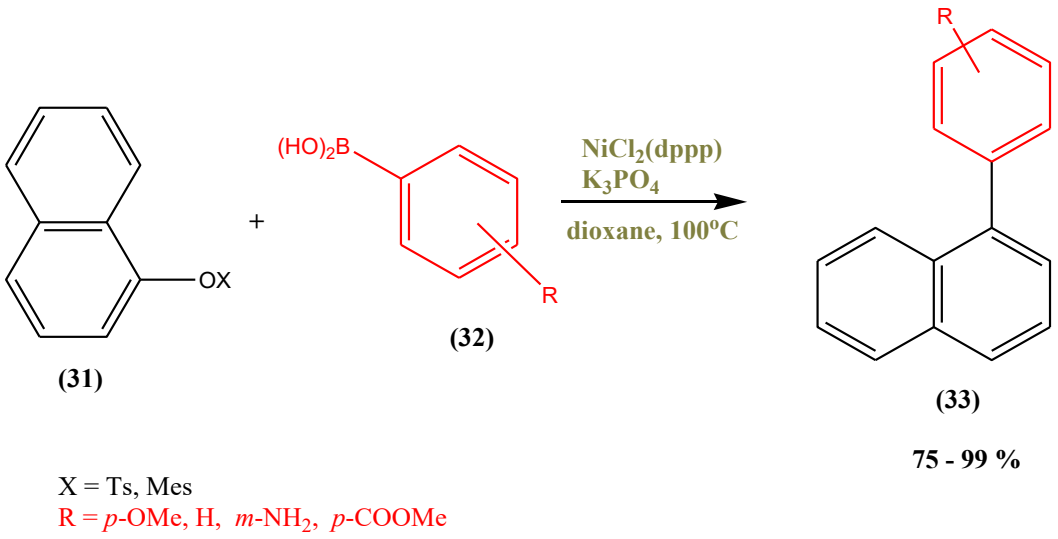
Scheme 2.9. Reactions of vinyl triflates with alkylbromides



Ligand	Bite angle	30-A		30-B
dppe	85.8°	8	:	1
dppp	90.6°	3	:	1
dppf	99.07°	no reaction		

Scheme 2.10. Reactions of alkylmagnesium bromide, demonstrating the effects of the ligands' bite angles on product formation.

The participation of pseudo-halides as electrophilic coupling partners is not only limited to the Kumada-type cross-coupling reactions. These versatile reagents have been shown to effectively react in different conditions. In 2011 Gao and co-workers demonstrated the Suzuki-Miyaura type coupling of aryltosylates and mesylates (31) with differently substituted boronic acids (32) (Scheme 2.11). To combat the low reactivity associated with aryl toysylates and mesylates, Gao discovered that the $NiCl_2$-dppp catalyst/ligand system was efficient and effective in affording the coupled products (33) in high yields.[31]



Scheme 2.11. Reactions between aryltosylates/mesylates with arylboronic acids

2.2.2. Non-Traditional Electrophilic Coupling Partners

The development and successful application of pseudo-halides to promote the formation of C-C bonds following the C-O cleavage had encouraged and persuaded researchers to find alternative electrophiles that are more environmentally friendly than organohalides along with the desire for economical procedures that make use of inexpensive materials.[33] Developments that have been made over the past few years have been remarkable that they have allowed more versatility and an efficient combination of a wide variety of electrophilic coupling partners in cross-coupling reactions.[34,35]

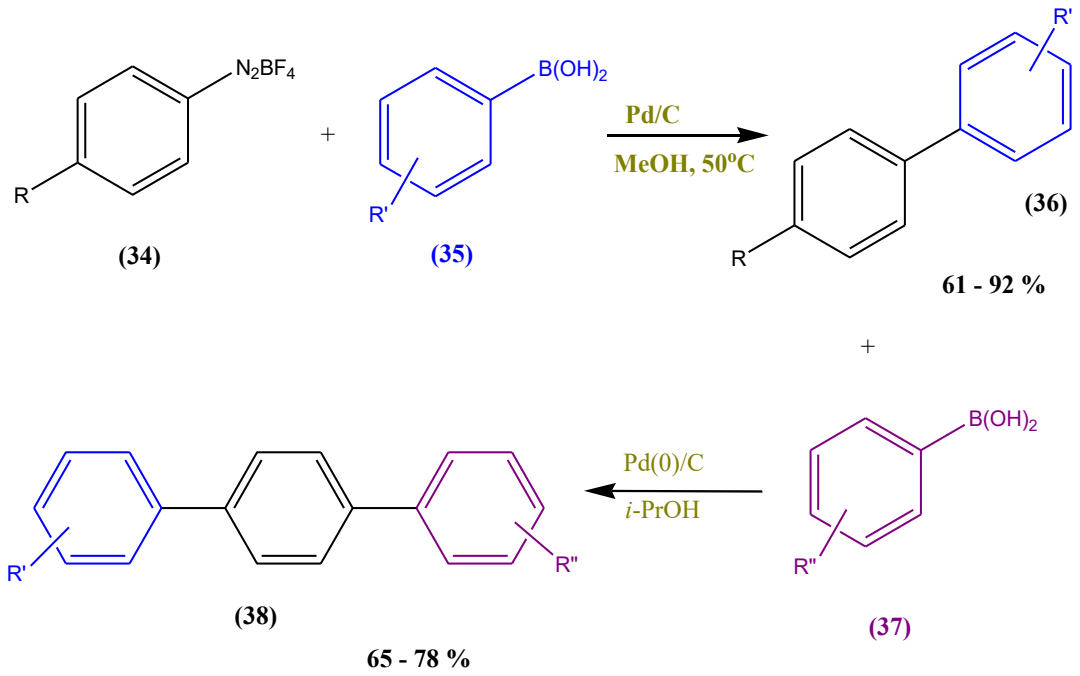
2.2.2.1. Non-Sulfur Electrophiles

2.2.2.1.1. Aryldiazonium Salts

The cross-coupling reactions of arenediazonium salts as electrophiles, which proceed *via* the C-N bond cleavage, have been well established. The interest to utilize arenediazonium salts as electrophilic coupling partners was sparked due their ease of

preparation from arylamines.[36] Arylamines are easily accessible than corresponding arylhalides and phenols, and possess high reactivity and environmental friendliness.[37]

The insensitivity of arenediazoinum salts towards the substituents' electronic and steric effects has made their cross-coupling reactions more attractive by allowing more versatility and thus their cross-coupling reactions reactions to not require any base.[38] For this reason, Feplin and co-workers exploited in 2007, aryldiazonium salts (34) as electrophilic coupling partners in a Suzuki-type cross-coupling reaction towards the synthesis of unsymmetrical terphenyls in good yields (38). The reactions were conducted in the absence of additives (bases and ligands) in the presence of Pd as a catalyst. The Pd-catalytic system allowed for fast reaction times under mild reaction conditions (Scheme 2.12).[39]



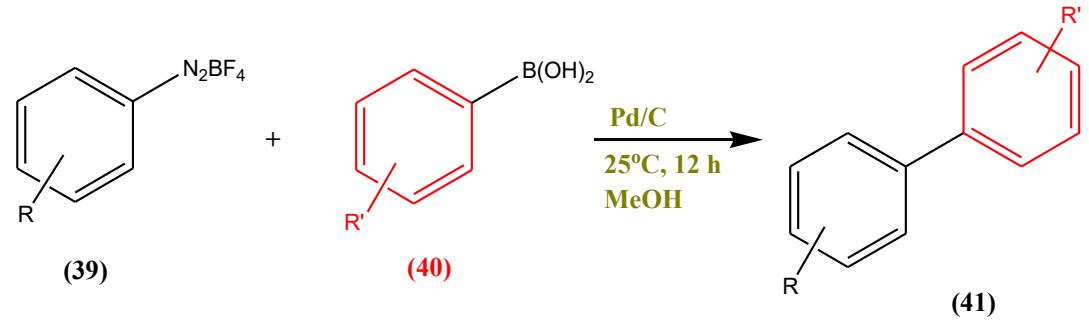
R = Br; OMe; NO_2

R' = 4-Cl; 3,4-diOMe; 2,3-diOMe

R" = H; 3,4-diOMe

Scheme 2.12. Sequential reactions of aryldiazonium salts with arylboronic acids.

Since the cross-coupling reactions of aryldiazonium salts Feplin had reported on in 2007 required a high loading of a scarcely available Pd-catalyst (5 mol% Pd);[39] in 2009 Feplin and co-workers reported an improved Suzuki-type reaction of aryldiazonium salts using cheap and robust catalysts that make use of non-anhydrous and non-degassed conditions at room temperature. Aryldiazonium salts (39) were allowed to react with arylboronic acids (40) bearing different substituents in the presence of a palladium catalyst to furnish biaryls (41) in good to excellent yields (Scheme 2.13).[40]



R = 2-NO_2-5-OMe; 3-NO_2-4-OMe; 4-NO_2; 2-NO_2; 3-Me; 3-CF_3; 2,4,6-triMe; 2-Cl

R' = 4-Cl; 4-OMe; H; 3-NO_2; 3,4-diOMe; 2-Me

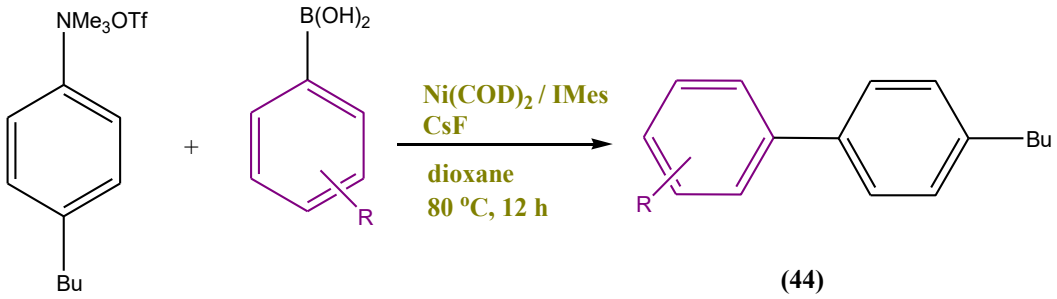
77 - 97%

Scheme 2.13. Reactions of aryldiazonium salts, reported by Feplin in 2009

2.2.2.1.2. Ammonium Triflates

It wasn't until the early 20th century that Ullman and Goldberg reported on their groundbreaking work involving C-N bond cleavage in the construction of new C-C bonds in cross-coupling reactions. However, their reaction conditions were not optimum as they required high temperatures, the aid of polar solvents and strong bases.[41,42] This led to the drift in focus involving C-N electrophilic coupling partners.

Over the years many developments and improvements have been made concerning cross-coupling reactions following the C-N bond cleavage and ammonium triflates have also emerged as alternative cross-coupling partners and some of their reactions reported on in 2003 by Blakey and McMillan. Blakey and co-workers reported on the reactions between *p-butyl*-trimethylammonium benzene triflate (42) and phenyl boronic acid (43) in an optimized catalytic system of Ni(0)/IMes (10 mol%) and CsF as a base to produce biaryls (44) in good to excellent yields (scheme 2.14).[43]



R = OMe, F, COMe, H

Scheme 2.14. Ni-catalysed reactions between *p*-butyl-trimethylammonium benzene triflate and phenylboronic acid

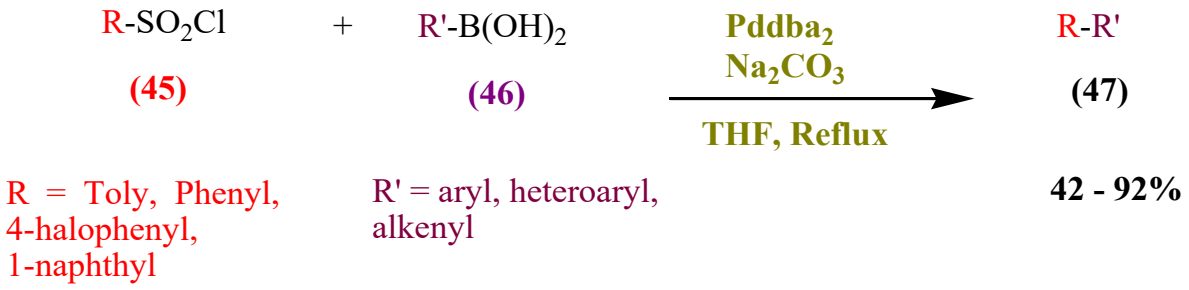
2.2.2.2. Sulfur-Based Electrophiles

Desulfitative cross-coupling reactions of thio-organics with different nucleophiles have drawn much attention because of their higher reactivities as well as easy preparation under milder reaction conditions than corresponding arylhydrazine substrates. For this reason, the C-S bond cleavage has emerged as one of the most attractive alternative method in cross-coupling reactions.[17]

2.2.2.2.1. Arylsulfonyl Chlorides

Arylsulfonyl chlorides have been engaged in cross-coupling reactions[17] as electrophilic coupling partners for a while and have been classically used as aryl sources.[16] They are vital compounds in organic synthesis,[44] and are particularly the most attractive as they are readily available and inexpensive.[45] arylsulfonyl chlorides have also been found to be generally more reactive than their corresponding bromide and sulfide counterparts.[33]

The chemistry of arylsulfonyl chlorides as electrophilic counterparts was exposed in one of the most prominent works reported in 2003 by Vogel *et al*. In this study, different arylsulfonyl chlorides (45) bearing electron withdrawing and electron donating functionalities were coupled with aryl, heteroaryl and alkenyl boronic acids (46) under Suzuki-Miyaura cross-coupling reactions (Scheme 2.15). The presence of carbene ligands was found to be essential for the coupling to take place, producing the desired products (47) in moderate to excellent yields.[33] However, the production of HCl as a byproduct through moisture has restricted the application of arylsulfonyl chlorides, especially in industrial settings.[33] Also, the instability and moisture sensitivity[16] of aylsulfonyl chlorides has hindered their use in cross-coupling reactions and hence the need to seek alternative desulfitative reactions.

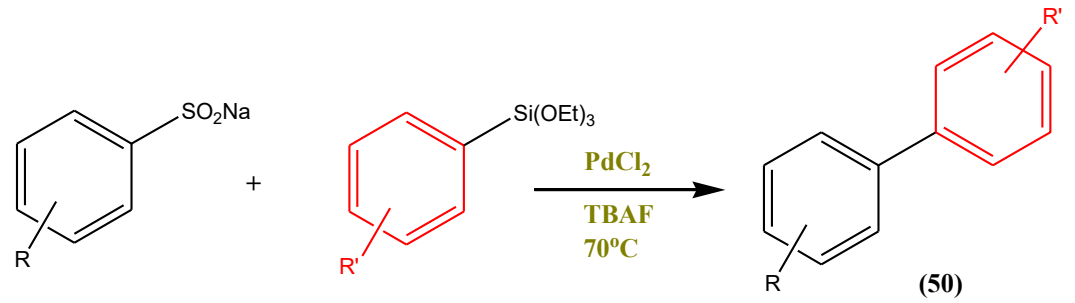


Scheme 2.15. Palladium Catalyzed coupling between arylsulfonyl chlorides and boronic acids.

2.2.2.2.2. Sodium Arylsulfinates

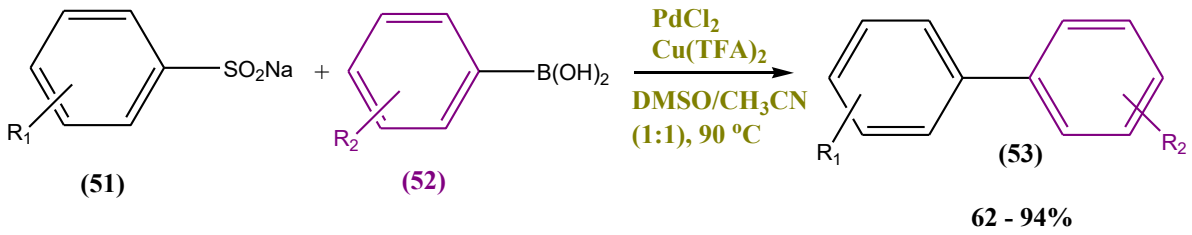
After the long engagement of arylsulfonyl chlorides in cross-coupling reactions, sodium Arylsulfinates have shown great potential as aryl sources and their reactions have been reported in cross-coupling reactions.[16,46] Relative to the aryl carboxylic acid electrophilic coupling partners, reactions involving sodium arylsulfinates were found to be milder.[47] It is also the wide availability of the arylsulfinate salts, ease in handling and stability that makes them attractive.[16,18]

Interested in the development of environmentally benign desulfitative conditions; Cheng and co-workers reported in 2003 the replacement of arylsulfonly chlorides with sodium arylsulfonates to eliminate the production of toxic HCl. In this study sodium arylsulfinates (48) were reacted with with arylsiloxanes (49) under Hiyama cross-coupling reactions producing the desired biaryls (50) in excellent yields (Scheme 2.16). TBAF as an additive was found essential in this reaction as a F^- donour which in turn increases the nucleophilicity of arylsiloxanes. These reactions were found tolerant to a wide range of functional groups.[16]



Scheme 2.16. Hiyama-type coupling reaction of sodium arylsulfinates and arylsiloxanes

In 2014, Cheng and co-workers extended the scope of the reactions to include arylboronic acids as nucleophiles. Structurally diverse sodium arylsulfinates (51) bearing electron withdrawing, donating and electronically neutral functional groups were efficiently coupled with arylboronic acid (52) producing the biaryls (53) in excellent yields in simple aerobic conditions. These reactions were found tolerant to a wide range of functional groups and insensitive both to the polarity and steric effect of the substituents. The presence of Cu(II) salts as co-catalysts was found vital in accelerating these reaction (Scheme 2.17).[18]



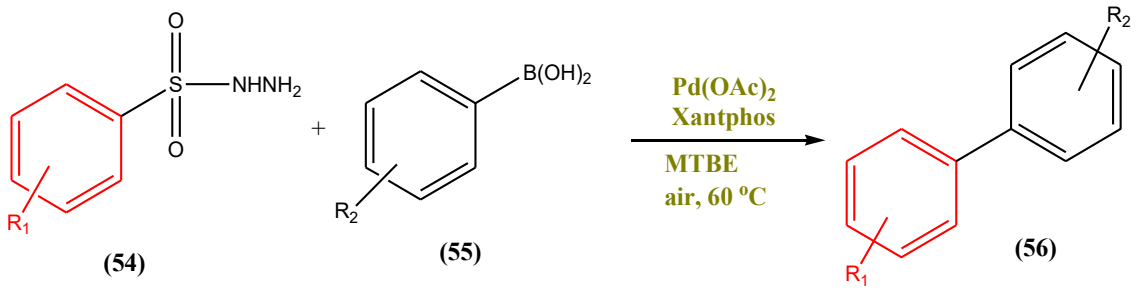
R_1 - H, Me, OMe, Br, F, NO_2, Cl, Ac
R_2 - NH_2, Me, OMe, Br, F, NO_2, Cl, H

Scheme 2.17. Pd-catalyzed reactions of sodium arylsulfinates and arylboronic acids

2.2.2.2.3. Sulfonyl Hydrazines

Arylsulfonyl hydrazines are attractive in organic synthesis as they can be easily prepared through a one-step synthesis of hydrazine hydrates with arylsulfonyl chlorides and they are also air-stable.[22] Over the past years, they have been used as aryl sources successfully in cross-coupling reactions via desulfitative-denitrogenative reactions[48,49] and in reactions, they are able to easily convert to diazo compounds which are very active and important in cross-coupling reactions.[48] The significance of sulfonyl hydrazines significant over the past years is their ability to serve as arylating reagents through desulfitation[50] and by means of denitrogenation, serve ideally as sulfonylating or thiolating agents.[34]

In attempt to conduct the reactions in the absence of co-catalysts and to investigate the effect of their absence for the construction new C-C bonds; in 2015 Zhong and co-workers reported the synthesis of biaryls (56) through the coupling of arylsulfonyl hydrazines (54) with boronic acids (55). The authors conducted these coupling reactions in the absence of expensive stoichiometric co-oxidants (e.g., copper and silver) and however the reactions still showed excellent selectivity and a wide tolerance of a variety of functional groups. Xantphos was found to be an ideal ligand for the reaction, found responsible for improving the reaction efficiency. The cross-coupling of different arylsufonyl hydrazines with different arylboronic acids (55) in the presence of $Pd(OAc)_2$ afforded biaryls (56) in good to excellent yields after the exclusion of SO_2 and N_2 gases (Scheme 2.18).[17]



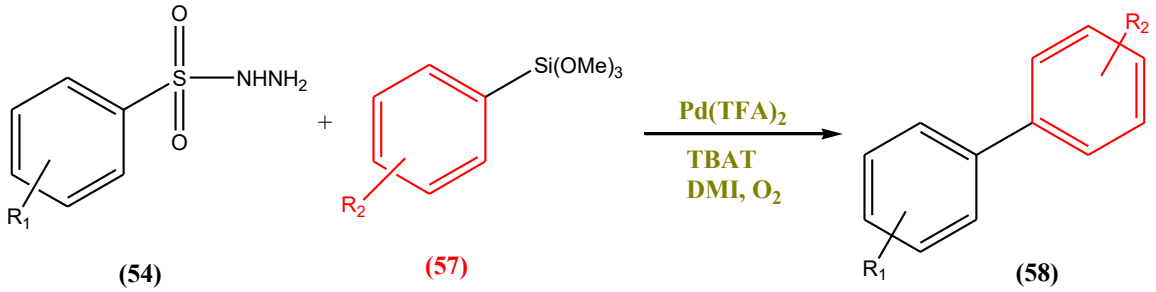
R_1 = H, Me, OMe, I, Cl, Br, NO_2

R_2 = H, Me, OMe, NO_2, Cl

Scheme 2.18. Reactions of arylsulfonyl hydrazines with arylboronic acids.

The reactivity of arylsulfonyl hydrazines in transition-metal catalyzed cross-coupling reactions was not limited to the Suzuki-Miyaura type conditions. In 2015 Zhong and co-workers demonstrated the use of arylsulfonyl hydrazines as arylating agents in the Hiyama-type coupling. The authors conducted the reactions of arylsulfonyl hydrazines (54) with arylsilanes (57) under the optimized Pd-catalytic conditions to synthesize biaryls

(58) in excellent yields in the absence of oxidants. The reactions were conducted under the atmosphere of oxygen. In conclusion Zhang reported that the desulfitative-denitrogenative reactions demonstrated versatility and tolerance of common functional groups such as nitro, halides, alkyl and alkoxides (Scheme 2.19).[51]



R_1 = H, 4-OMe, 4-F, 4-Cl, 4-Br, 4-NC, 4-I, 3-Me, 2-Me, 4-NO_2

R_2 = H, 3-Me, 2-Me, 4-NO_2, 4-Cl, 4-OMe, 4-F

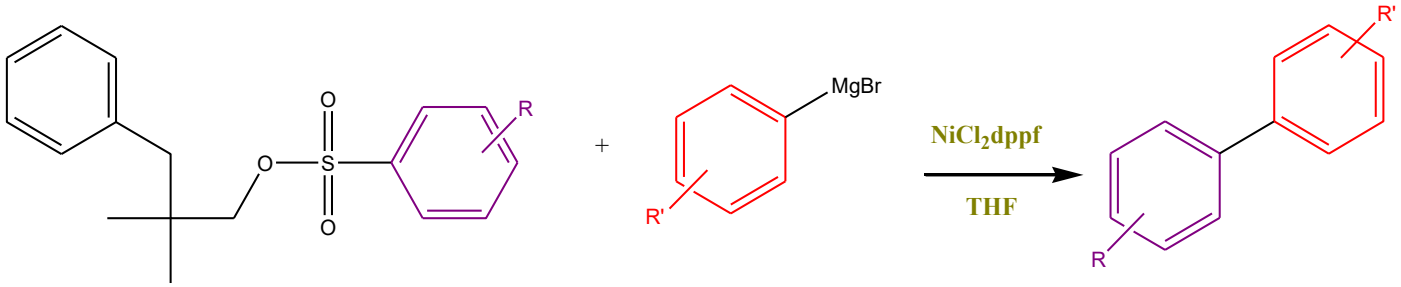
Scheme 2.19. Cross-coupling reactions of arylsulfonyl hydrazines and arylsilanes.

2.2.2.2.4. Aryl Arenesulfonates

Aryl arenesulfonates can be easily synthesized from inexpensive arenesulfonyl chlorides and widely available phenols. In comparison to aryltriflates, aryl arenesulfonates are much more stable, easy to prepare and are cheaper. It is in light of these properties that researchers are driven to develop more protocols that utilize aryl arenesulfonates as electrophilic coupling partners in transition-metal catalyzed reactions.[52]

In 2003, Park and co-workers reported on the cross-coupling reactions of neopentyl arenesulfonates (59) with arylmagnesium bromides (60) in nickel catalyzed optimum conditions to produce terphenyls and oligophenyls (61) in high yields (Scheme 2.20). This novel study demonstrated its use in the creative elimination of alkylsulfonly groups from

aromatic compounds. Park observed the effect of the substituents' position in the benzene ring. He reported on how those substituents positioned on the *para*-site had no influence on the reactivity despite their bulkiness e.g. 4-tertbutyl (*para*-positioned) did not limit the reactivity of the sulfonate. When the *ortho*-positioned substituents were utilized lower yields were obtained as some starting material remained unreacted and this effect was mainly due to steric hindrance.[53]



(59) **(60)** **(61)**

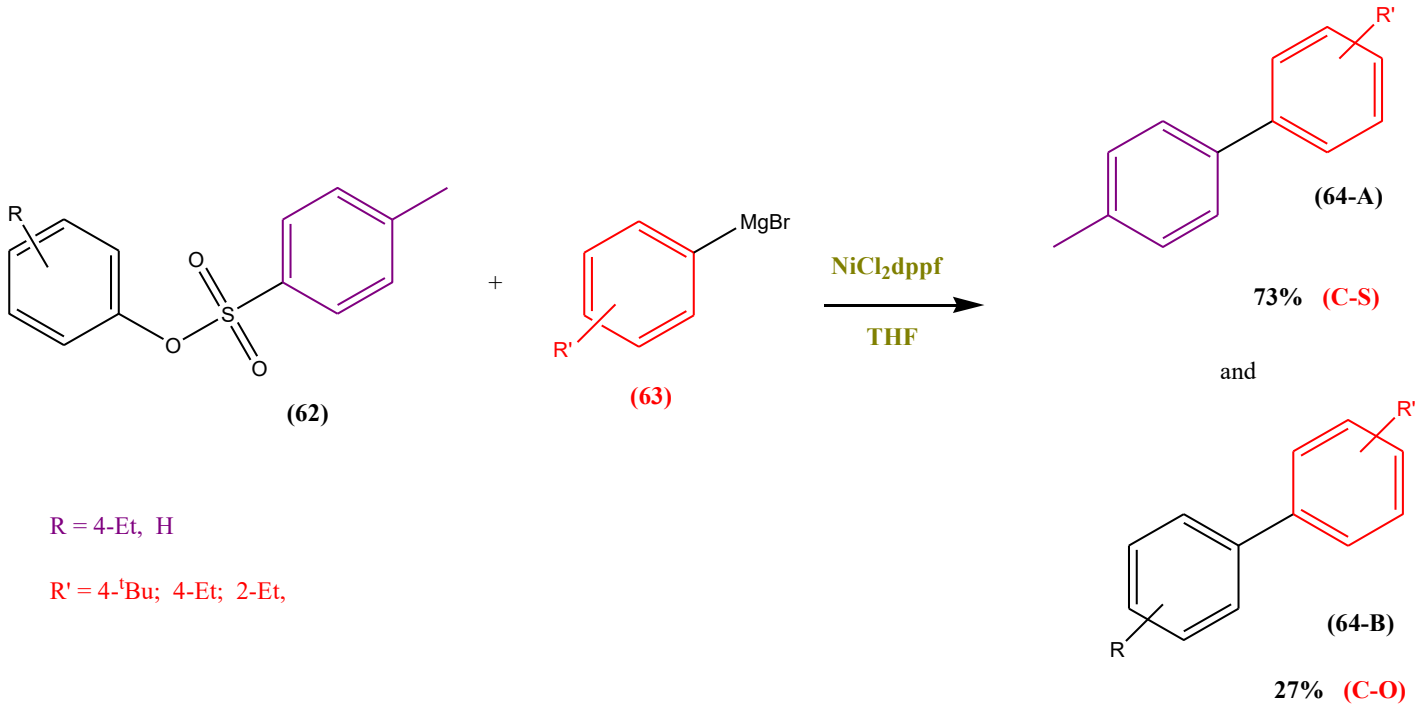
7 - 84%

R = 4-Me; 4-^{t}Bu; 2,4,6-triMe; 4-OMe

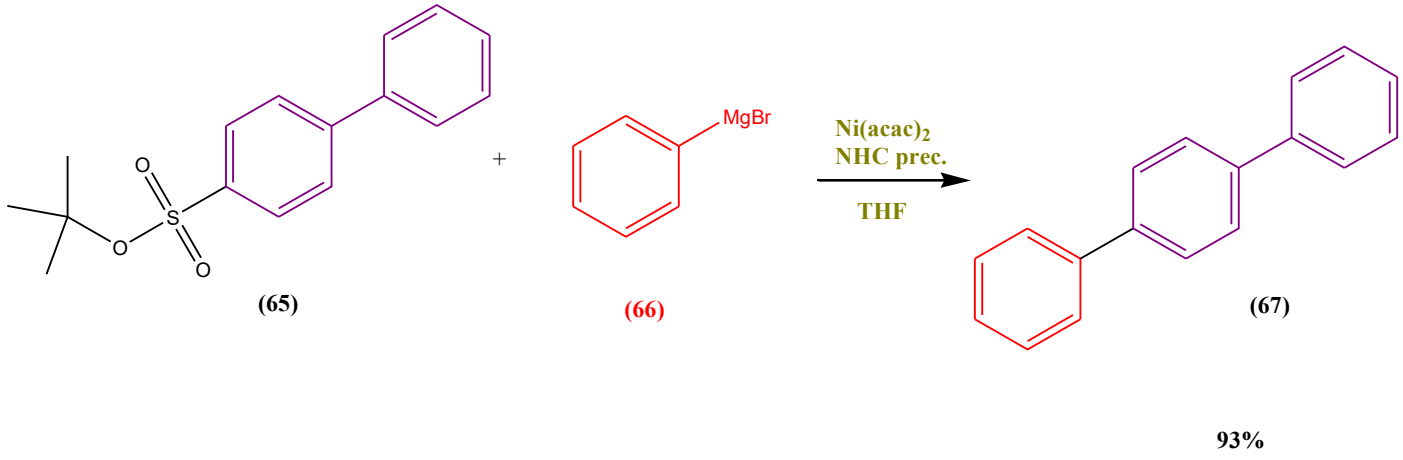
R' = 4-^{t}Bu; 4-Et; 2-Et,

Scheme 2.20. Reactions of neopentyl arenesulfonate with differently substituted Grignard reagents.

Park further expanded the study of arylsulfonates as electrophilic coupling partners to investigating the selectivity of the substituents. They conducted reactions of phenyl-4-methyl benzenesulfonate (62) and Grignard reagents (63) under the Ni-catalyst to construct biaryls (64) (Scheme 2.21). In this study, a competition between the C-S and C-O bond cleavage was observed and this was due to the reduced selectivity of the electron donating substituents on the Grignard reagents and in turn yielding a mixture of biaryls. In attempt to reduce the competition between the C-S and the C-O bond cleavages, they discovered that when tert-butyl-(1,1-biphenyl)-4-sulfonate (65) was reacted with a grignard reagent (66) in $Ni(acac)_2$ catalytic conditions it yielded the desired product (67) in excellent yields (Scheme 2.22).[53]



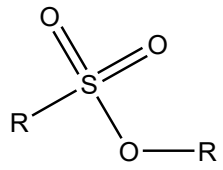
Scheme 2.21. Reaction showing the competition between the C-S and C-O bond cleavages.



Scheme 2.22. Reaction showing selective coupling for the reactions of sulfonates

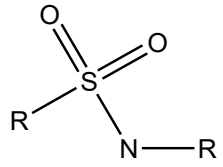
2.3. AIMS OF THE PROJECT

With research having explored only the S-O (Figure 2.2.) and the S-N (Figure 2.3) bond cleavages in transition-metal catalyzed reactions, to our knowledge the S-S bond cleavage has not been explored for any electrophilic coupling partners. Therefore, the overarching aim of this study is to develop procedures that provide the formation of new C-C bonds by taking advantage of the S-S bond of thiosulfonates. Thiosulfonates will be used as electrophilic coupling partners in the cross-coupling reactions coupled with Grignard and organoboron reagents as nucleophilic partners. Thiosulfonates in this study are expected to react under optimum conditions to produce biaryls with minimum production of byproducts.



R = Alkyl, Aryl

Figure 2.2. Arenesulfonate compounds (S-O bond cleavage)



R = Alkyl, Aryl

Figure 2.3. Sulfonylhydrazines (S-N bond cleavage)

2.3.1. Objectives

The first study of this project will see the synthesis of differently substituted, unsymmetrical benzene thiousulfonates from disulfides. Symmetrical and unsymmetrical benzene thiosulfonates (Figure 2.4) will also be synthesized through direct reduction. Product confirmation will be done through the analysis of ^{1}H, ^{13}C Nuclear Magnetic Resonance, Mass spectroscopy and melting point technique.

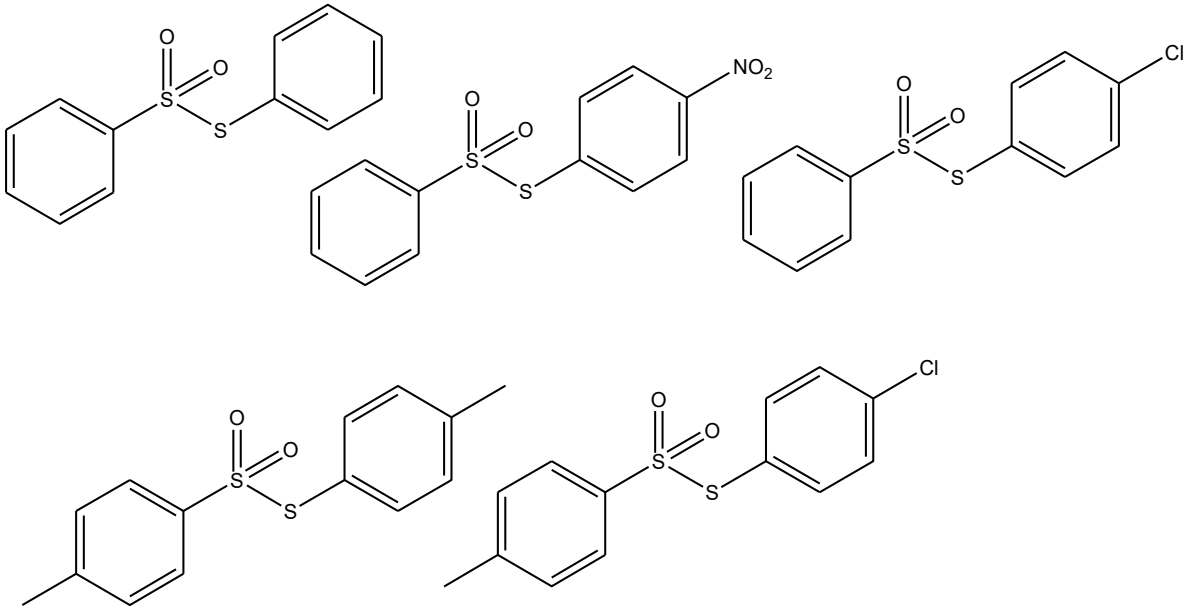


Figure 2.4. Symmetrical and Unsymmetrical Benzene Thiosulfonate

With different *S*-arylthiosulfonates in hand, their reactivity as electrophilic coupling partners in transition metal catalyzed C-C bond forming cross-coupling reactions, namely: Kumada-Corriu and Liebeskind-Srogl in an attempt to expand the scope of electrophilic coupling partners in organic synthesis portal will be investigated.

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CHAPTER THREE

RESULTS AND DISCUSSION

Transition-metal-catalyzed cross-coupling reactions have been demonstrated as useful and powerful methodologies in the construction of new C-C and C-heteroatom bonds in modern organic synthesis.[1,2] Traditionally relying on organohalides and pseudohalides as electrophilic coupling partners, cross-coupling reactions of organohalides and pseudohalides have been well developed and documented proceeding *via* the C-X (X = Br, Cl and I) and C-O bond cleavage respectively.[3] Although this is the case, reactions of organohalides have been shown to be disadvantageous as they produce corrosive halogen salts.

Over the years, new methodologies making use of alternative electrophilic coupling partners have been developed due to a high demand in diversifying compound structures.[4] Although the cross-coupling reactions of organosulfur compounds (desulfitative reactions) as electrophiles have often been overlooked in transition-metal catalyzed reactions, these compounds have been found as attractive alternatives to the traditionally used organohalides[5] and this is because of their inexpensive nature and availability.[6]

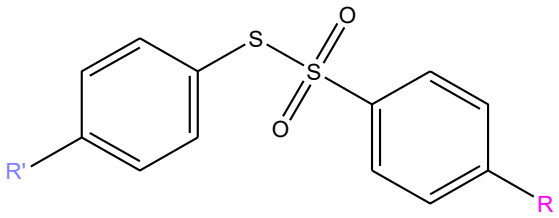
In all of the desulfitative cross-coupling reactions, sulfonyl chlorides (S-Cl bond cleavage) have received most of the attention as electrophilic coupling partners.[6] Even though other electrophiles such as sulfonamides (Scheme 3.1.)[7] and aresulfonates (Scheme 3.2.)[8] proceeding *via* S-N and S-O bond cleavages, respectively have been reported in literature, not much effort has been put in popularizing these compounds as electrophilic coupling partners (Figure 3.1.).

R = alkyl, Aryl

Sulfonate **Sulfonamide**

Figure 3.1. Organosulfur compounds

Due to a lack of applications reporting on the S-S bond cleavages in cross-coupling reactions, the aim of the dissertation was to expand the scope by investigating the electrophilic nature of phenyl thiosulfonates as coupling partners. To our knowledge, reactions of thiosulfonates (S-S bond cleavage) as electrophilic coupling partners in the transition-metal catalyzed reactions have not yet been reported making this a novel study. Herein, we report the cross-coupling reactions of thiosulfonates (Figure 3.2.) with boronic acids and Grignard reagents towards the synthesis of biaryls.

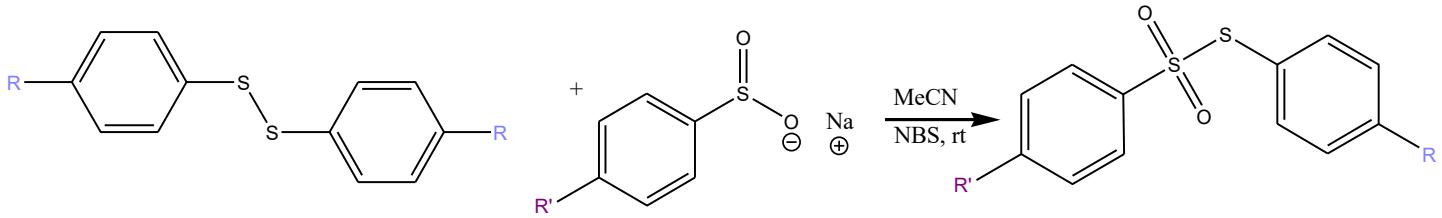


R = H, Me, Cl, OMe
R' = H, Me, Cl, OMe

Figure 3.2. Arylthiosulfonate

3.1. SYNTHESIS OF STARTING MATERIALS

Before commencing our coupling studies to utilize thiosulfonates as electrophilic coupling partners, unsymmetrical arylthiosulfonates were synthesized from disulfides (Scheme 3.1.). To achieve this, we had to find the best reaction conditions to synthesize disulfides.



R = H, Me, Cl, NO_2
R' = H, Me

Scheme 3.1. General scheme for the synthesis of arylthiosulfonates from disulfides

3.1.1. Synthesis of Disulfides

Disulfides are of vital importance in organic chemistry and synthesis as they are versatile reagents in the synthesis of several compounds (including thiosulfonates which are of interest in this project) and partake in important roles in both chemical and biological procedures.[9] Thus far, the most efficient method for the synthesis of disulfides is the dimerization of thiols[10] through oxidation. The method is attractive as thiols are easy to prepare and are widely available.[11]

Many procedures documenting the oxidation of thiols to their corresponding disulfides have been reported and they make use of reagents such as halogens[12], permanganates[13], hydrogen peroxide[14], sodium chlorite[15], oxides of transition metals[16], ferric chloride[17], salts of cerium (IV)[10], etc. (Scheme 3.2.). However, most procedures that make use of the above-mentioned reagents suffer from drawbacks as most of these

reagents are either expensive, strong acids or strong oxidizing agents which makes them hazardous.

R = alkyl, aryl

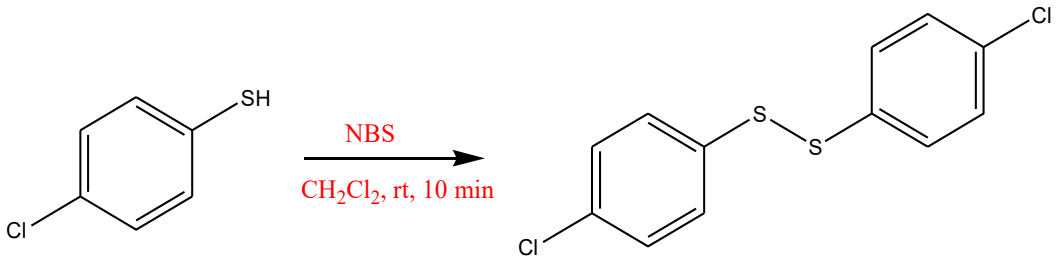
Reagent = Acids, Oxidizing agents

Scheme 3.2. General Scheme for the synthesis of Disulfides

To combat this problem, Ghafuri and Hasheni reported an economical, time-efficient, catalyst-free oxidation of thiols using NBS. NBS as an oxidizing agent is attractive as it is a mild oxidant, less expensive, less hazardous and the succinimide byproduct can be regenerated back to NBS.[11] To synthesize disulfides, the above method proposed by Ghafuri[11] was adopted in this report.

3.1.1.1. Synthesis of *bis*(4-chlorophenyl) disulfide (70)

Following the general procedure reported in literature[11], a DCM solution of 4-chloro-thiophenol (68) and NBS (69) was stirred for 10 minutes at room temperature. This reaction furnished a cream white powder of *bis*(4-chlorophenyl) disulfide (70) obtained in an 83% yield (Scheme 3.3.).



(68) **(70)**

Scheme 3.3. Synthesis of *bis*(4-chlorophenyl) disulfide (70)

^{1}H NMR (Figure 3.3) was run to confirm the product (70) formation. The ^{1}H NMR spectrum shows a doublet that is residing further downfield at a frequency range of 7.41 – 7.45 ppm, integrating for 4 protons. The peak with a chemical shift of range of 7.41 – 7.45 ppm is consistent with the protons located closer to the chlorine atom since these are experiencing a higher deshielding effect of the more electronegative chlorine atom. Another doublet in the aromatic region with chemical shift range of 7.29 – 7.31 ppm integrated for 4 protons. The peak is consistent with the protons located to lesser electronegative sulfur atom. The total integration for the ^{1}H NMR is 8 protons, this is consistent with the total number of protons for compound 8, with each benzene ring possessing 4 identical protons.

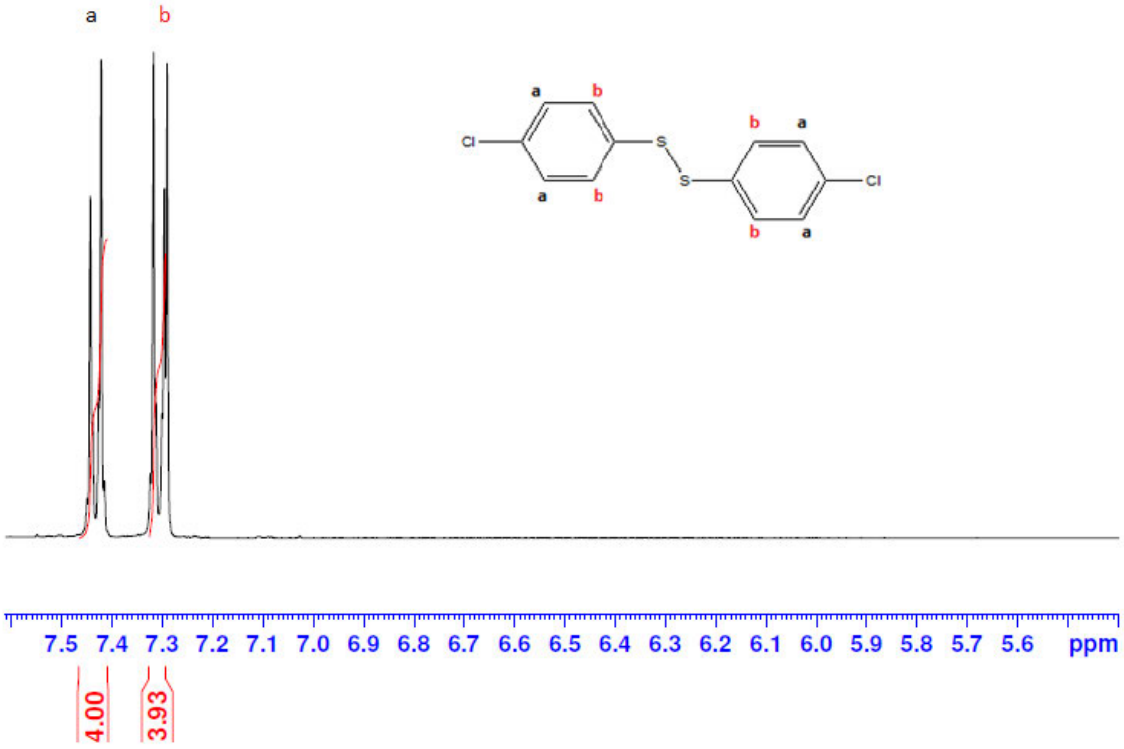


Figure 3.3. ^{1}H NMR Spectrum of *bis*(4-chlorophenyl) disulfide (70)

The ^{13}C NMR spectrum (Figure 3.4.) was also obtained in $CDCl_3$ confirming the production of compound. From the spectrum, 4 carbon peaks can be seen, and this is due to the symmetry of the compound. The peaks located further downfield on the spectrum are those of the carbons experiencing the most deshielding effect of the highly electronegative elements in the compound (i.e. Sulfur and Chlorine). All the peaks in the spectrum correlate with those expected for the compound, further confirming the production of the compound.

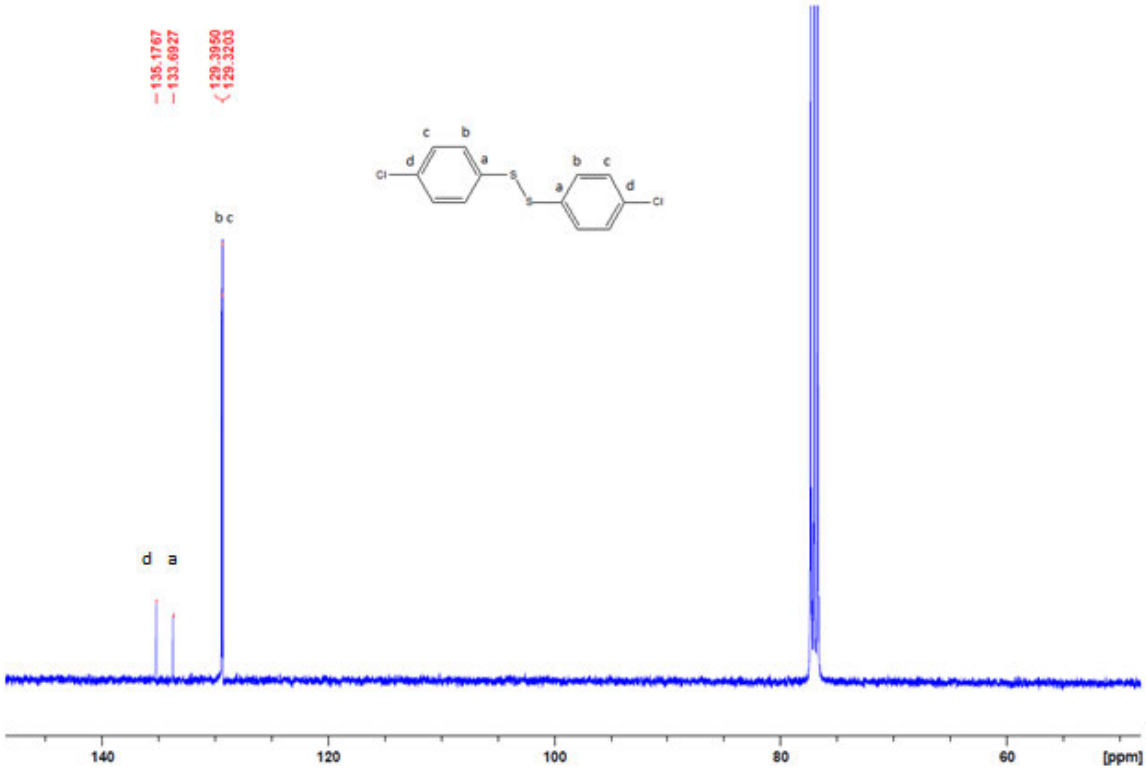


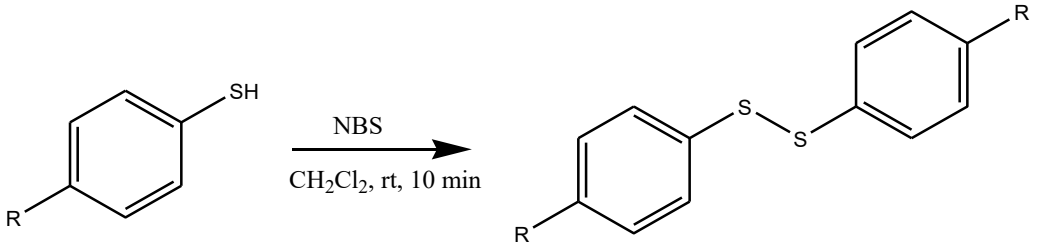
Figure 3.4. ^{13}C NMR Spectrum of *bis*(4-chlorophenyl) disulfide (70)

To further confirm the production of *bis*(4-chlorophenyl) disulfide (70), the melting point technique was used which gave a melting point range of 67.6 ˚C – 69.2 ˚C which is in correlation with the reference value of 68 ˚C. From GC-MS results, a peak of 286 [M^+]

was obtained which correlates with the mass of the compound, confirming the formation of the desired product.

3.1.1.2. Synthesis of Differently Substituted Disulfides

The disulfides reported in Table 3.1. were all synthesized following the procedure reported by Ghafuri and Hasheri[11] (Scheme 3.4.). Table 3.1. summarizes the results obtained when differently substituted thiols were reacted in the presence of NBS.

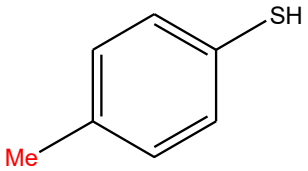
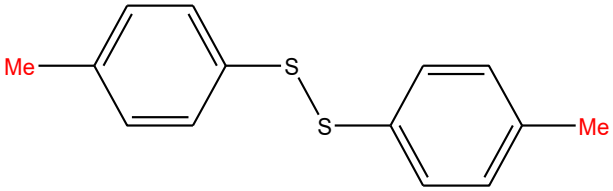
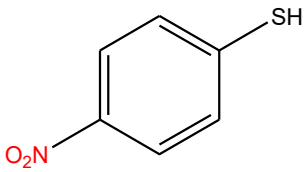
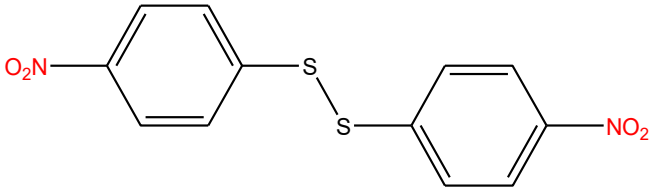
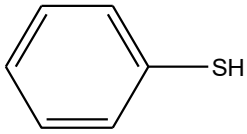
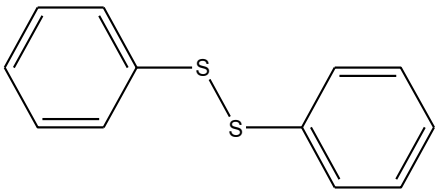
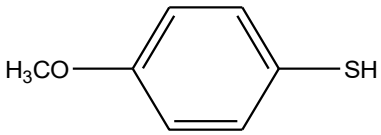
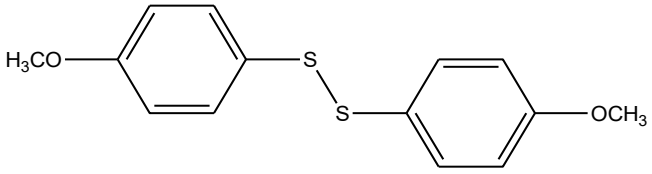


R = NO_2, OMe, Me, H

Scheme 3.4. Synthesis of disulfides

Table 3.1. Oxidation of Differently substituted thiols to Furnish Disulfides

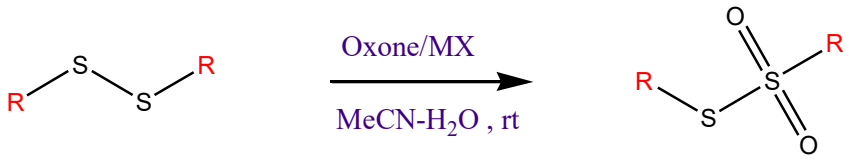
Entry	Starting Material (Thiol)	Product (Disulfide)	Yield %

1.	 **71**	 **72**	70
2.	 **73**	 **74**	79
3.	 **75**	 **76**	75
4.	 **77**	 **78**	70

The products reported above were all synthesized successfully following a previously reported procedure.[11] All the reactions were run at room temperature in the presence of NBS and the reactions progresses monitored by TLC. To confirm the formation of products the melting point technique, ^{1}H NMR and ^{13}C NMR were employed. The melting points of the synthesized products were all in correlation with the literature values (see experimental section). This was the same case with the ^{1}H and ^{13}C NMR spectra that were obtained which were consistent with the expected peaks and integration. GC-MS was also run which further confirmed the successful synthesis of the disulfides.

3.1.2. Synthesis of Phenyl Thiosulfonates

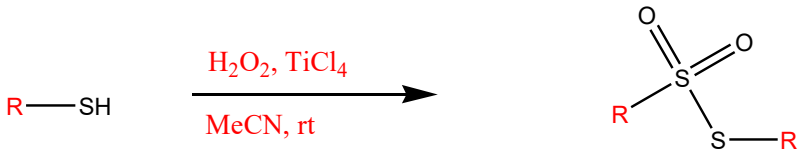
Thiosulfonates are organic compounds with a general formula R-SO_2S-R' (R and R' = alkyl or aryl groups) possessing a strong sulfenylating ability.[18] Thiosulfonates are important and have demonstrated their usefulness in biological systems for their fungicidal and antimicrobial activities, wide industrial applications and organic synthesis.[19, 20] Generally, thiosulfonates are prepared through direct oxidation of disulfides (Scheme 3.5.)[20] or thiols (scheme 3.6.)[21] but several other methods have been reported for their preparation.[22]



R = Alkyl, Aryl

MX = KBr, KCl, NaBr, NaCl

Scheme 3.5. Oxidation of disulfides towards the synthesis of thiosulfonates



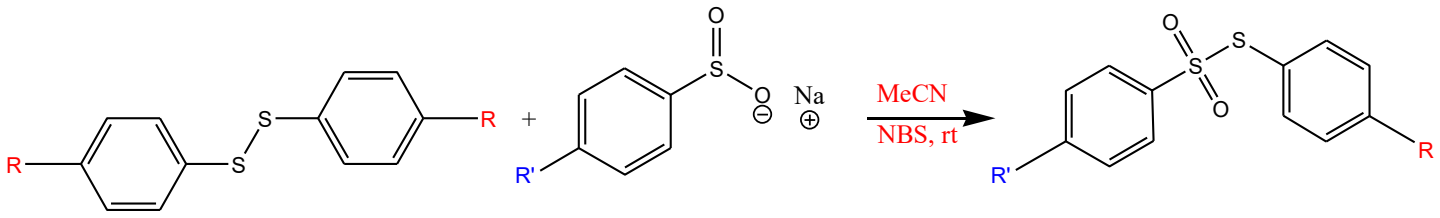
R = Alkyl, Aryl

Scheme 3.6. Direct oxidation of thiols towards the synthesis of thiosulfonates

Herein, we report the synthesis of symmetrical and unsymmetrical thiosulfonates which in turn were used to synthesize biaryls.

3.1.2.1. Synthesis of Unsymmetrical Phenylthiosulfonates

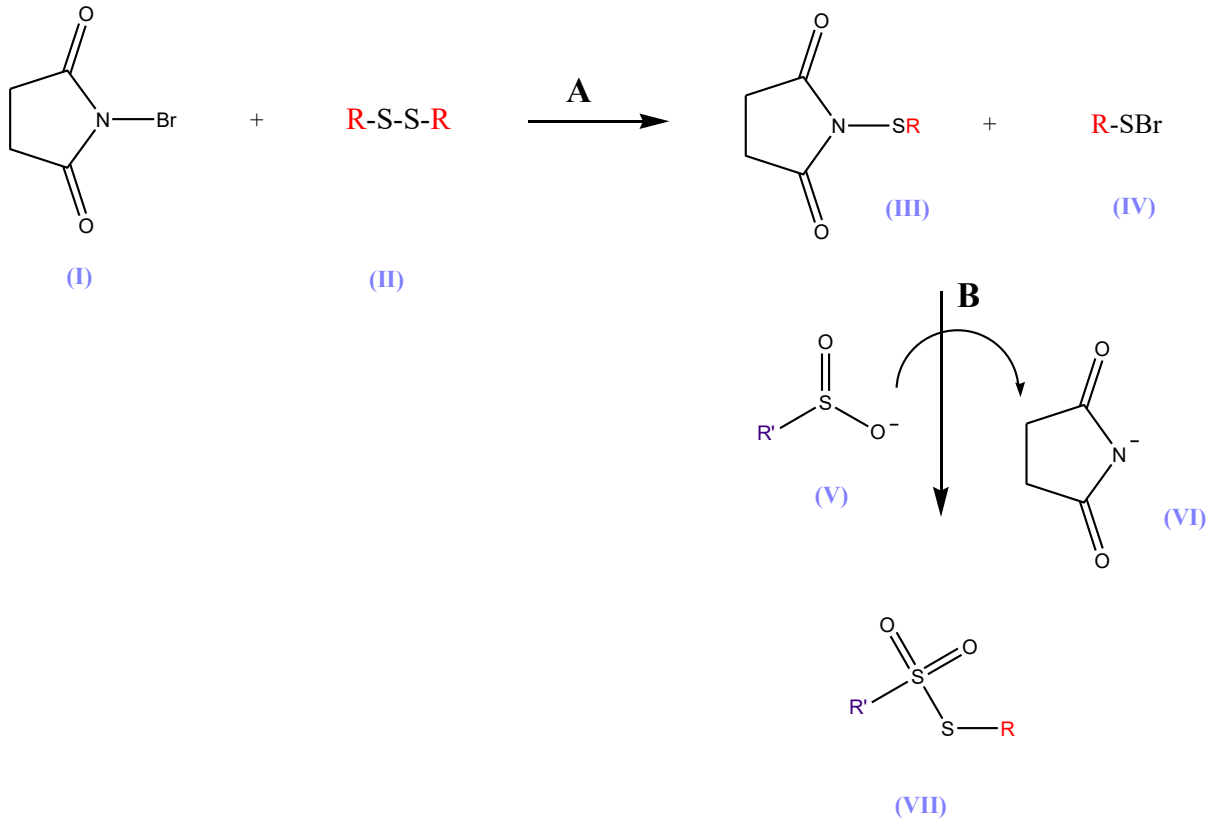
Since most transformations rely on direct oxidation of disulfides[20] and thiols[21] in order to furnish thiosulfonates, they are only able to afford symmetrical thiosulfonates. In an effort to extend the scope of the synthesis of unsymmetrical thiosulfonates, Liang and Liu[22] reported a different strategy through the sulfenylation of sulfinic acids (Scheme 3.7.).



R = H, Me, Cl, NO_2
R' = H, Me

Scheme 3.7. General scheme for the synthesis of arylthiosulfonates from disulfides

To explain in detail, the occurrence of the reaction, the authors[22] proposed a mechanism (Scheme 3.8).



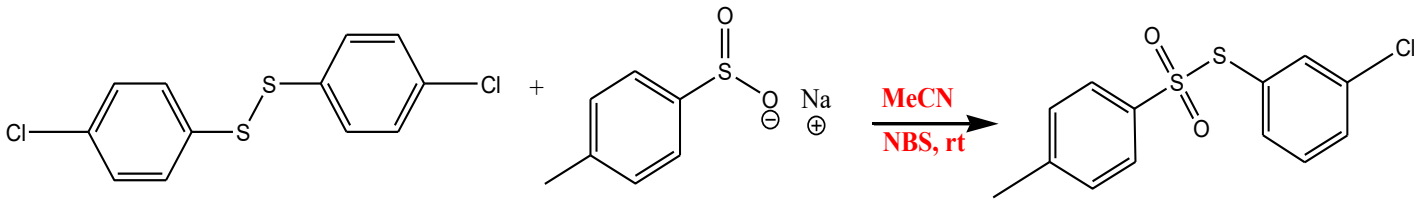
Scheme 3.8. Mechanism for the sulfenylation of sulfinic acids

On the first step of the mechanism (A), the NBS (I) promotes the S-S bond cleavage of the disulfide molecule (II) affording a reactive N-(organothio) succinimide (III). The second step (B) shows the sulfinate (V) undergoing facile sulfenylation with the reactive N-(organothio) succinimide (III), furnishing the desired thiosulfonate (VII).[22]

With the disulfides at hand, the next step of the project was to synthesize the desired unsymmetrical arylthiosulfonates which were expected to act as electrophilic coupling partners in the synthesis of biaryl products. Having read on the atom-economic procedure proposed by Liang[22], their method was adopted to synthesize unsymmetrical thiosulfonates in this study.

3.1.2.1.1. Synthesis of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate (80)

S-4-chlorophenyl-4-methylbenzenesulfonothioate (80) was synthesized following a previously reported procedure by Liang and Liu.[22] A mixture of 1,2-bis(4-chlorophenyl) disulfane (70) with sodium *p*-toluenesulfinate (79) in CH_3CN was stirred at room temperature overnight in the presence of NBS. The reaction afforded the unsymmetrical product 10 as a white crystalline solid in a 73% yield (Scheme 3.9.)



(70) (79) (80)

Scheme 3.9. Synthesis of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate (80)

To confirm the formation of the desired product (80), a ^{1}H NMR spectrum (Figure 3.5.) was obtained and analyzed. The spectrum below was found consistent with the production of compound 80. From the spectrum, a singlet residing further upfield in the non-aromatic region is observed, integrating for 3 protons. This peak is assigned to the methyl group attached in the *para* position of the phenyl ring. The NMR spectrum below integrated for 9 protons in the aromatic region, consistent with the anticipated compound structure.

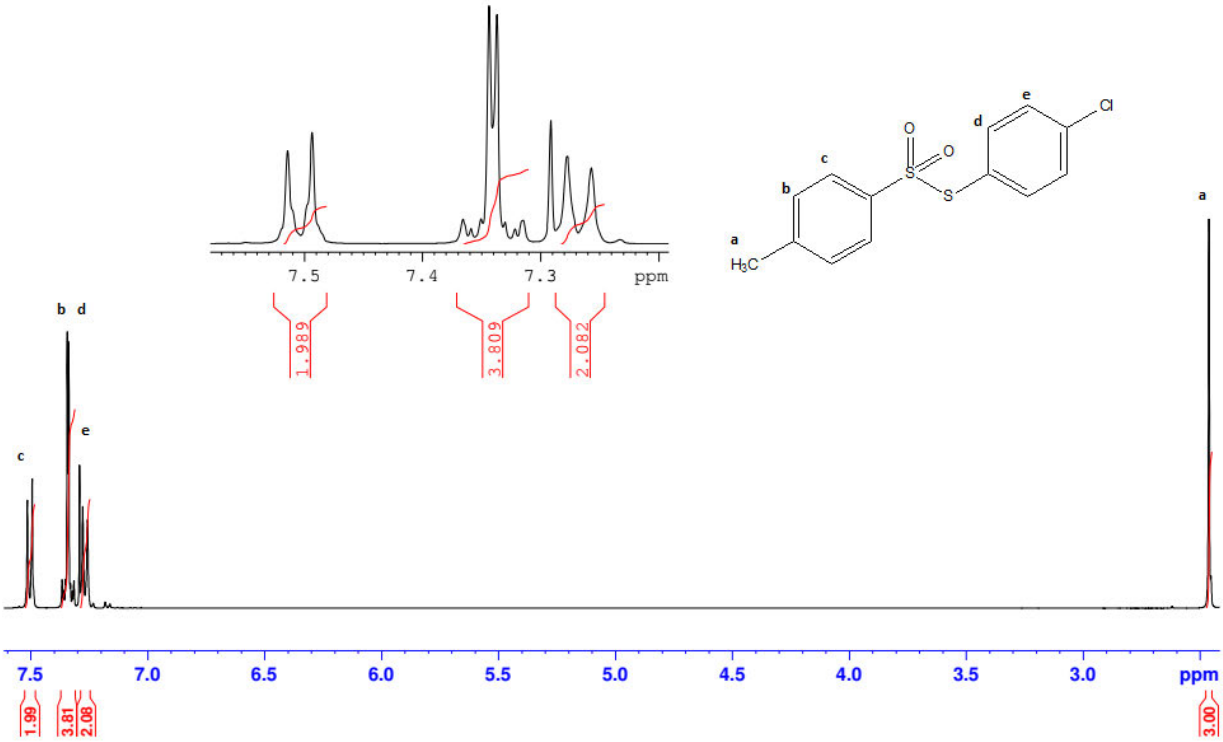


Figure 3.5. ^{1}H NMR spectrum of *S*-4-chlorophenyl 4-methylbenzenesulfonothioate (80)

^{13}C NMR spectrum of compound 80 (Figure 3.6.) was also obtained which was in agreement with the ^{1}H NMR spectrum, further confirming the successful production of 4-

methylbenzenesulfonothioate. 8 peaks are present in the aromatic region, consistent with the expected number of peaks (which include 4 peaks containing two chemically equivalent carbons). A single peak located further upfield, resonating at 30.84 ppm can be seen in the spectrum and this is in correlation with the methyl carbon (e) of the compound. Carbons a and d are located more downfield in the aromatic zone of the spectrum and this is due to the EWG (SO_2) which withdraws electrons through resonance, leading to a decreased electron density on the *para*-positions of the phenyl ring. This effect is opposite to what the para-positioned carbon I experiences as this peak is located more upfield due to EDG (sulfur-atom) which donates electrons through resonance shielding the carbon in the *para*-position.

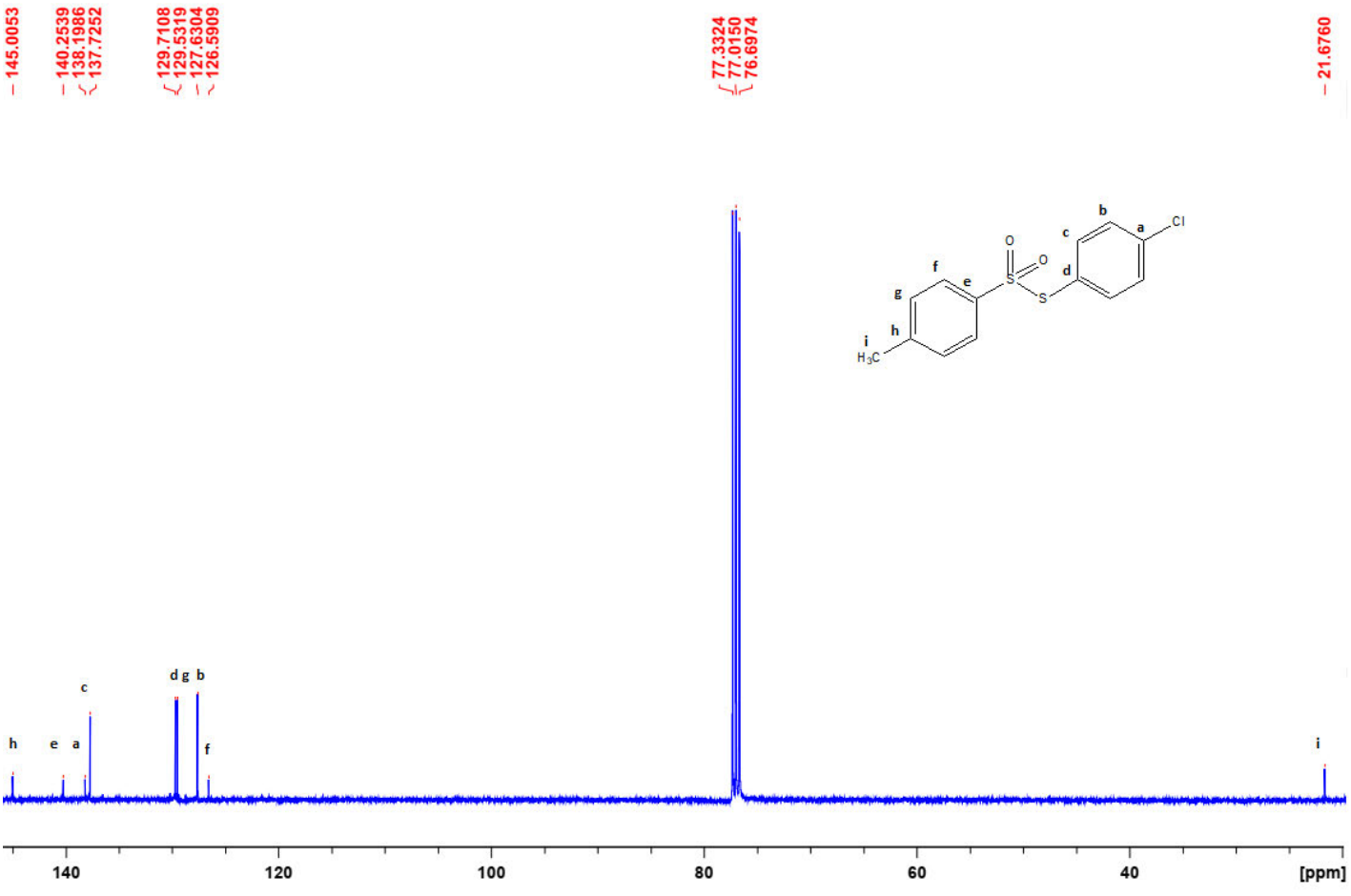
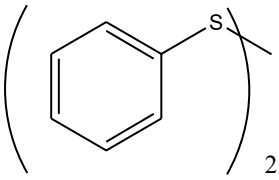
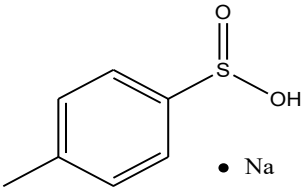
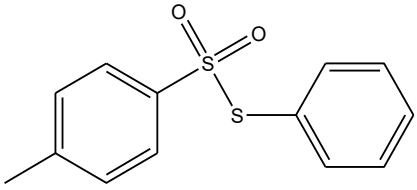
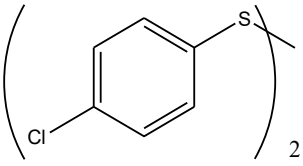
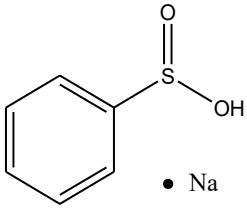
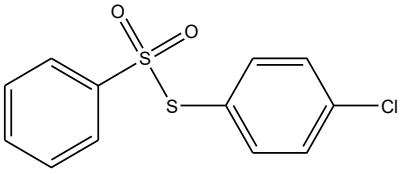


Figure 3.6. ^{13}C NMR of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate (80)

In attempts to further confirm the successful synthesis of *S*-phenyl 4-methylbenzenesulfonothioate; melting point, IR spectroscopy and a mass spectrum were obtained. From the melting point technique, a melting point range of 54.0 – 55.6 ^{o}C which is consistent with the literature value of 54 ^{o}C[22]. On the IR spectrum, an appearance of the S=O stretch peak is visible residing at a frequency of 1313.40 cm^{-1}.

Table 3.2. Synthesis of Unsymmetrical Arylthiosulfonates

entry	Starting Material (Disulfide)	Starting material (Sulfinate)	Product (Thiosulfonate)	% Yield
1.	 **72**	 **79**	 **81**	71
2.	 **70**	 **82**	 **83**	70

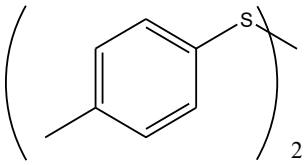
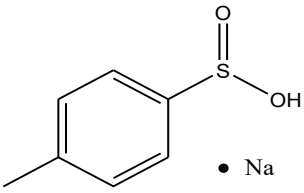
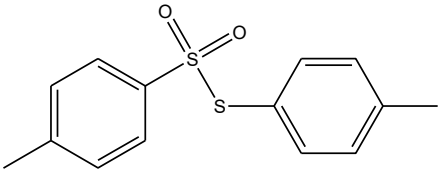
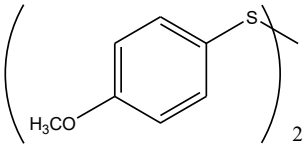
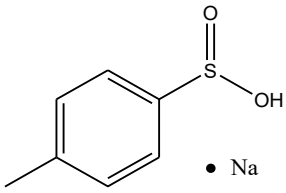
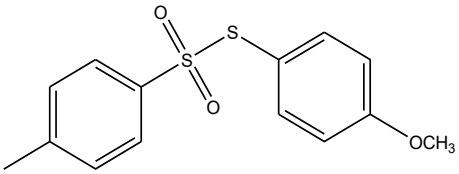
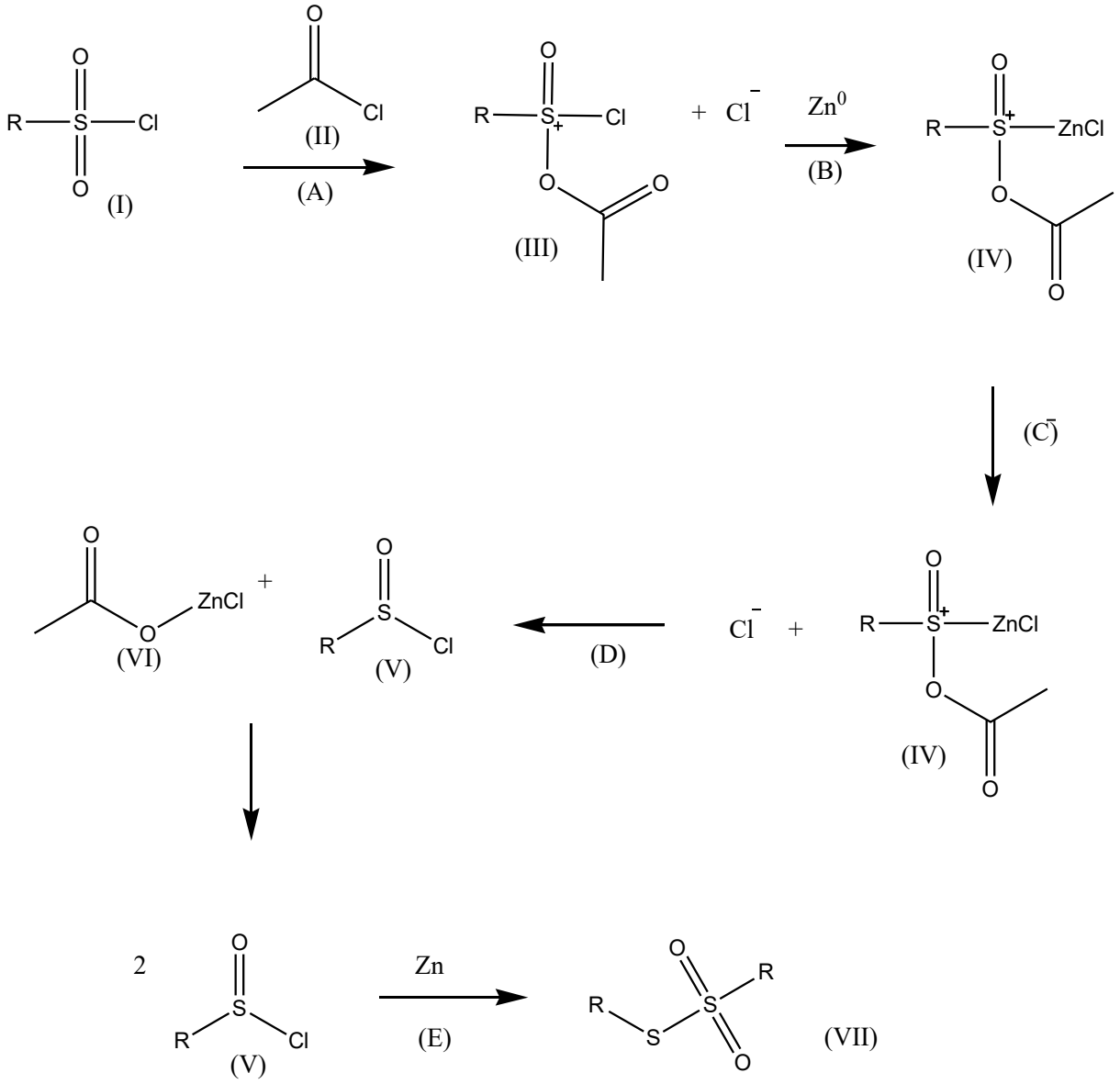
3.	 **72**	 **79**	 **84**	70
4.	 **78**	 **79**	 **85**	69

Table 3.2. summarizes the results obtained following a procedure previously reported by Liang and Liu.[22] The above NBS-promoted reactions were run in MeCN at room temperature, overnight. The reactions progresses were monitored by TLC with the desired products furnished in impressive yields. To confirm the production of the desired products, ^{1}H NMR, ^{13}C NMR, GC-MS and IR spectra were run and obtained, proving the successful synthesis.

3.1.2.2. Synthesis of Symmetrical Phenyl Thiosulfonates

To synthesize symmetrical thiosulfonates, we adopted a method which was previously reported by Chelma and Karoyan[23] which involves the reduction of sulfonyl chloride as the only starting material. Not only is the method attractive because of the use of the commercially available and cheap sulfonyl chloride, but its use of sulfonyl chloride as the

only starting material also makes the reaction economical. To gain full understanding on how the reaction proceeds, Chemla[23] proposed a mechanism to explain the formation of thiosulfonate from sulfonyl chloride (Scheme 3.10.).



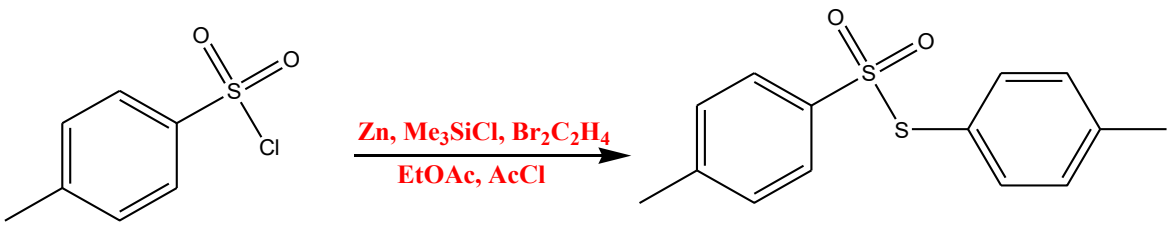
Scheme 3.10. Mechanism explaining the reduction of sulfonyl chloride.

The first step of the mechanism (A) starts with the activation of sulfonyl chloride (I) with acyl chloride (II) to form the oxosulfonium ion intermediate (III). Complex (V) is formed in the second step (B) when the intermediate (III) reacts with zinc dust. Step C is the nucleophilic attack by the negatively charged chlorine ion to the positively charged sulfur atom of the complex (IV) which forms zinc salt (VI) along with sulfinic chloride (V). On the final step (E), 2 molecules of sulfinic chloride (V) are reduced by zinc dust, affording the desired thiosulfonate product (VII).[23]

With a concrete understanding of how the reaction mechanism works and feeling motivated by the simplicity of the reaction, we were confident to begin our reactions.

3.1.2.2.1. Synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothioate (84)

The successful synthesis of S-p-tolyl-4-methylbenzenesulfonothioate (84) was conducted following the procedure reported by Chemla and Karayan.[23] Zinc dust, dibromoethane and trimethylsilane were heated to reflux in ethyl acetate. Tolylbenzenesulfonyl chloride (86) was later added, followed by a dropwise addition of acetyl chloride. The reaction afforded product 13 as a white crystalline solid in excellent yields of 82% (Scheme 3.11.).



(86) (84)

Scheme 3.11. Synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothioate (84)

In order to confirm if the desired product (84) had been successfully synthesized, a melting point technique was first used and gave a melting point range of 42.8 – 44.7 ^{o}C which is consistent with the literature value of 44 ^{o}C[23]. The IR spectrum showed the presence of the S=O bond stretch resonating at 1318.84 cm^{-1}. Results from MS confirmed a 278 [M^{+}] (55) molecular peak, consistent with the molecular mass of the product.

In attempts to further confirm the successful synthesis of the desired product (84), ^{1}H and ^{13}C NMR spectra of the white crystaline solid were acquired. The number of signals obtained from the ^{1}H NMR spectrum were consistent with the protons from the compound structure. Two upfield singlet peaks, integrating for 3 protons can be seen on the spectrum and belonging to the methyl protons (c and f) of the structure.

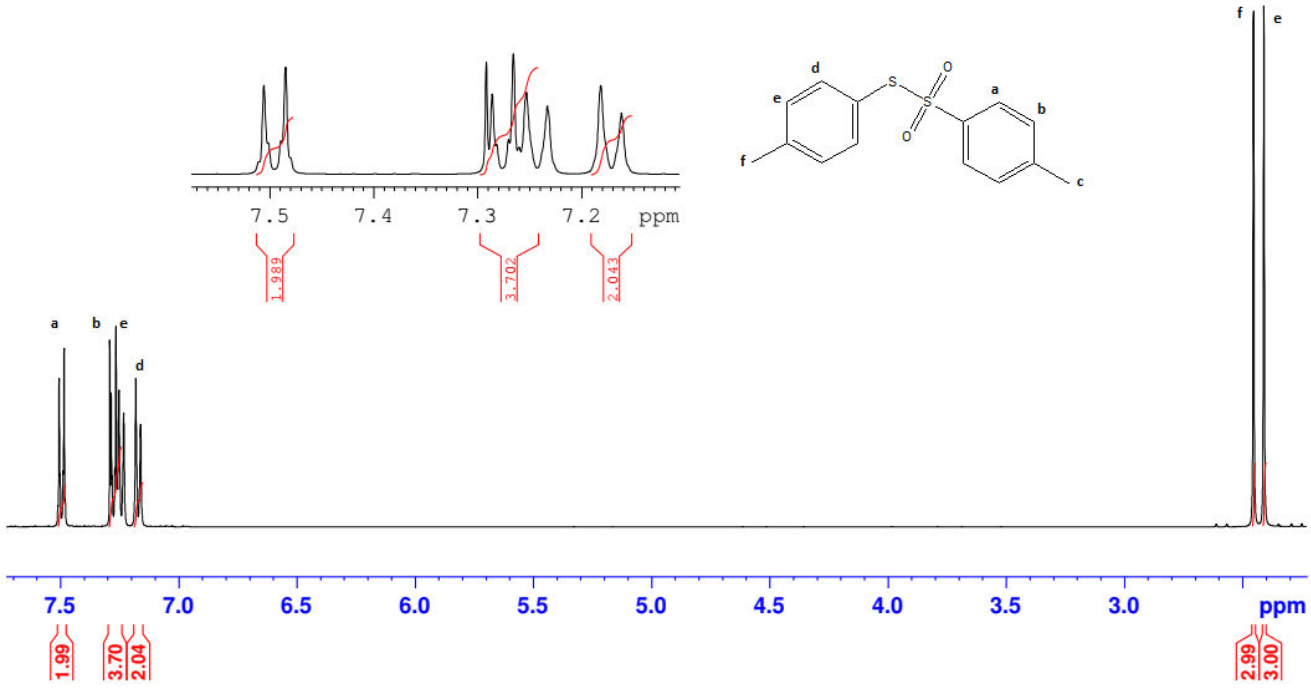


Figure 3.7. ^{1}H NMR of *S*-*p*-tolyl-4-methylbenzenesulfonothiate (84)

The ^{13}C NMR spectrum of the compound was also obtained (Figure 3.8.). Two peaks residing further upfield in the non-aromatic region of the spectrum correspond to the methyl carbons (j and e). 8 peaks are in the aromatic region of the spectrum, with 4 of them integrating for two chemically equivalent carbons each which further confirms the successful synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothiate.

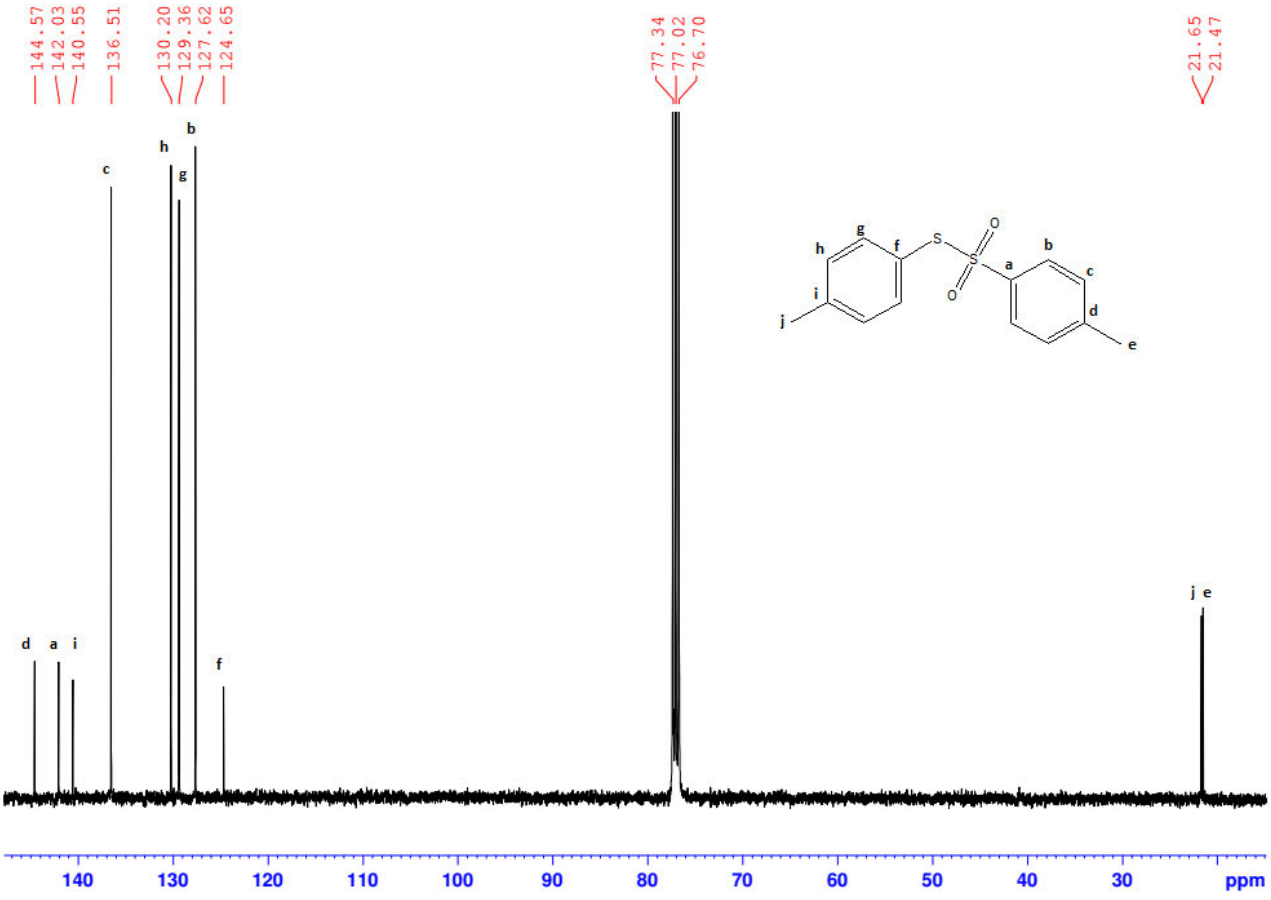
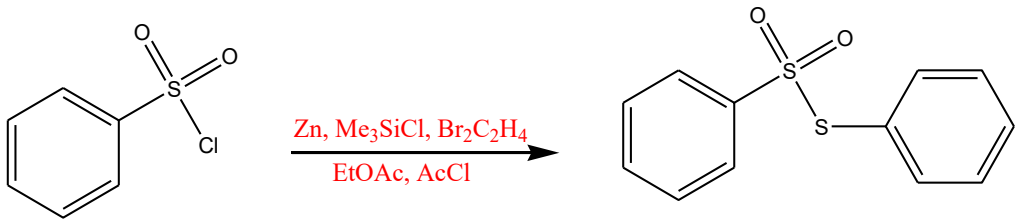


Figure 3.8. ^{13}C NMR of *S*-*p*-tolyl-4-methylbenzenesulfonothiate (84)

3.1.2.2.2. Synthesis of *S*-phenyl benzenesulfonothioate (88)

Following the previously reported synthetic procedure by Chemla and Karoyan[23], a mixture of zinc dust, dibromoethane and trimethylchlorosilane in ethyl acetate was heated

to reflux followed by the addition of benzenesulfonyl chloride (87) followed by the dropwise addition of acetyl chloride. The reaction afforded the product (88) in high yields of 80% as a yellow oil (Scheme 3.12.).



(87) (88)

Scheme 3.12. Synthesis of *S*-phenyl benzenesulfonothioate (88)

TLC was first used to confirm the disappearance of the starting material and after the stipulated time above, the starting material was no more. Melting point technique was used and a melting point range of 38.9 °C – 39.6 °C was obtained, consistent with the melting point of 36 - 53°C[23] reported in literature. From the IR spectrum, an S=O peak resonating at 1309.87 cm^{-1} was obtained, implying the formation of the desired product. Mass spectrometry results confirmed a 250 [M^+] (69) molecular peak which is in line with the molecular mass of the desired product.

Figure 3.9. below is the ^1H NMR spectrum of *S*-phenyl benzenesulfonothioate (88) which was obtained to further confirm the synthesis of the product (88). From the spectrum, only peaks resonating in the aromatic region are present and in total integrating for a total of 10 protons. These number of protons are consistent with the protons present in the structure, therefore further confirming the successful synthesis of product 88.

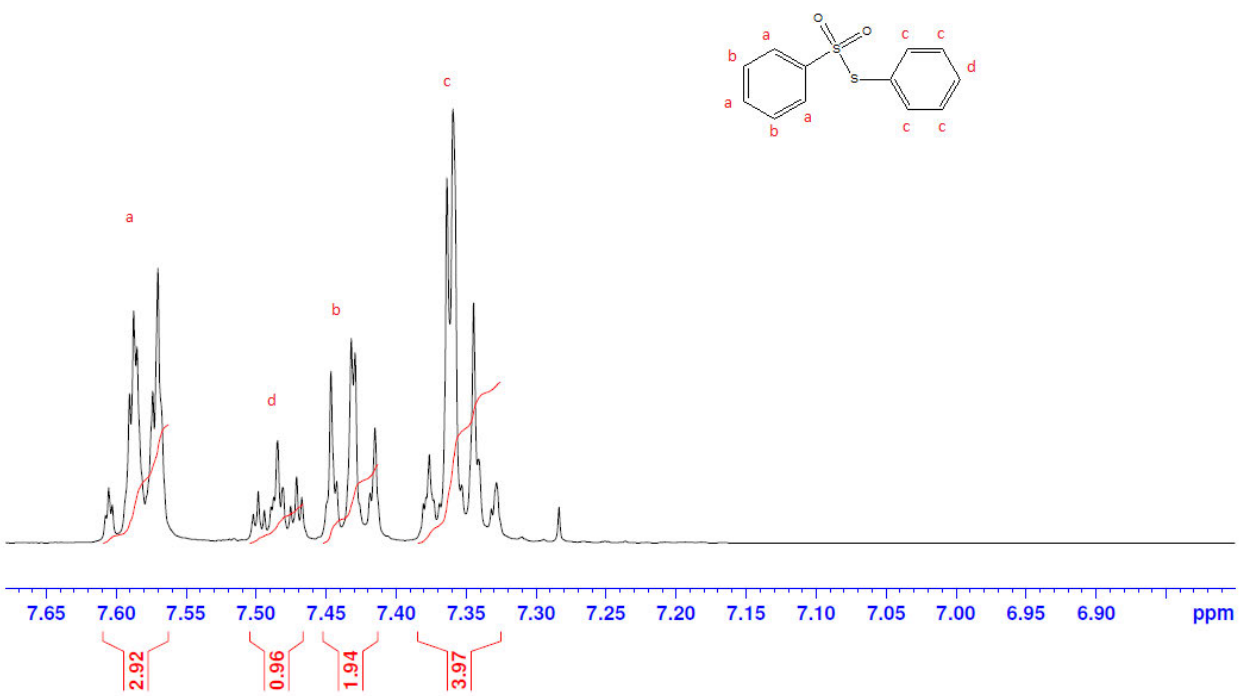
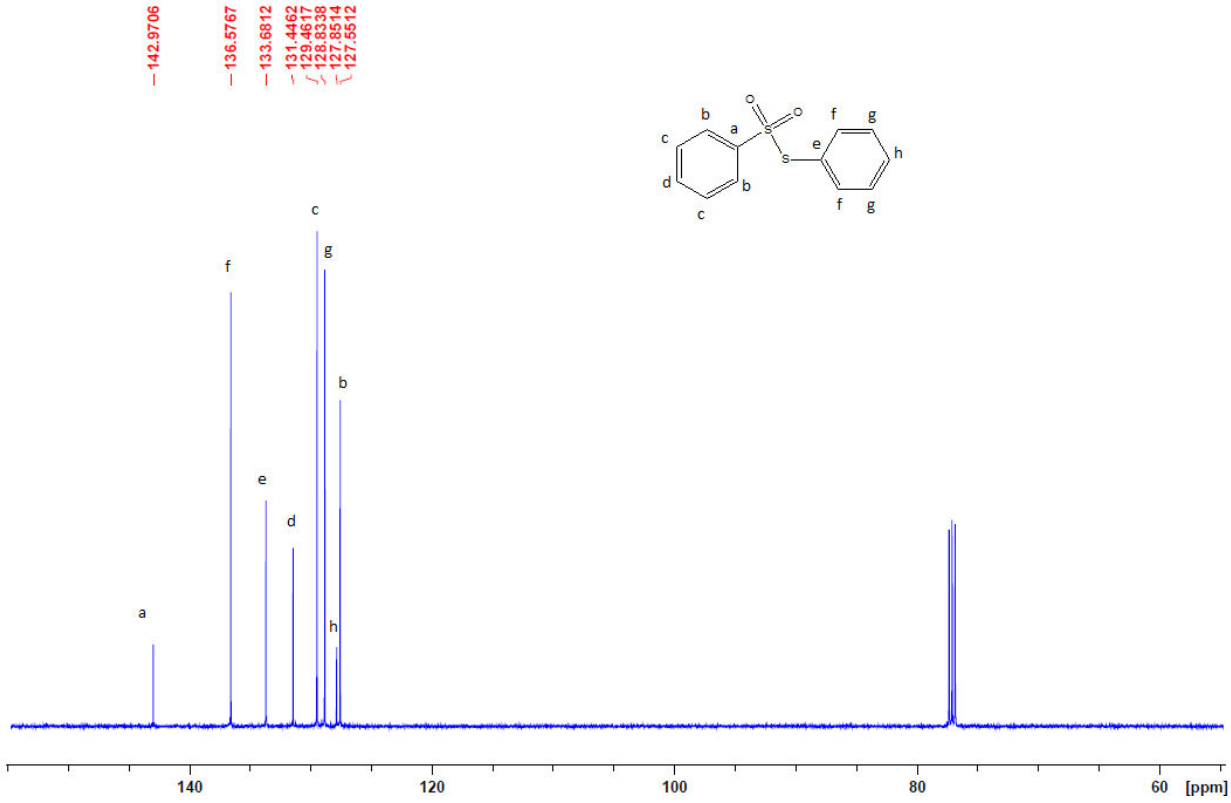


Figure 3.9. ^{1}H NMR of *S*-phenyl benzenethiosulfonate (88)

^{13}C NMR spectrum (Figure 3.10) of product 88 was obtained and was also found to confirm the successful synthesis of the product. From the spectrum, 8 carbon peaks in the aromatic region can be seen, and these are consistent with the carbons of the product structure, including the 4 pairs of chemically equivalent carbons in the structure as shown below.

Figure 3.10. ^{13}C NMR of *S*-phenyl benzenethiosulfonate (88)



3.2. SYNTHESIS OF BIARYLS

In light of the symmetrical and unsymmetrical phenylthiosulfonates at hand, our aim was to synthesize biaryls. The biaryl framework is widespread in its existence and is often found in functional and biologically active compounds.[24,25] The biaryl substructure is highly privileged and is of high importance in a wide range of applications, including liquid crystals for LCD screens[26], agrochemical sector[27] and the pharmaceutical industry[28]; where approximately 4.3% of all known drugs[29] contain the biaryl framework.

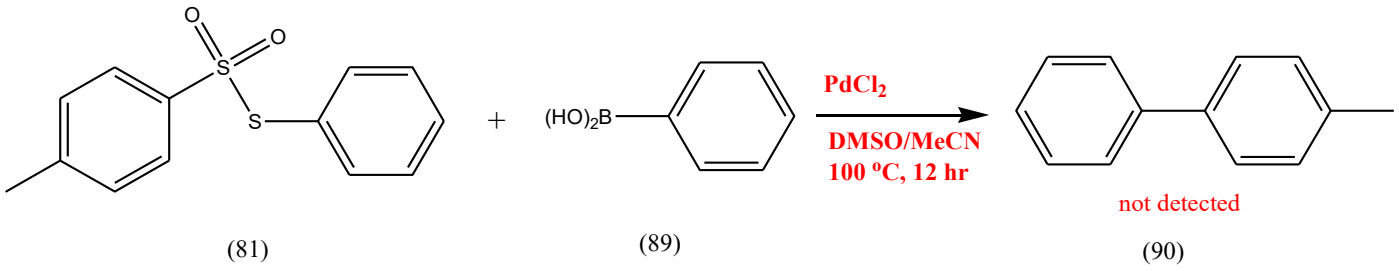
A number of cross-coupling procedures have been reported for the synthesis of biaryls and these include the Suzuki,[30-33] Grignard,[34] Ullmann synthesis[35] and Negishi[36] with most of these often-employing aryl halides. Below, we report an attempted synthesis of biaryls through the coupling thiosulfonates with aryl boronic acids (Liebeskind-Srogl cross-coupling) and aryl magnesium bromides (Kumada-Corriu cross-coupling).

3.2.1. Synthesis of Biaryls Through Coupling of Thiosulfonates and Boronic Acids

In the subsection below, we report the synthesis of biaryls through the coupling of the previously synthesized arylthiosulfonates and arylboronic acids following a Liebeskind-type cross-coupling. The reactions were conducted under different catalytic, temperature and solvent conditions in pursuit of optimum conditions for the synthesis of biaryls.

3.2.1.1. Attempted synthesis of 4-methyl-1,1'-biphenyl (90)

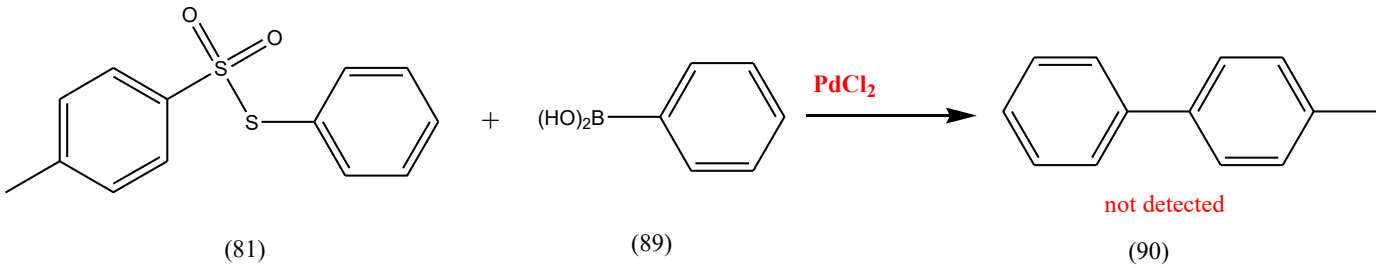
Testing the suitability of *S*-*p*-tolyl-4-methylbenzene sulfonothioate (90) as a potential electrophilic coupling partner in the Liebeskind-Srogl cross-coupling, the thiosulfonate (81) was reacted with arylboronic acid (89) at 100 ^{o}C in the presence of $PdCl_2$ as a catalyst in DMSO/MeCN (50/50). After 2 hours, the reaction progress was monitored by TLC and no product (90) had been formed. The mixture was heated further for 10 hours where to our disappointment, no product had been formed (Scheme 3.13).



Scheme 3.13. $PdCl_2$ catalyzed attempted synthesis of 4-methyl-1,1'-biphenyl (90)

Following the first failed attempt, several other reactions were conducted as summarized by Table 3.3. below.

Table 3.3. Attempted synthesis of 4-methyl-1,1'-biphenyl (90)



(81) (89) (90)

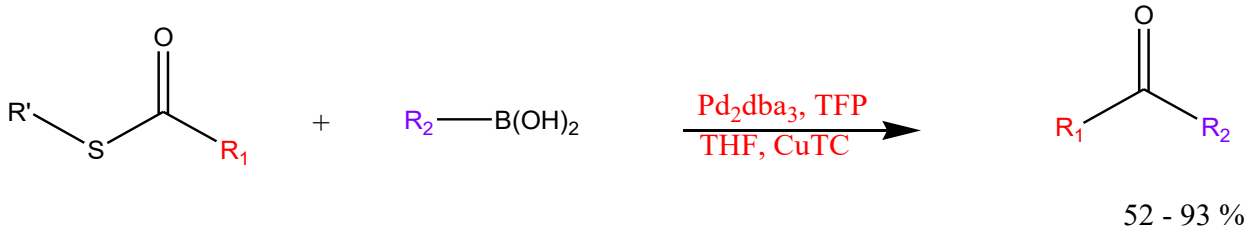
Entry	Solvent	Temperature °C	Reaction Time hr.	Product (90) Yield %
1.	DMSO/MeCN (50/50)	100	24	Not detected
2.	DMSO/THF (50/50)	100	12	Not detected
3.	THF	60	12	Not detected

Still in pursuit of finding the optimum conditions that would be conducive to the production of 4-methyl-1,1'-biphenyl (90), several more reactions followed as reported in table 3.3. Table 3.3. summarizes the results obtained from the reactions of *S*-*p*-tolyl-4-methylbenzene sulfonothioate (81) and arylboronic acid (89) under different solvent conditions and reaction times. From the first entry of the table, the reaction time was increased to 24 hours using the solvent mixture of DMSO/MeCN, but no product (90) was formed. Upon changing the solvent to DMSO/THF (entry 2), a dark residue was obtained but the TLC analysis revealed that our anticipated product had not been formed. When we changed the solvent THF with $PdCl_2$ as the catalyst the reaction was refluxed for 12 hours leading to a formation of a light brown residue and the desired product had not been formed.

The cross-coupling reactions of thiosulfonate as an electrophilic coupling partner in the presence of $PdCl_2$ as a catalyst under Liebeskind-type coupling were unsuccessful. A

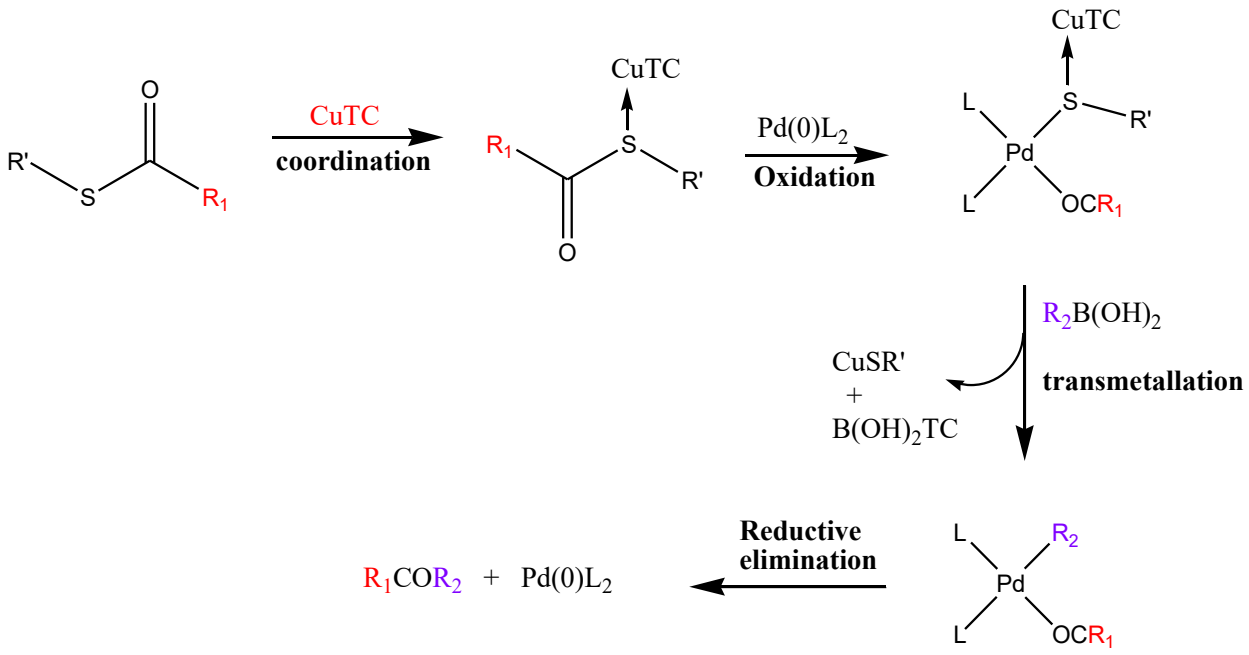
factor that had to be taken into consideration was the solvent and ligand choice. Coordinating solvents and ligands have a negative effect on the outcome of base-free reactions, at times even blocking the occurrence of a reaction.[37]

Given the above information, it was sensible that the reactions ran in acetonitrile did not work out. However, a confusion stood as to why the reactions of THF and DMSO were unsuccessful. These failed attempts were attributed to a second factor, which is the very discriminating nature of the stable C-S bond.[37] To overcome this, on the first reported Liebesking-Srogl cross-coupling reaction, Liebeskind and co-workers stressed on the importance of copper as an additive (Scheme 3.14.). Specifically, in their case, the authors reported that the oxidative addition of CuTC initiated the cross-coupling between the thiol ester and the boronic acid and this is explained in detail by the mechanism they proposed (Scheme 3.15.).[37]



R_1 = alkyl, aryl, octyl
R_2 = alkyl, aryl
R' = alkyl, aryl

Scheme 3.14. First reported Liebeskind-Srogl cross-coupling reaction



Scheme 3.15. Liebeskind-Srogl mechanism

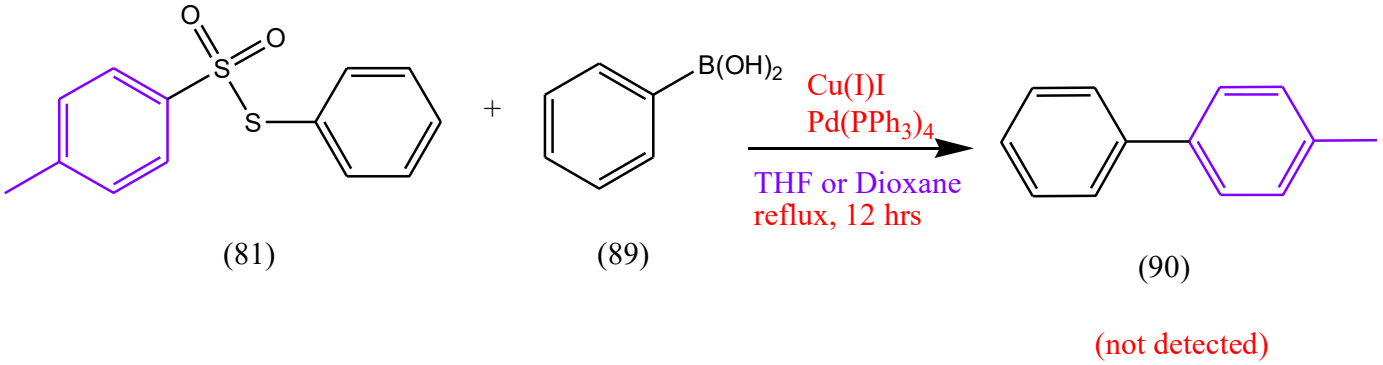
On the transmetallation step of the mechanism, CuTC through its coordination to sulfur, polarizes the Pd-S bond while at the same time the carboxylate part of CuTC coordinates to the boron atom, activating the boronic acid.[38] Considering the information, it became evident that the presence of copper is vital for reactions of organosulfur compounds. Therefore, for our reactions to occur and possibly run into completion, a copper source was to be present.

3.2.1.2. CuI-mediated synthesis of 4-methyl-1,1'-biphenyl (90)

Acknowledging the importance of copper as well documented by previous studies, *S-p*-tolyl-4-methylbenzene sulfonothioate (81) was reacted with arylboronic acid (89) in the presence of Cu as a co-catalyst; in attempts to synthesize 4-methyl-1,1'-biphenyl (90). The reaction was run in THF as a solvent, using stoichiometric amounts of Copper (I)

Iodide with $Pd(PPh_3)_4$ as a catalyst. The reaction was heated to 12 hours with constant monitoring through TLC analysis. After 12 hours, no product (90) had been formed.

Still in pursuit of the optimum conditions, the above reaction was repeated using dioxane as a solvent. After refluxing for 12 hours, TLC analysis revealed that the anticipated product (90) had not been formed (Scheme 3.16).



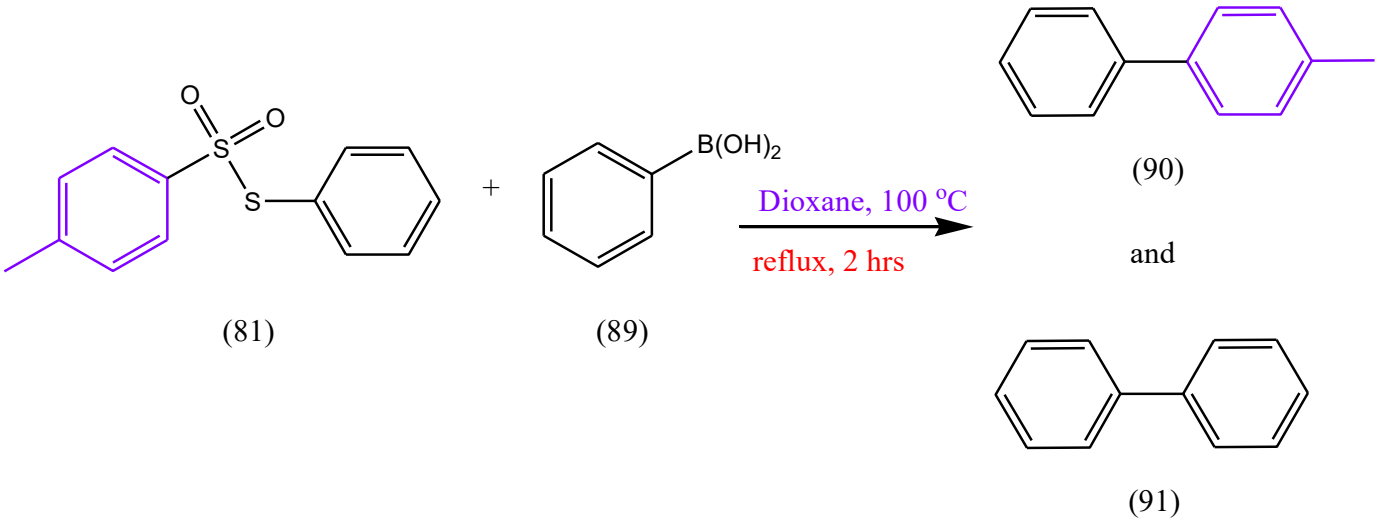
Scheme 3.16. Cu(I)Iodide – mediated attempted synthesis of 4-methyl-1,1'-biphenyl (90)

Following the failed attempts, it became evident that the presence of Copper(I) Iodide was ineffective for our reactions. Liebeskind and coworkers on their seminal work, had reported on the ineffectiveness of Cu(I)halides in mediating desulfitative reactions. However, they discovered that the carboxylate anion in combination with the Cu(I) cation was crucial in activating the boronic acid in the transmetallation step (Scheme 3.13).[37,38]

3.2.1.3. Cu(I)TC/MeSal-mediated synthesis of 4-methyl-1,1'-biphenyl (90)

In the following segment of the study, we report on Cu(I)TC and Cu(I)MeSal mediated synthesis of biaryls (90) in pursuit of optimum conditions following the findings of Liebeskind[37]. The results obtained are summarized on Table 3.4 below.

Table 3.4. Optimization Studies



(81) (89)

Entry	Boronic acid (mmol)	Additive	Catalyst	Supporting ligand	Product A (90)	Product B (91)
1.	1.5	CuTC (1.5 mmol)	$Pd(PPh_3)_4$	-	24 %	8 %
2.	1.5	CuTC (2 mmol)	$Pd(OAc)_2$	PPh_3	32 %	10 %
3.	2	CuMeSal (2 mmol)	$Pd(OAc)_2$	PPh_3	30 %	11 %
4.	2	CuMeSal (2 mmol)	$Pd(PPh_3)_4$	-	27 %	9%

The reactions reported in Table 3.4. were all heated to reflux at 100 °C and after having learnt about the negative effects of coordinating solvents and ligands[37], the reactions were run in dioxane due to its non-coordinating effect. Different copper co-catalysts were utilized, and it was discovered that lower copper loading gave smaller yields. As a result, the copper loading was increased in attempts to increase the reaction yields. Through constant monitoring with TLC, after 2 hours we observed that the reaction conditions were no longer changing and the desired products (90) had been formed. The desired product

(90) was obtained as a white crystalline solid along with product (91) also as a white crystalline solid. It is highly likely that product (91) was formed as a result of either the homocoupling of the excess boronic acid or as a result between the boronic acid (89) and the 2nd phenyl ring of the thiosulfonate (81). From the results obtained, it was observed that an increment in the stoichiometric amounts of copper from 1.5 to 2 equivalents had no visible impact on the outcome of the reaction. To confirm the synthesis of the two products 90 and 91, for each of the entries in Table 3.4. above, ^{1}H NMR, ^{13}C NMR and GC-MS spectra were obtained.

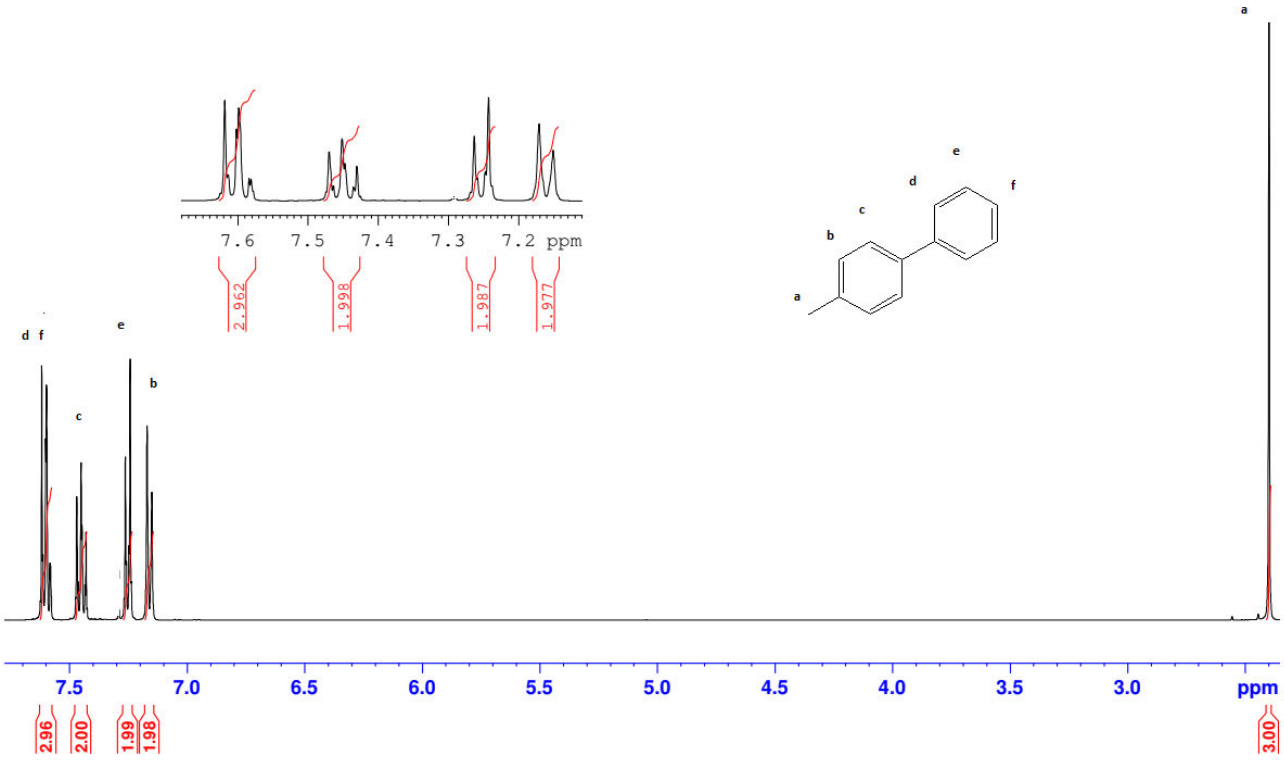


Figure 3.11. ^{1}H NMR of 4-methyl-1,1'-biphenyl (90)

Figure 3.11. is the proton spectrum of 4-methyl-1,1'-biphenyl (90) which is consistent with the product structure. A singlet peak (a) located upfield on the spectrum, integrating for four peaks is present and this is the peak consistent with the methyl group of the compound. On the aromatic region of the spectrum, peaks integrating for 9 protons are

present and these are also consistent with the number of protons in the aromatic ring of the structure.

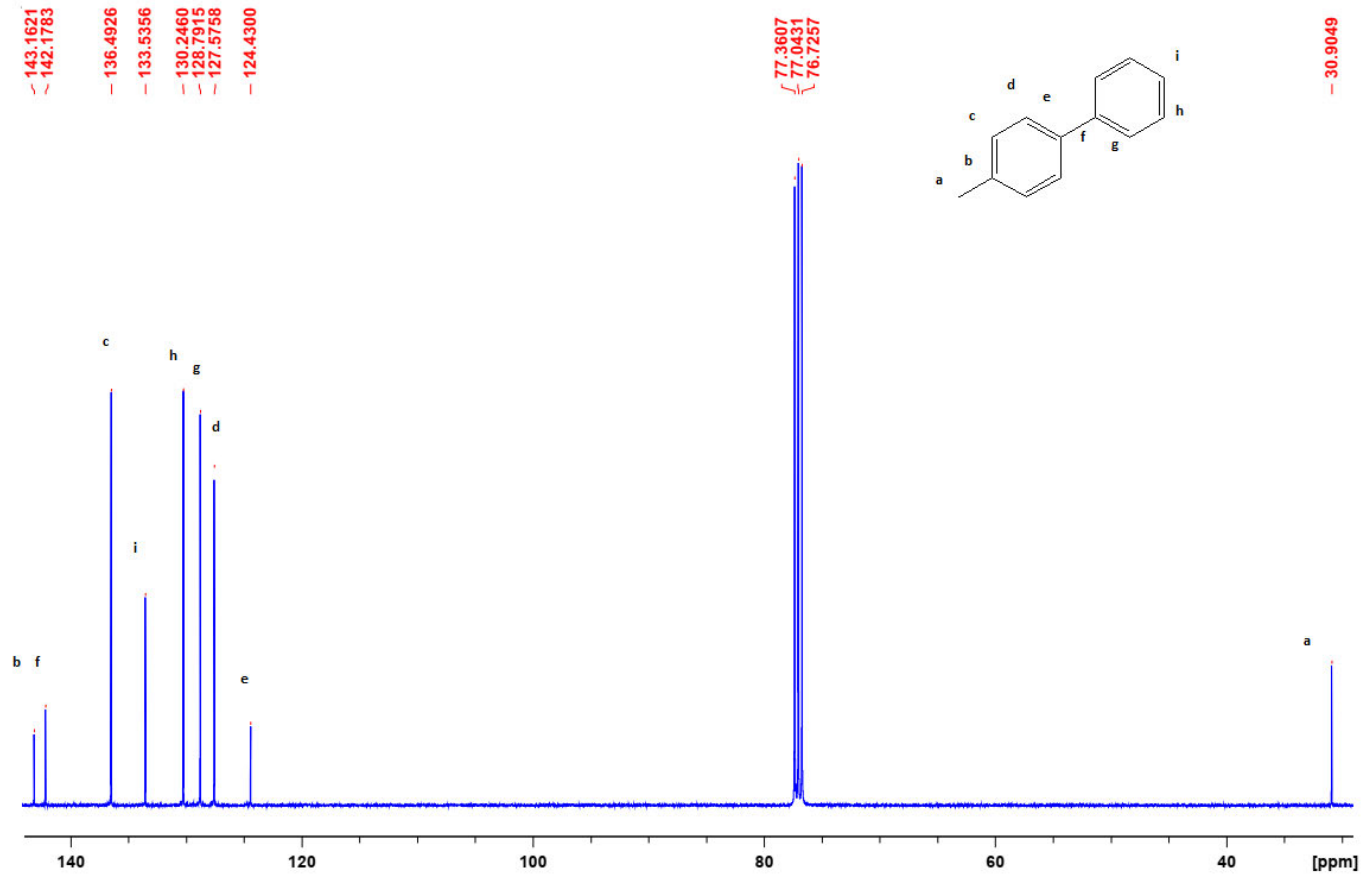
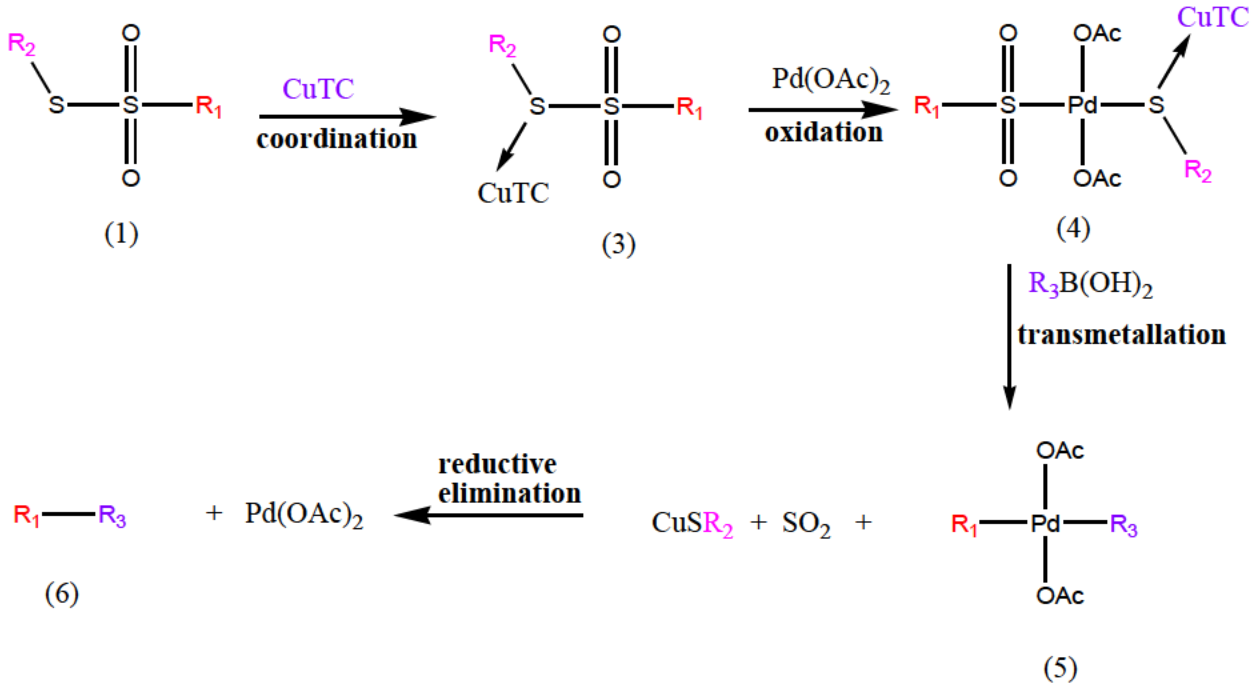


Figure 3.12. ^{13}C NMR of 4-methyl-1,1'-biphenyl (90)

The ^{13}C NMR spectrum of 4-methyl-1,1'-biphenyl (90) is shown in figure 3.12. This spectrum is also consistent with the total number of carbons found on the structure, further confirming the synthesis of the desired biaryl (90). From the GC-MS spectrum, a mass peak of 168 [M^+] (100) is present and this peak is consistent with the molecular mass of the anticipated product (90).

Along with 4-methyl-1,1'-biphenyl (90), 1,1'-biphenyl (91) was also synthesized as a side-product. To confirm its synthesis, ^{1}H NMR, ^{13}C NMR and GC-MS spectra were also obtained. The NMR spectra obtained indicated the absence of a substituent in the structure and had peaks only in the aromatic region. The results from GC-MS gave a 154 [M^{+}] (100 %) peak, which is in line with the molecular mass of the compound.

Following the results, although a homocoupled product (91) was obtained, the formation of the desired product (90) was a breakthrough in our study, confirming the thiophilicity of the soft Cu(I)MeSal/TC and its effectiveness in these coupling reactions. This also confirmed that arylthiosulfonates compounds indeed are electrophilic enough to couple in Libeskind-type cross-coupling reactions. To explain the reaction findings, we proposed a reaction mechanism (Scheme 3.17).



Scheme 3.17. Mechanism for the base-free coupling reactions of thiosulfonates and boronic acids

The mechanism above illustrates the cross-coupling between phenylboronic acid and arythiosulfonate under Liebeskind-type conditions. On the first step of the mechanism, we propose that CuTC (or CuMeSal) coordinates to coordinatively unsaturated sulfur atom of thiosulfonate (1), weakening the S-S bond. The oxidative addition of $Pd(OAc)_2$ (or $Pd(PPh_3)_4$ follows next as the S-S bond has been weakened, forming complex (4). Complex (4) undergoes transmetallation to form organopalladium species (5) through the exclusion of sulfur dioxide gas (SO_2). The last step is the reductive elimination which leads to the formation of the desired biaryl (6) and the regeneration of the catalyst.

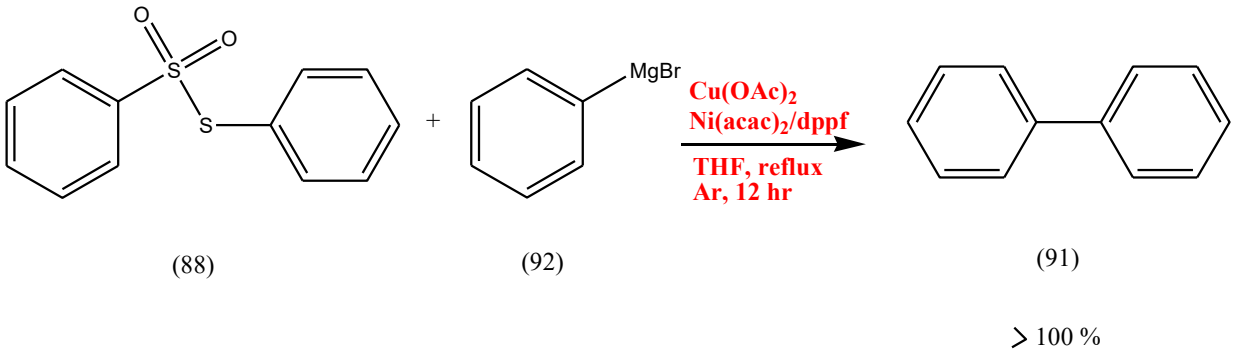
3.2.2. Synthesis of Biaryls Through Kumada-Corriu Cross-Coupling

Following the successful synthesis of biaryls through Cu(I)-mediated cross-coupling of thiosulfonates and phenylboronic acids, we were inspired to further investigate the electrophilic nature of thiosulfonates as coupling partners under Kumada-Corriu cross-coupling reactions.

3.2.2.1. Synthesis of 1-1'-biphenyl (90)

In pursuit of optimum conditions, having learnt about the thiophilicity of the soft copper atom[39] and its importance in desulfitative reactions[37,38,39] in weakening the S-S bond, it was clear that the presence of stoichiometric amounts of copper on our reactions was crucial. The challenge laid in finding the correct copper additive. The solvent choice was also important as we had previously learnt that coordinating solvents affect reaction outcomes negatively.[37] Since palladium catalysts along with their supporting ligands are expensive,[9] for this study, the Nickel-catalyst system was found highly desirable as it is associated with great stability, activity and low cost.[11]

Given the above information, phenylthiosulfonate (88) was reacted with phenylmagnesium bromide (92) in the presence of THF as a solvent and $Ni(acac)_2$/DPPF as a catalyst under reflux for 12 hours with the reaction progress was monitored by TLC. This $Cu(OAc)_2$-mediated reaction was run in an inert atmosphere and saw the synthesis of our desired product (91) as a white crystalline solid in yields of >100 % (scheme 3.18).



(88) (92) (91)

> 100 %

Scheme 3.18. Synthesis of 1,1'-diphenyl (91)

^1H NMR spectrum was obtained to confirm the successful synthesis of 1-1'-diphenyl. Two peaks are visible in the aromatic region, integrating for 5 protons each, proving the successful synthesis of the desired product.

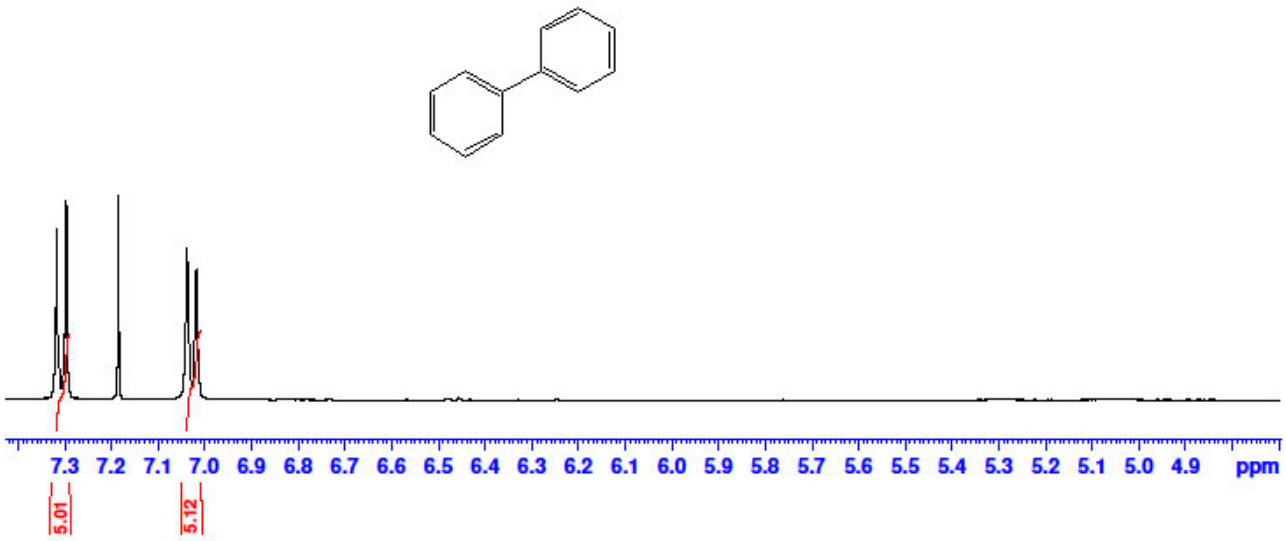


Figure 3.13. ^{1}H NMR spectrum of 1,1'-diphenyl (91)

The ^{13}C NMR spectrum on Figure 3.14. also confirmed the formation of the biphenyl product which forms as a result of homocoupling. In the aromatic region of the spectrum, 4 peaks are visible in the spectrum, indicating the symmetry of the compound which is consistent with the homocoupled product.

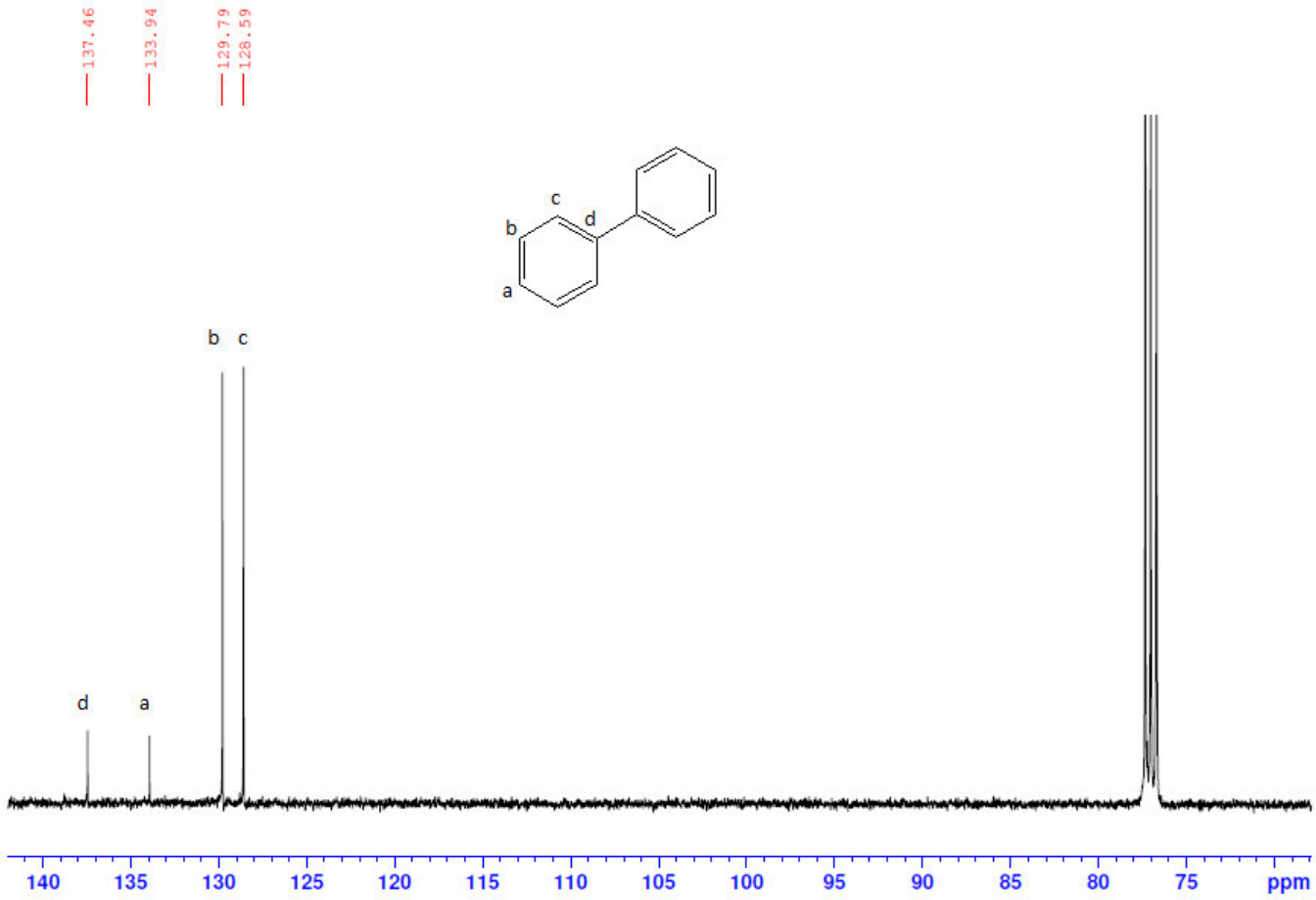
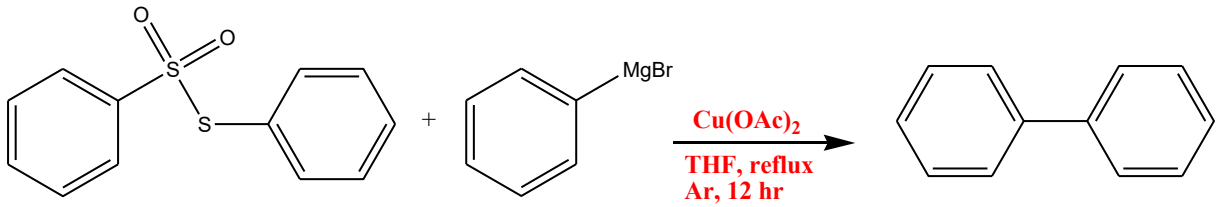


Figure 3.14. ^{13}C NMR Spectrum of 1-1'-biphenyl (91)

Although the desired product (91) was obtained as confirmed by the ^{1}H and ^{13}C NMR spectra, it was however concerning that the product yields were so high and >100 %. It was suspected that the excess product was as a result of homocoupling from the Grignard reagent since it was added in excess.

Still in pursuit of optimum conditions, more reactions were conducted as indicated on Table 3.5.

Table 3.5. Ni-catalyzed Cross-Coupling of Phenylthiosulfonate (88) With Phenylmagnesium Bromide (92)



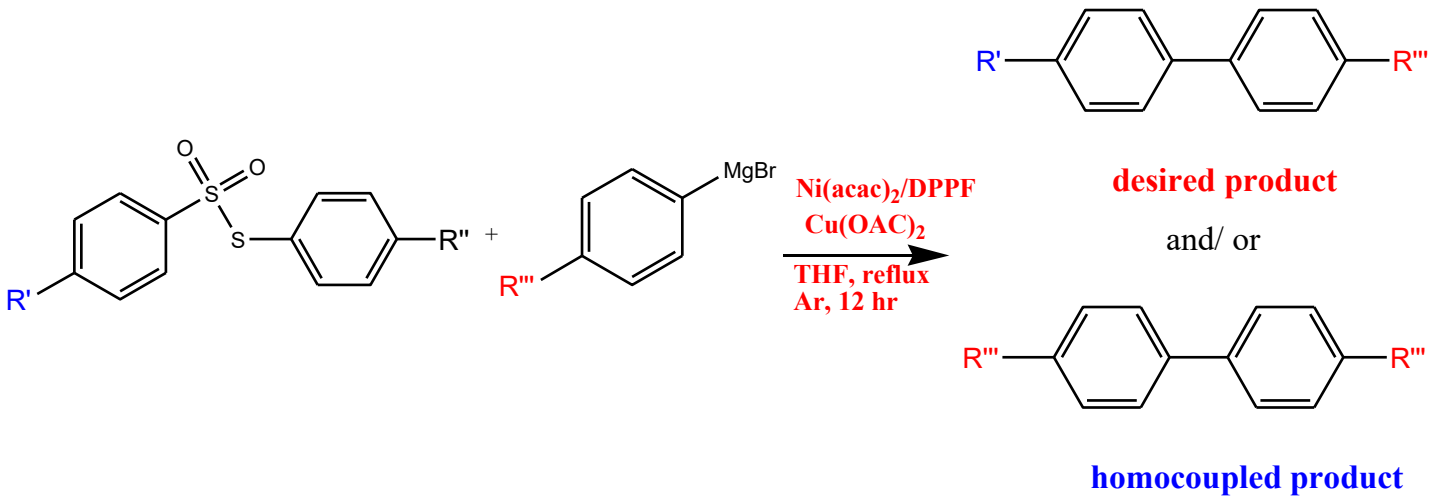
(88) (92) (91)

Entry	Catalyst	Supporting ligand	1-1'-bephenyl % (91)
1.	$Ni(dppf)_2$	DPPF	136
2.	$Ni(acac)_2$	DPPE	114
3.	$Ni(dppf)_2$	DPPE	112

Table 3.5. summarizes the results obtained when reactions were done to find the best catalytic system. For all reactions mentioned above, their progresses were monitored by TLC and run under an inert atmosphere of argon due to the hydrophilic nature of the Grignard reagent. When the reactions were complete, the biaryls (91) were obtained as white crystalline solids and all the yields were greater than 100% although the desired products were synthesized (as confirmed by ^{1}H NMR, ^{13}C NMR and GC-MS spectra). The unusually higher yields obtained were attributed to the homocoupling of the excess Grignard reagent.

To avoid the homocoupling of the excess Grignard reagent, Park and co-workers[42] suggested that the Grignard reagent be added dropwise, in intervals of 30 minutes to the sulfonate-catalyst mixture. Due to uncertainty as to whether the excess yields were solely from the homocoupling of the Grignard reagent, for the following reactions, some of the reactions were between differently substituted Grignard and thiosulfonic compounds.

Table 3.6. Optimised Cross-Coupling of Phenylthiosulfonates With Grignard Reagents

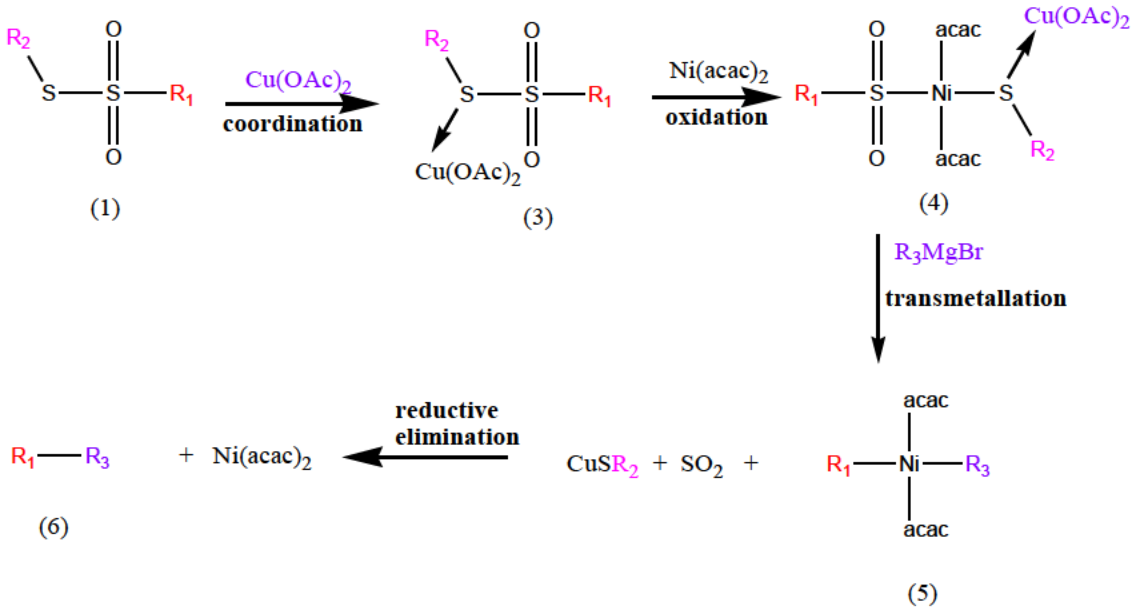


Entry	R'	R''	R'''	Desired Product Yield%	Homocoupled Product Yield%
1.	Me	Me	H	Not detected	47
2.	H	Me	H	Not detected	40
3.	Me	Me	Cl	Not detected	Not detected
4.	Me	Cl	H	Not detected	25
5.	H	Cl	H	Not detected	Not detected

Table 3.6. summarizes the results obtained in attempts to synthesize biaryls from the coupling of phenylthiosulfonates and Grignard reagents. The results were obtained following the conditions summarized on the scheme above, with the exception of entry 4, where $Ni(dppf)Cl_2$ was used instead of $Ni(acac)_2$ The reactions were ran in at inert atmosphere of argon, with their progresses monitored by TLC and to confirm the synthesis of desired products spectral analysis (^1H NMR, ^{13}C NMR and MS) was done. The results obtained in tables 3.5 and 3.6 when compared differ quite immensely which was quite unexpected. When the unsubstituted phenylmagnesium bromide and the

unsubstituted arylthiosulfonate were reacted (Table 3.5), the yields were high. However, it was observed that the presence of substituents on the thiousulfonate and the grignard reagent (Table 3.6) had a negative impact on the outcome of the reactions.

Following the recommendation by Park, *et al*[42] of adding the Grignard reagent dropwise, in intervals of 30 min the reactions were expected to proceed via the mechanism shown below (Scheme 3.19.). However, when the reactions were conducted only the homocoupled products were produced and this could be attributed to a lot of factors. One could be that the benzenethiosulfonates are not electrophilic enough to couple with the Grignard reagent. Another plausible explanation could be the strength of the copper-source used. From coordination step of the mechanism (Scheme 3.17.), due to the thiophilicity of copper, $Cu(OAc)_2$ was supposed to coordinate with the unsaturated sulfur of the thiosulfonate, but instead from the reactions it was discovered that after 12 hours the starting material was still present. Therefore, this finding could've been an indication that the $Cu(OAc)_2$ was not thiophilic enough to lead to the S-S bond cleavage, hence the homocoupled product.

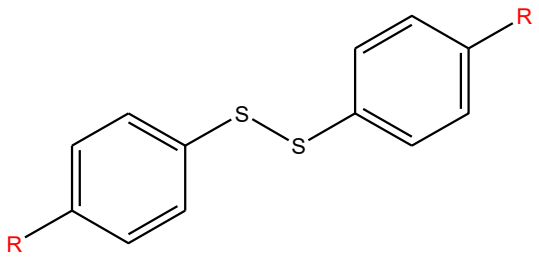


Scheme 3.19. Mechanism for the coupling of thiousulfonates through Kumada-type coupling to synthesize biaryls

The first step of the mechanism sees the coordination of Cu(II) to the thiosulfonate which leads to the weakening of the S-S bond. The following step is the oxidative addition of $Ni(acac)_2$ which forms complex (4). Complex (4) undergoes transmetallation to form organonickel species (5) through the exclusion of sulfur dioxide gas (SO_2). The last step sees the formation of the desired biaryl and the regeneration of the catalyst by reductive elimination.

3.3. CONCLUSIONS

In conclusion, the dissertation reports on the use of organosulfur compounds (benzenethiosulfonothioates) as electrophilic coupling partners in transition-metal catalysed reactions with boronic acids and Grignard reagents. Disulfides (Figure 3.15) which are precursers for the synthesis of thiosulfonates were successfully synthesized in good yields and their synthesis confirmed by ^{1}H NMR, ^{13}C NMR, MS and the melting point technique.



R = Cl, MeO, Me, NO_2, H

Figure 3.15. Disulfides synthesized

Symmetrical and asymmetrical benzenethiosulfonates (Figure 3.16), which are the electrophilic coupling partners were successfully using two different methods. To synthesize unsymmetrical benzenethiosulfonates, a method by Liang and Liu[22] was adopted and in comparison, to the synthetic route proposed by Chemla and Karayan[23] this route led to smaller yields due to the retention of some starting material as the reactions did not run into completion. However, the method proposed by Liang[22] is more versatile compared to the method proposed by Chemla[23] as it was able to lead to the production of both symmetrical and unsymmetrical thiousulfonates whilst the one proposed by Chemla was restrictive and it can only produce symmetrical thiosulfonates. Overall, both methods were successful, leading to the production of the desired products in good yields. Product confirmations were conducted using the melting point technique

along with spectral analysis such as ^{1}H NMR, ^{13}C NMR, GC-MS and IR (which was helpful in identifying the appearance of the S=O group).

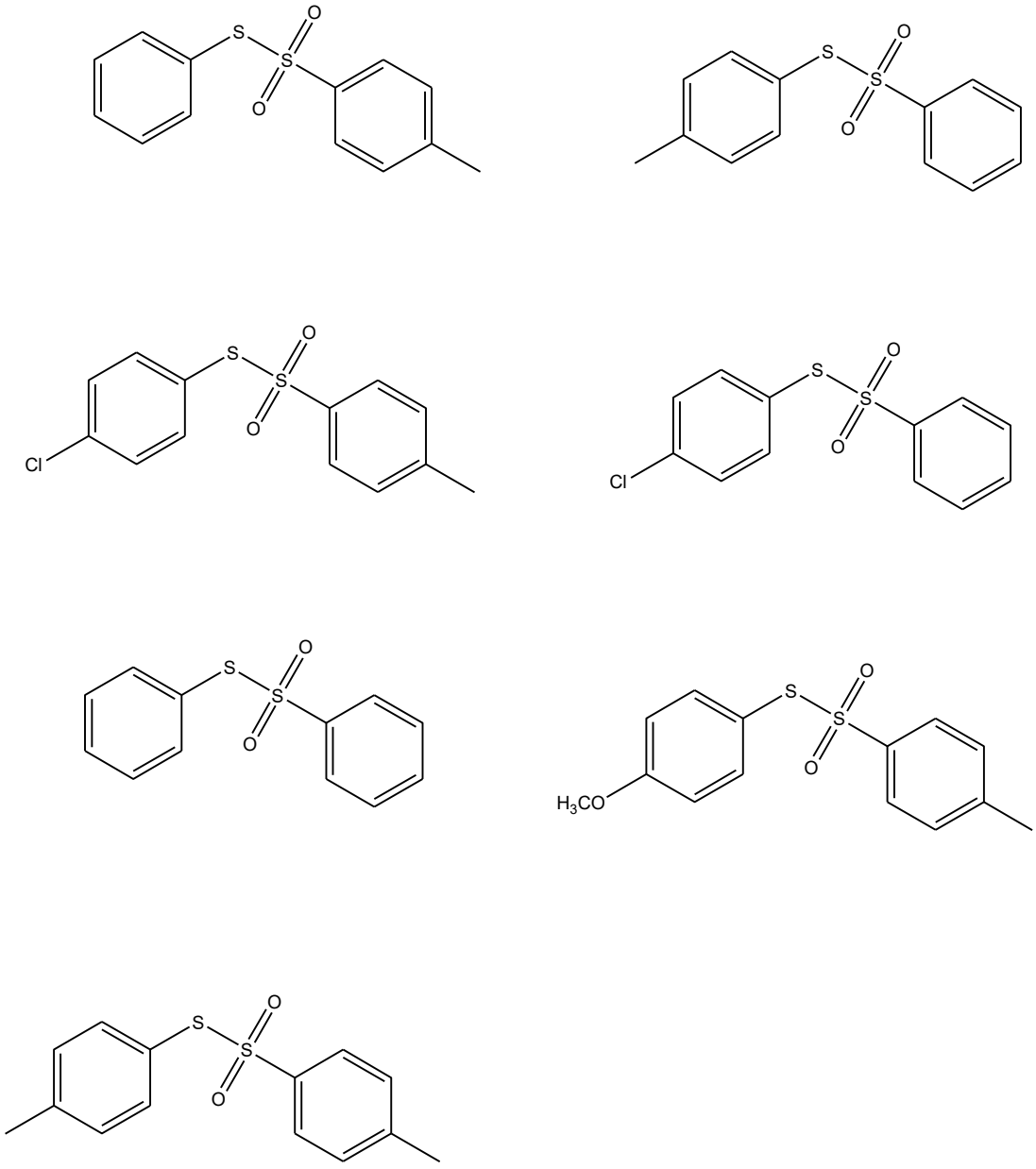


Figure 3.16. Synthesized Benzenethiousulfonates.

The *S*-*p*-tolyl-benzene sulfonothioate (81) synthesized was successively used in Pd-catalysed cross-coupling reaction with boronic acids where they proved to be electrophilic in the synthesis of biaryls. This was a remarkable breakthrough as this novel study

provides an alternative route to synthesizing biaryls. However, when coupled with Grignard reagents, benzenethiousulfonates were found not compatible as the anticipated biaryls were not produced. A lot of factors were suspected for the let-down, with one of them being $Cu(OAc)_2$ not being thiophilic enough to cleave the S-S bond.

3.4. RECOMMENDATION FOR FUTURE-WORK

Since not all disulfides were utilized to synthesize arylthiosulfonates, going into the future, we will look into synthesizing nitro and methoxy-based unsymmetrical thiosulfonates (Figure 3.17). For the coupling reactions with Grignard reagents, we will look at different copper sources which might be thiophilic enough also Pd-catalysts will be tried out also.

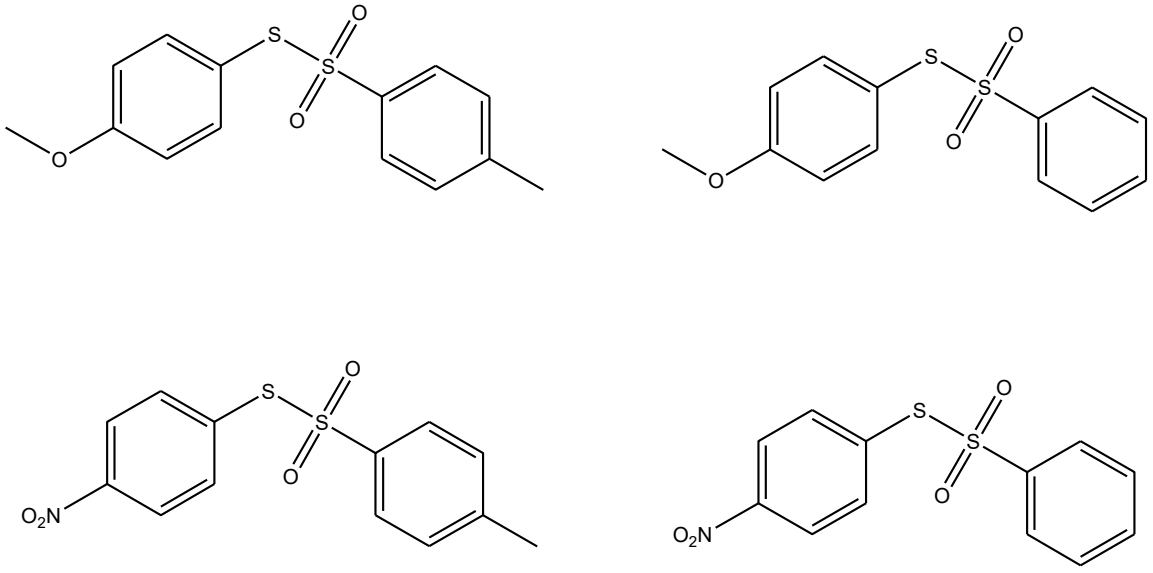


Figure 3.17. Compounds to Be Synthesized in Future

3.5. REFERENCES

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CHAPTER FOUR

EXPERIMENTAL

4.1. CHEMICALS AND INSTRUMENTATION

All air-sensitive reactions (Grignard reactions) were carried out in oven-dried glassware equipped with a dry septum and magnetic stirrer bar under argon atmosphere. Hexane was freshly distilled for use in chromatography, with the reaction progresses and product purification was done using centrifugal preparative thin-layer chromatography and column chromatography on Merk silica gel and Fluka silica gel, 70 – 230 mesh.

Product confirmation through NMR was done using 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR which were recorded on a Bruker Advance III 400 (9.4 T) spectrometer in glass NMR tubes with the NMR samples prepared as solutions in deuterated chloroform. NMR spectra of the prepared NMR solutions were reported using tetramethyl silane (TMS) as an internal standard in parts per million (ppm). Product melting points were measured on a Reichert Austria apparatus using 22 x 22 mm deck Glaser and were uncorrected.

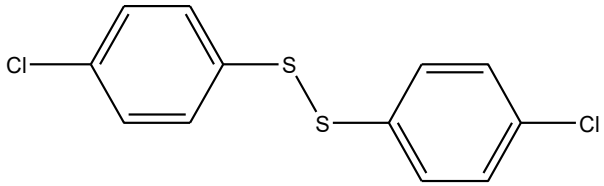
4.2. SYNTHESSIS OF DISULFIDES

4.2.1. General experimental procedure A

A mixture of thiophenol (1 mmol) and NBS (0.5 mmol) was stirred in DCM at room temperature for 10 min with the reaction progress monitored by TLC. When the reaction was complete, DCM (10 mL) was added to the mixture and the resulting solution was washed with water (2 x 20 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified

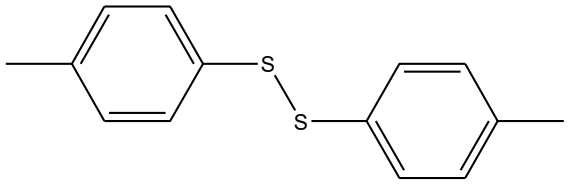
using column chromatography on silica gel with a mixture of hexane/ethyl acetate (9:1) as an eluent to afford the purified, desired product.[1]

4.2.2. Synthesis of *bis*(4-chlorophenyl) disulfide 70



***bis*(4-chlorophenyl) disulfide**: the compound was synthesized as a cream white crystalline solid (0.421g, 98%) following the general procedure A. **Melting point**: 67.6 – 69.2 °C (Lit.: 68 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.40 (d, 8.6 Hz, 4H), 7.28 (d, 8.6 Hz, 4H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 129.32, 129.39, 133.70, 135.19. **MS (EI), m/z (%)**: 18 (1), 39 (3), 50 (3), 63 (10), 75 (8), 85 (5), 108 (50), 113 (5), 139 (3), 143 (100), 155 (1), 175 (1), 207 (1), 222 (5), 251 (1), 286 [M^+] (80).

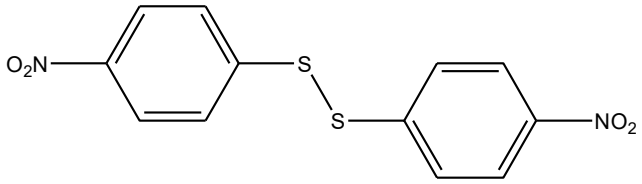
4.2.3. Synthesis of *bis*(4-methylphenyl) disulfide 72



***bis*(4-methylphenyl) disulfide**: 4-methylthiophenol was reacted following the general procedure A, affording compound 2 as a white crystalline powder (0.432 g, 70%). **Melting point**: 47.8 °C – 50.4 °C (Lit.: 47.5 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.38 (ddd, 8.2 Hz, 4H), 7.10 (ddd, 8.1 Hz, 4H), 2.3 (s, 6H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 21.03,

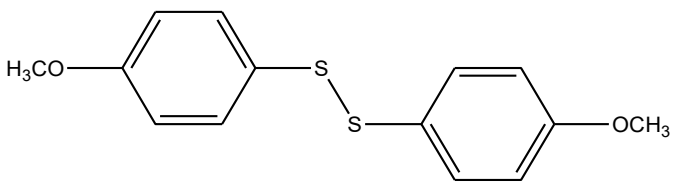
128.57, 129.75, 133.91, 137.48. **MS (EI), m/z (%)**: 14 (1), 39 (10), 45 (27), 69 (8), 77 (20), 91 (8), 108 (5), 123 (100), 126 (12), 153 (3), 167 (4), 181 (3), 198 (2), 213 (4), 231 (1), 246 [M^+] (100).

4.2.4. Synthesis of *bis*(4-nitrophenyl) disulfide 74



***bis*(4-nitrophenyl) disulfide**: Following experimental procedure **A**, *bis*(4-nitrophenyl) disulfide was successfully synthesized as a cream white powder (0.765, 95%). **Melting point**: 179.5 °C – 184.2 °C (Lit.: 181 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 8.32 (dd, 8.3 Hz, 2H), 7.84 (dd, 8.2 Hz, 2H), 7.58 (ddd, 15.5 Hz, 2H), 7.40 (ddd, 15.5 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 146.13, 134.93, 134.52, 127.23. **MS (EI), m/z (%)**: 41 (5), 69 (10), 95 (20), 124 (10), 139 (100), 140 (10), 167 (5), 183 (3), 203 (2), 235 (3), 246 (300, 264 93), 278 (75), 280 (20), 306 (15), 308 [M^+] (40).

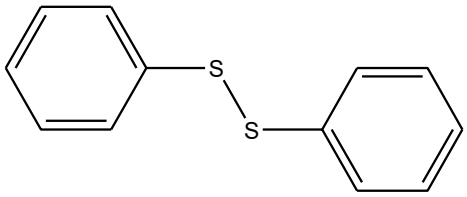
4.2.5. Synthesis of *bis*(4-methoxyphenyl) disulfide 78



bis(4-methoxyphenyl) disulfide: compound 5 was synthesized from 4-methoxythiophenol following the general experimental procedure A as a white crystalline solid (0.892 g, 70%). **Melting point**: 42.8 °C – 44.7 °C (Lit.: 44 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.40

(ddd, 8.8 Hz, 4H), 6.84 (ddd, 8.9 Hz, 4H), 3.80 (s, 6H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 55.04, 114.46, 128.12, 132.28, 159.61. **MS (EI), m/z (%)**: 27 (1), 41 (4), 69 (10), 96 (15), 98 (5), 124 (10), 139 (100), 140 (10), 278 [M^+] (65), 280 (5).

4.2.6. Synthesis of 1,2-diphenyldisulfane 76



1,2-diphenyldisulfane: Following the direct oxidation of benzenethiol through experimental procedure A, 1,2-diphenyldisulfane was synthesized as a white crystalline solid (0.402 g, 75%). **Melting point**: 61.5 °C – 164.1 °C (Lit.: 62 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.54 (dddd, 15.00 Hz,4H), 7.34 (dddd, 15.01 Hz, 4H), 7.27 (tt, 19.48 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm. **MS (EI), m/z (%)**: 27 (1), 39 (10), 51 (5), 65 (20), 77 (8), 109 (60), 123 (1), 139 (4), 154 (20), 181 (10), 203 (1), 218 [M^+] (100).

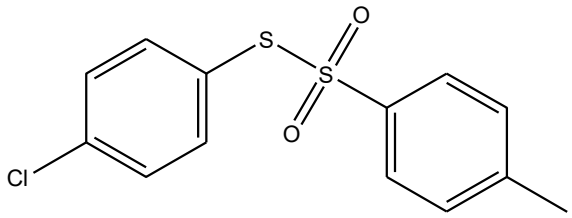
4.3. SYNTHESIS OF ASYMMETRICAL THIOSULFONATES

4.3.1. General experimental procedure B

Sulfinate (0.8 mmol) was mixed with NBS (0.4 mmol) and disulfide (0.2 mmol) in MeCN (3 mL) and stirred at room temperature overnight. The reaction progress was monitored by TLC and after the reaction was complete, the resulting mixture was washed with water and extracted with ethyl acetate. With the organic phase separated, it was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was

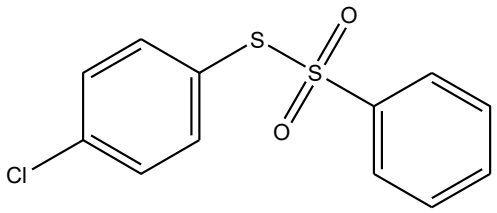
purified by column chromatography on silica gel using a mixture of hexane/ ethyl acetate (9:1) as an eluent to produce the desired unsymmetrical thiosulfonates.[2]

4.3.2. Synthesis of *S*-4-chlorophenyl-4-methylbenzenesulfonothioate 80



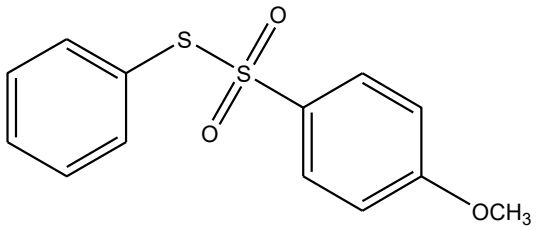
***S*-4-chlorophenyl-4-methylbenzenesulfonothioate**: a mixture of 4-toluenesulfinate and *bis*(4-chlorophenyl) disulfide was reacted following procedure B to furnish compound 9 as a white crystalline solid (0.830 g, 73%). **Melting point**: 88.3 °C – 93.2 °C (Lit.: 87 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.47 (d, 8.4 Hz, 2H), 7.31 (d, 2.8 Hz, 3H), 7.24 (t, 8.12 Hz, 3H), 2.43 (s, 3H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 21.77, 126.59, 127.63, 129.55, 129.72, 137.72, 138.20, 140.25, 145.00. **MS (EI), m/z (%)**: 27 (3), 31 (15), 45 (5), 65 (30), 77 (10), 91 (100), 107 (10), 123 (20), 139 (80), 140 (10), 157 (40), 171 (35), 186 (20), 198 93), 214 (3), 246 (3), 278 (45), 280 (10), 298 [M^+] (50).

4.3.3. Synthesis of *S*-4-chlorophenylbenzenesulfonothioate 83



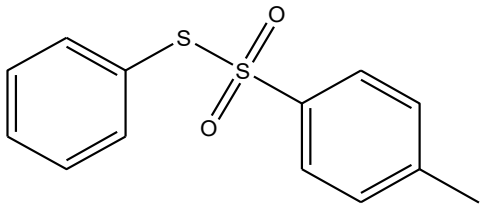
***S*-4-chlorophenylbenzenesulfonothioate**: Following general procedure **B**, *S*-4-chlorophenylbenzenesulfonothioate was synthesized from the reaction of benzene sulfinate and *bis*(4-chlorophenyl) disulfide as a white crystalline solid (0.683g, 70%). **Melting point**: 67.0 °C – 72.6 °C (Lit.: 72 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm. 7.63 (dtd, 8.03 Hz, 2H), 7.48 (tt, 7.55 Hz, 1H), 7.34 (ddd, 8.22 Hz, 2H), 7.33 (dddd, 8.03 Hz, 2H), 7.29 (ddd, 8.22 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 142.92, 138.34, 137.71, 13.84, 129.77, 128.95, 127.61. **MS (EI), m/z (%)**: 76 (10), 77 (100), 97 (15), 108 (85), 125 (75), 126 (5), 143 (77), 159 (50), 176 (10), 184 (30), 220 (40), 224 (20), 284 [M^+] (40).

4.3.4. Synthesis of *S*-phenyl-4-methoxybenzenesulfonothioate 85



***S*-phenyl-4-methoxybenzenesulfonothioate**: Following the experimental procedure B, product 12 was furnished as a white crystalline solid (0.592 g, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 3.86 (s, 3H), 6.87 (ddd, 8.72 Hz, 2H), 7.24 (ddd, 8.72Hz, 2H), 7.29 (dddd, 8.38 Hz, 2H), 7.42 (tt, 8.37 Hz, 1H), 7.49 (ddd, 8.38 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 30.90, 55.47, 114.64, 114.96, 118.80, 127.63, 129.39, 132.66, 138.34, 140.41, 144.56. **MS (EI), m/z (%)**: 41 (3), 64 (15), 77 (25), 92 (20), 107 (20), 124 (15), 139 (100), 140 (10), 155 (65), 171 (75), 188 (2), 214 (1), 231 (2), 246 (4), 278 (3), 294 [M^+] (20).

4.3.5. Synthesis of *S*-phenyl-4-methylbenzenesulfonothioate 81



***S*-phenyl-4-methylbenzenesulfonothioate**: A mixture of benzene sulfinate and 1,2-di*p*-tolyldisulfane furnished product 13 as a white crystalline solid (1.120 g, 71%) following the reported procedure B. **Melting point**: 54.0 °C – 55.6 °C (Lit.: 54 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm; 7.57 (t, 14.7 Hz, 3H), 7.42 (t, 15.8 Hz, 2H), 7.22 (d, 8.2 Hz, 2H), 7.13 (d, 8.13 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 30.84, 124.38, 127.52, 128.71, 130.20, 133.48, 136.47, 142.14, 143.18. **MS (EI), m/z (%)**: 26 (5), 39 (17), 65 (25), 77 (20), 91 (70), 108 (5), 123 (43), 139 (100), 140 (10), 155 (30), 181 (3), 198 (5), 214 (5), 246 (2), 264 [M^+] (60).

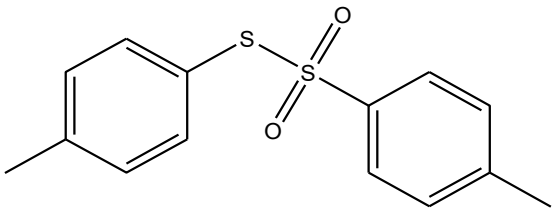
4.4. SYNTHESIS OF SYMMETRICAL THIOSULFONATES

4.4.1. General Experimental Procedure C

A mixture of zinc dust (16 mmol), 1,2-dibromoethane (2 drops) and trimethylchlorosilane (3 drops) in ethylacetate (60 mL) was heated to reflux until the zinc became bright and flakey. Sulfonyl chloride (10 mmol) was added in one portion after the mixture had been cooled, followed by a dropwise addition of acetyl chloride (10 mmol). Initially, the mixture turned green and over time turned yellow. The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was washed with 1M HCl in water,

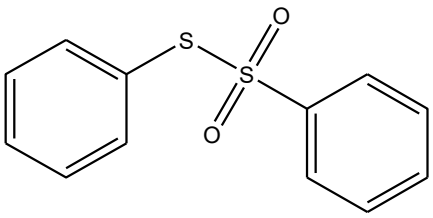
followed with brine and was dried over Na_2SO_4. The solvent was evaporated, and the remaining crude product was purified over column chromatography using the mixture of hexane/ethyl acetate (9:1) as an eluent to furnish the desired product.[3]

4.4.2. Synthesis of *S*-*p*-tolyl-4-methylbenzenesulfonothioate 84



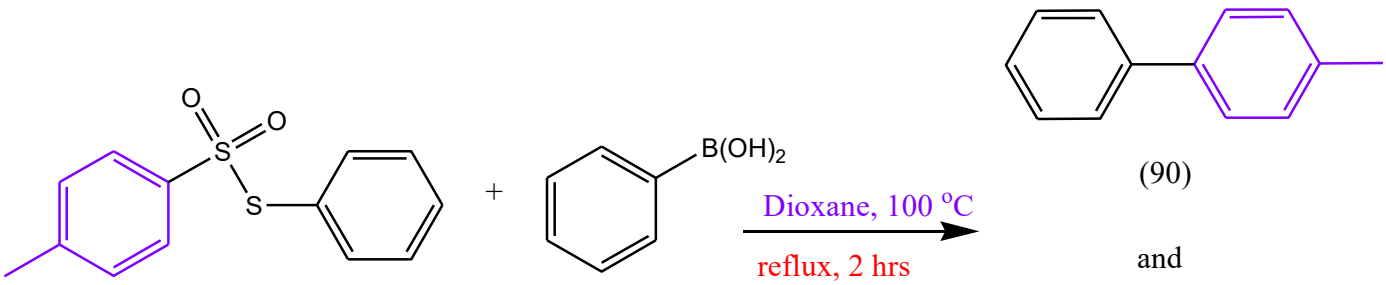
***S*-*p*-tolyl 4-methylbenzenesulfonothioate**: Following experimental procedure C, compound 13 was synthesized from 4-methylbenzene-1-sulfonyl chloride and was achieved as a white crystalline solid (1.02 g, 82%). **Melting point**: 42.8 °C – 44.7 °C (Lit.: 44°C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.41 (s, 3H), 2.45 (s, 3H), 7.14 (ddd, 7.8 Hz, 2H), 7.21 (ddd, 8.3 Hz, 2H), 7.24 (ddd, 8.2 Hz, 2H), 7.46 (ddd, 8.3 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 21.38, 124.56, 127.53, 129.12, 130.03, 136.42, 140.41, 141.89, 144.40. **MS (EI), m/z (%)**: 26 (3), 39 (15), 65 (25), 77 (12), 91 (70), 108 (5), 123 (50), 139 (100), 155 (30), 181 (3), 198 (2), 214 (2), 246 (3), 278 [M^+] (55), 280 (5).

4.4.3. Synthesis of *S*-phenyl benzenesulfonothioate 88



***S*-phenyl benzenesulfonothioate**: following the reaction of benzenesulfonyl chloride, the desired product 14 was furnished following the general experimental procedure C as white crystalline solid (1.321 g, 80%). **Melting point**: 38.9 °C – 39.6 °C (Lit.: 36 - 53°C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 7.91 (dtd, 8.03 HZ, 2H), 7.73 (tt, 7.55 Hz, 1H), 7.53 (dddd, 8.03 Hz, 2H), 7.34 (dddd, 8.02 Hz, 2H), 7.28 (dddd, 8.02, 2H), 7.24 (tt, 7.62 Hz, 1H). **^{13}C NMR** (100MHz, $CDCl_3$): δ ppm 126.6, 128.0, 128.9, 129.7, 130.9, 137.8, 145.3. **MS (EI), m/z (%)**: 26 (5), 39 (15), 65 (25), 77 (15), 108 (5), 123 (50), 139 (100), 155 (30), 181 (3), 198 (2), 214 (3), 246 (5), 250 [M^+] (69)

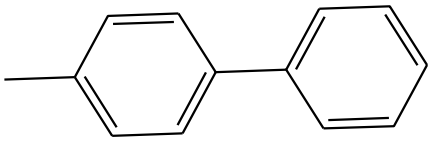
4.5. LIEBESKIND-SROGL SYNTHESIS OF 4-METHYL-1-1'-BIPHENYL 90



(81) (89) (90) (91)

4-methyl-1-1'-biphenyl was synthesized following a Liebeskind-Srogl reaction.[4] A mixture of *S*-*p*-tolyl-4-methylbenzene sulfonothioate (1.0 mmol) and arylboronic acid (1.5 mmol) in dioxane, was stirred for 2 hours at 100 °C using $Pd(OAc)_2$ (10% mmol) as a catalyst and CuTC (2.0 mmol) as an additive. The reaction progress was monitored by TLC and after the reaction was complete, the crude product was purified over flash chromatography using a mixture of hexane/ethyl acetate (9:1) as a white solid in a 32% yield along with a homocoupled product (1-1'-biphenyl) as a white solid in a yield of 10%.

4-methyl-1-1'-biphenyl 90 (desired product):

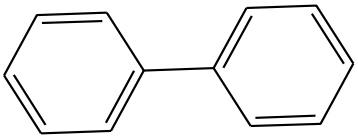


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.60 (dd, 2H), 7.45 (tt, 3H), 7.24 (dd, 2H), 7.17 (dd, 2H), 2.40 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ ppm 143.16, 142.18, 136.49, 133.54, 130.25, 128.79, 127.58, 124.43, 30.90.

MS (EI), m/z (%): 27 (3), 39 (8), 51 (10), 63 (15), 82 (14), 91 (10), 115 (18), 139 (7), 152 (30), 167 (70), 168 [M^+] (100)

1-1'-biphenyl 91 (homocoupled product):

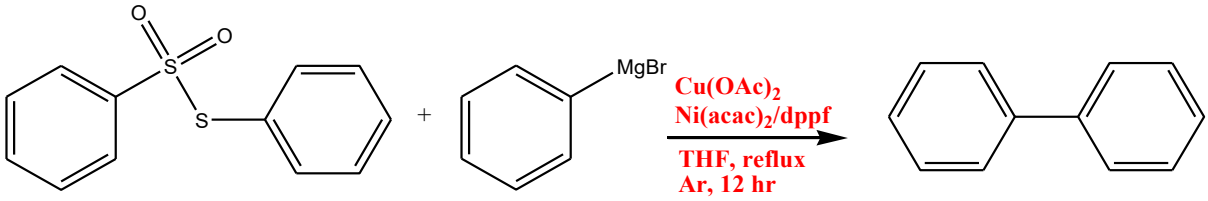


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.34 (dd, 5H), 7.09 (dd, 5H).

^{13}C NMR (100MHz, $CDCl_3$): δ ppm 137.46, 133.94, 129.79, 128.59

MS (EI), m/z (%): 26 (2), 39 (3), 51 (12), 63 (10), 76 (22), 89 (3), 102 (5), 128 (5), 153 (55), 154 [M^+] (100).

4.6. KUMADA-CORRIU SYNTHESIS OF 1-1'-BIPHENYL 91



(88) (92) (91)

> 100 %

Phenylthiosulfonate **88** (1 mmol) was reacted with phenylmagnesium bromide **92** (1.5 mmol) in the presence of 10 mL of THF as a solvent and $Ni(acac)_2$/DPPF (5% mmol/ 10% mmol) as a catalyst under reflux for 12 hours with the reaction progress was monitored by TLC.[4,5,6] This 1.2 equivalent $Cu(OAc)_2$-mediated reaction was run in an inert atmosphere and saw the synthesis of our desired product **91** as a white crystalline solid in yields of >100 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.34 (dd, 5H), 7.09 (dd, 5H).

^{13}C NMR (100MHz, $CDCl_3$): δ ppm 137.46, 133.94, 129.79, 128.59.

MS (EI), m/z (%): 26 (2), 39 (3), 51 (12), 63 (10), 76 (22), 89 (3), 102 (5), 128 (5), 153 (55), 154 [M^+] (100).

4.7. REFERENCES

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