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Presente

Estimad Dr. Uribe,

Mediante la presente, hago constar que el trabajo doctoral del ***M.C. SIDDHANT VILAS KOKATE*** titulado *"*Applications of Organometallic Chemistry in Synthesis*"*, **ha sido cabalmente completado**. Considero que cumple con los requisitos necesarios para que su defensa de su tesis sea llevada a cabo en la fecha y hora que la Coordinación del Posgrado en Química autorice.

Atentamente,
La Verdad os Hará Libres
Guanajuato, Gto. a 10 de septiembre de 2021

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UNIVERSITY OF GUANAJUATO

APPLICATIONS OF ORGANOMETALLIC CHEMISTRY IN SYNTHESIS:

(1) *Functionalization of cyclobutendione oligothiophenes by means of cross-coupling reactions*

(2) *Synthesis of porphyrin-BODIPY hybrids*

by

Siddhant Vilas Kokate

Thesis Submitted in Fulfillment of the
Requirements for the Degree of
Doctor in Chemical Sciences

in the
Campus Guanajuato
Department of Chemistry
Division of Natural and Exact Sciences

under the guidance of
Dr. Eduardo Peña Cabrera (director)
Dr. Miguel Ángel Vázquez (co-director)

University of Guanajuato
September 2021

To my parents, Nisarg, Dr. Pratiksha, Veetrag and Madison

Approval

Name:	**Siddhant Vilas Kokate**
Degree:	**Doctor in Chemical Sciences**
Title:	**Applications of organometallic chemistry in synthesis:** **(1) Functionalization of cyclobutendione oligothiophenes by means of cross-coupling reactions** **(2) Synthesis of porphyrin-BODIPY hybrids**
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Date Defended/Approved:	September 2021

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Siddhant Vilas Kokate

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CONACYT
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LABORATORIO NACIONAL
DE CARACTERIZACIÓN DE PROPIEDADES
FISICOQUÍMICAS Y ESTRUCTURA MOLECULAR
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List of abbreviations

°A	Armstrong unit
Ar	aryl
$AsPh_3$	triphenylarsine
atm.	atmospheric pressure
$Ba(OH)_2$	barium hydroxide
BODIPY	Boron dipyrromethene
9-BBN	9-borabicyclo[3.3.1]nonane
bs	broad signal
t-Bu	*tert*-butyl
BuOH	butanol
°C	degree Celsius
$CDCl_3$	deuterated chloroform
CH_3CN or ACN	acetonitrile
CH_3I	methyl iodide
cm	centimeter
$CSCl_2$	thiophosgene
Cs_2CO_3	caesium carbonate
CsF	caesium fluoride
CuDPP	copper(I) diphenylphosphinate
CuI	copper(I) iodide
CuMeSal	copper(I) 3-methylsalicylate
CuTC	copper(I) thiophene-2-carboxylate
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DMA	dimethylacetamide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DME	dimethoxyethane
DMF	dimethyformamide
DMSO	dimethylsulfoxide
EtOH	ethanol
eq	equation
Equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
FTIR	Fourier-transform infrared spectroscopy
g	gram
HCl	hydrochloric acid
Het	heterocyclic
HIO_3	iodic acid
H_2O_2	hydrogen peroxide
HRMS	high resolution mass spectroscopy
IR	infrared
J	coupling constant

KBr	potassium bromide
K_2CO_3	potassium carbonate
KF	potassium fluoride
KOH	potassium hydroxide
KOAc	potassium acetate
K_3PO_4	potassium phosphate
LiCl	lithium chloride
M	molar
m	multiplet
MeOH	methanol
MHz	mega hertz
min	minute
mg	milligram
mL	millilitre
mmol	milimol
Mp	melting point
$NaBH_4$	sodium borohydride
Na_2CO_3	sodium carbonate
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NaI	sodium iodide
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NH_4Cl	ammonium chloride
nm	nanometer
NMR	nuclear magnetic resonance
Nu-H	general nucleophile
O_2	oxygen
OAc	acetate
OTES	triethylsilyl ether
OTMS	trimethylsilyl ether
$PdCl_2(ACN)_2$	bis(acetonitrile)palladium(II) dichloride
$PdCl_2(PPh_3)_2$	palladium acetate
$Pd[P(t\text{-}Bu)_3]_2$	bis(tri-tert-butylphosphine)palladium(0)
$Pd(OAc)_2$	tris(dibenzylideneacetone)dipalladium(0)
$Pd_2(dba)_3$	tetrakis(triphenylphosphine)palladium(0)
$Pd(PPh_3)_4$	protecting group
$POCl_3$	phosphoryl chloride
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
$P(o\text{-tol})_3$	tris(*o*-tolyl)phosphine
Pr	propyl
iPr	*iso*-propyl
PTSA	*p*-toluenesulfonic acid
Rf	retention factor
r.t.	room temperature
s	singlet
$SOCl_2$	thionylchloride
TBTA	tris(benzyltriazolylmethyl)amine

TEA	triethylamine
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
tol	toluene
Ts	tosyl
UV light	ultraviolet light

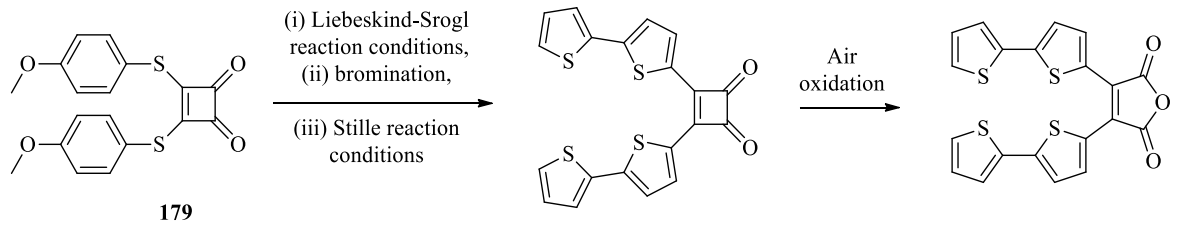
Abstract

The thesis describes the work developed during four years of doctoral studies, which consist of two projects, framed around a general theme that is the application of organometallic chemistry in synthesis. The doctoral projects were developed in the organic synthesis laboratory of the University of Guanajuato under the direction of Dr. Eduardo Peña Cabrera.

The thesis consists of a general introduction, two projects, the experimental part and spectroscopic data of the compounds obtained in those two projects and bibliography.

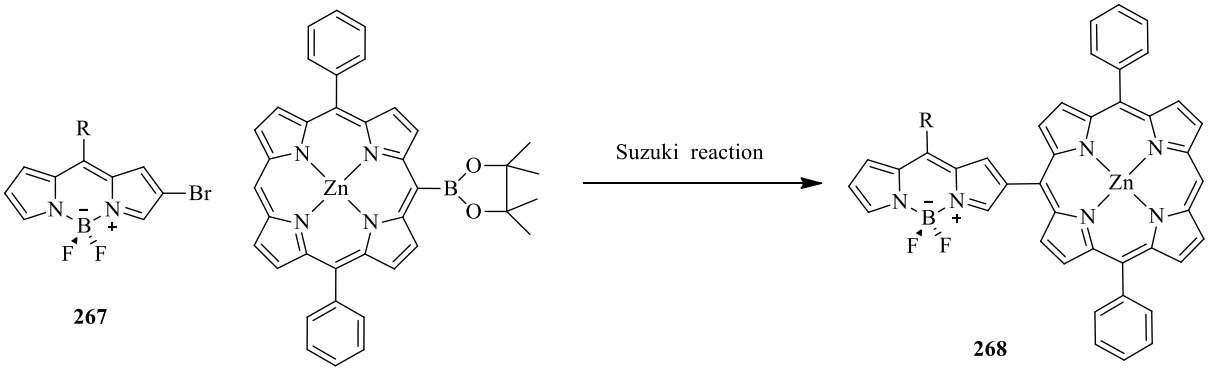
The first chapter involves a brief look over the history of chemistry, along with the meticulous knowledge about the chronicles of organometallic chemistry. Also, an emphasis on the use of organometallic chemistry in industries as well as its industrial applications has been provided. For the better understanding of the two research projects, the crucial basis of cross-coupling reactions as well as use of palladium metal catalysts in cross-coupling reactions has been provided. The cross-coupling reactions, like Liebeskind-Srogl, Suzuki, Stille and Sonogashira has been used in the two research projects, so, the comprehensive information about these reactions including their mechanisms and applications, has been provided. Additionally, the synthetic pathways of BODIPY and use of cross-coupling reactions to synthesize its derivatives were discussed, in order to understand the colossal field of BODIPY chemistry.

In the second chapter involves the functionalization of cyclobutendione oligothiophenes by means of cross-coupling reactions. For that purpose, three different types of cross-coupling reactions, viz., Liebeskind-Srogl, Suzuki and Stille were used. In this chapter, the synthesis of bis-thienyl-substituted cyclobutenedione *via* the Liebeskind-Srogl and Stille cross-coupling reactions was successfully demonstrated. The 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione (bis-thienyl-substituted cyclobutenedione) **192** was successfully synthesized and its photochemical air oxidation to give the 2,3-bis(5-[2,2']-bithien-5-yl) maleic anhydride **193** was also explained.



179 **192** **193**

The third chapter involves the synthesis of porphyrin-BODIPY hybrids. First, the porphyrin boronic ester **261** was synthesized in 7 different steps starting from pyrrole. Then, the *meso-β* linked porphyrin-BODIPY hybrids were synthesized by carrying out the Suzuki coupling between 2-bromo *meso* substituted BODIPY derivatives **267** and the porphyrin boronic ester **261**.



267 **261** **268**

Chapter 1: Introduction

1.1 A glance over the history of Chemistry.

Chemistry as a subject is very important in our day to day lives and also for the society in general. All the things on earth are made of chemicals. Chemistry assists us to figure out how items around us are made. So basically, chemistry is very essential and well-studied branch of science. But what is chemistry? *Chemistry is the branch of science which involves the scientific study of the constituents of matter such as ions, molecules, atoms etc.; and their properties, the changes that matter undergo, energy associated with those changes, its structure, and interactions between the constituents of matter.* All the things surround us, including human body, are made of constituents of matter. Our daily activities are full of chemistry, right from when we wake up, get rid of a blanket, (a thermal insulator which is made of polymer) and jump into the shower to wash our hair and body with formulated soaps and shampoo using purified water. Then we beautify ourselves with different pleasant-smelling gels (pigmented), clothes (dyed fibres made by polymerization), footwear (also made by polymerization), and some attractive jewellery (metal-alloy). After gorging ourselves with a nutrient-enriched cereals (carbohydrates) in milk (consists of proteins, monosaccharides, and fats) and a cup of hot coffee (an aqueous extract consisting of stimulating alkaloid), we cleanse our teeth with a toothbrush (made by polymerization) and toothpaste (colloidal dispersion of dental-hardening agents, which have artificially flavour), grab our electronic devices, like laptop (containing ultrathin, micro etched semiconductor layers powered by a series of voltaic cells), get into our car (a vehicle made of metal-vinyl ceramic, consisting fuel made of hydrocarbons, and leave to the work (Figure 1). Clearly, having knowledge of chemistry is very important to understand the world we see and experience. Today, chemistry has grown into a very diverse field. Occasionally, owing to the interrelation of chemistry with different other areas of STEM (STEM-areas of study in the science, technology, engineering, and field of maths), it is mentioned as “the central science”. Chemistry plays a vital role in biology, medicine, materials science, forensics, environmental science, and many other fields. All these branches of science have crucial overlap between each other, for example, physical chemistry (physics and chemistry), biochemistry (biology and chemistry), chemical engineering (engineering and chemistry), and medicinal chemistry (chemistry and medicine), etc.[1,2]

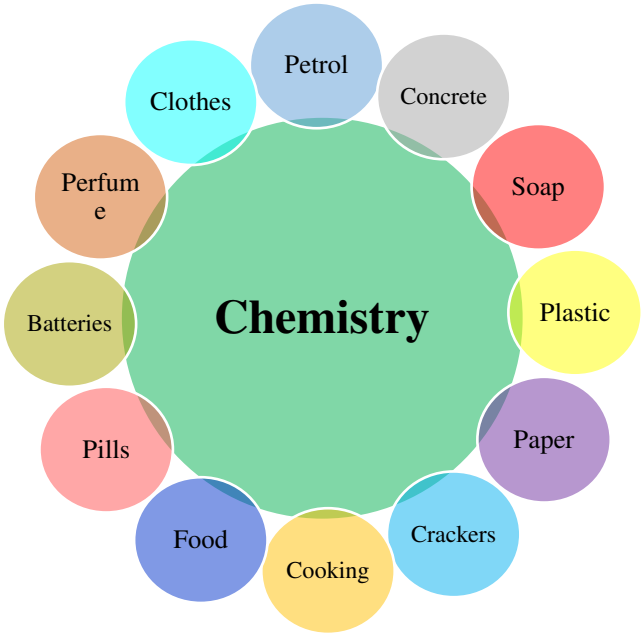


Figure 1. Vast scope of Chemistry.

But how and where it all started? Let's have a glance over chemistry timeline. Chemistry has been around for ages. As a matter of fact, Chemistry is known to mankind since the prehistoric times. Considering the fact that chemistry is known to human race so long, the science is divided into four general chronological periods. The first period was prehistoric times to beginning of Christian era (black magic), the second period was beginning of the Christian era to end of 17th century (alchemy), the third period was end of 17th century to mid-19th century (traditional chemistry) and fourth period was mid-19th century to present (modern chemistry). To give a glance over timeline of chemistry, here, I have mentioned only few discoveries.

Democritus (465 BC)

In the 5th century BC, Democritus was the first to argue that all matter was consists of small, finite particles, which he termed as *atomos*, in Greek which means "indivisible". He thought that atoms had different shapes and sizes, and were moving particles, which also could combine together to form matter.[1]

ARISTOTLE (300 BC)

Later, in the 4th century BC, Aristotle claimed that the matter was made of different combinations of 4 "elements", viz., water, air, earth, and fire, and it could be infinitely divided. He also claimed that matter had four properties- wet, dry, cold and hot.[1]

Alchemists (300 BC -300 AD)

Afterwards, inspired by Aristotle and other Greek philosopher's speculations on composition of matter and with the available chemical technologies, alchemists attempted to transform base metals, like lead and mercury, to noble metals, like silver and gold, by using a mythical alchemical substance called Philosopher's stone (Figure 2).[1]

Figure 2. Alchemist at work.[1]

ELIXIR OF LIFE (1520)

Alchemists also tried to create the elixir of life, a chemical potion, which was supposed to cure all the diseases and help to extend life of people. However, alchemists were never able to achieve this elixir of life.[1]

Dalton's Atomic Theory (1766-1844)

In 1807, after over 2000 years of Aristotle's theory of the composition of matter, an English schoolteacher named John Dalton published atomic theory about the behaviour of matter, which postulated that the matter is composed of atoms, which were exceedingly small and indivisible, which means an atom is the smallest unit of an element that can take part in chemical reaction.[1]

Cathode rays (1879) and discovery of electrons (1897)

In 1879, William Crookes discovered cathode rays by using glass vacuum tube filled with metal electrodes. Those rays were generated at the cathode (negative electrode) and that's why they were termed as cathode rays. In 1897, Sir J. J. Thomson discovered negatively charged cathode ray particles, which now we know them as electrons, by applying magnetic field to the cathode ray tube. He calculated the charge to mass ration of those particles, electrons, and found that they were much lighter than atoms, which was contrary to the Dalton's atomic theory.[1,2]

Radioactive elements (1897)

With Pierre Curie, Marie Curie discovered and isolated radium and polonium (1897). She also studied radioactivity of uranium and won Nobel Prize in physics in 1903 and in chemistry in 1911.[1]

Neutrons (1932) and nuclear fission (1939)

In 1932, James Chadwick discovered the uncharged subatomic particles, neutrons, which have approximately the same mass as that of protons. In 1939, the first nuclear fission was reported by three German scientists, Lise Meitner, Otto Hahn, and Fritz Strassman. They reported that when a slow neutron hit the nucleus of fissionable U-235, it got absorbed and formed an unstable U-236 nucleus. The unstable U-236 nucleus then spontaneously got divided into two smaller nuclei (Ba-141 and Kr-92) along with three neutrons, and discharges a vast quantity of energy (Figure 3).[1]

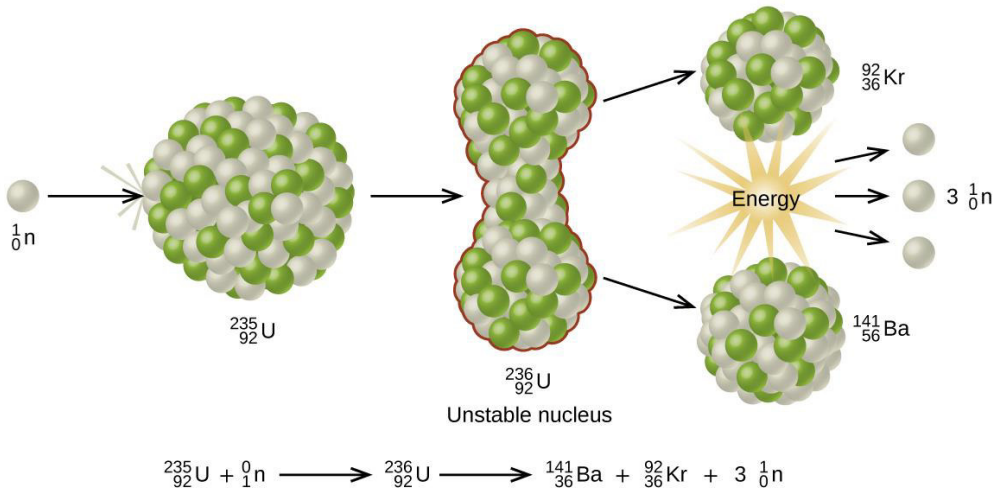


Figure 3. A typical nuclear fission reaction.[1]

1.2 Organometallic Chemistry

1.2.1 Introduction

Organometallic chemistry is the branch of chemistry which deals with the study of organometallic compounds. Organometallic compounds are the chemical compounds which contain at least one chemical bond between a metal and carbon atom of an organic moiety. The metal in organometallic compounds can be transition metals, alkaline, and alkaline earth metals, lanthanides, or metalloids like silicon, boron, arsenic, and tin as well. In more simple words, organometallic chemistry deals with the compounds containing bonds between carbon atoms and metals. Predominantly, those bonds are covalent in nature. Organometallic chemistry is the amalgam of both inorganic chemistry and organic chemistry worlds. Common inorganic species involve dative as well as ionic bonds with variable oxidation states, while the organic compounds largely involve covalent bonds with somewhat restricted valences. Figure 4 is the Venn diagram, which explains how the organometallic compounds are the amalgam of both inorganic and organic compounds, where they consist of inorganic metal centres, M, which are bounded to carbon atom of organic moieties by covalent bonds. Predominantly, organometallic compounds consist of M-C or M-H bonds, however, M-N or M-O bonding interactions are also possible.[3,4]

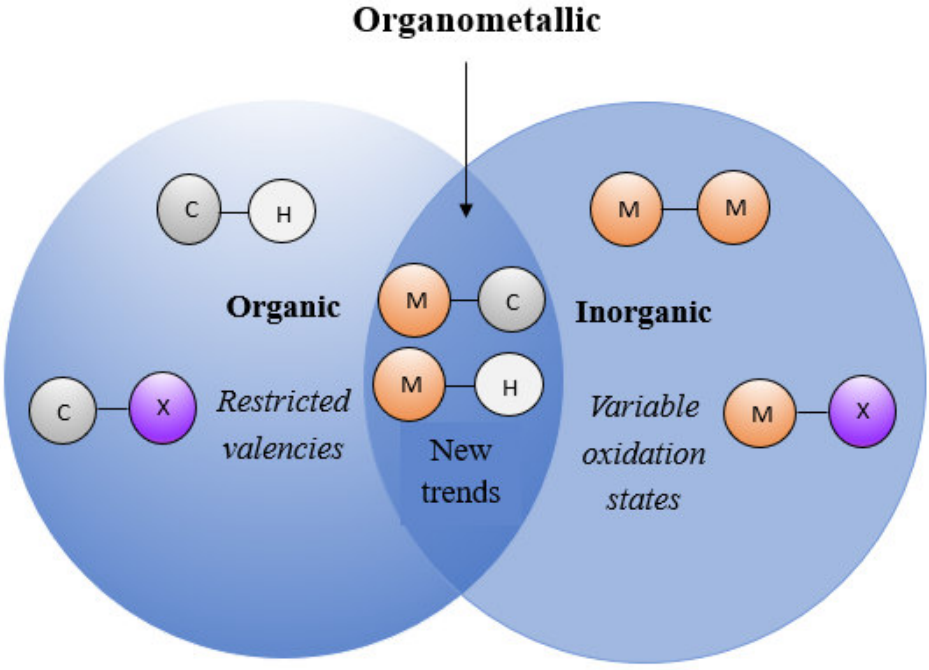


Figure 4. Venn diagram explaining the formation of organometallic compounds by the amalgam of organic and inorganic compounds.

In organometallic compounds, generally, the electrons are unequally shared when the covalent bonds are formed between the metal atoms and the carbon atoms, which makes that covalent bond a polarized bond, where one end is positive and the other one is negative. The strength of the metal atom to bind the electrons dictates the magnitude of polarization. This bond polarity of organometallic compounds separates them from organic compounds. The organometallic compounds have $M^{\delta+}$-$C^{\delta-}$ bond polarity, where carbon containing moieties are carbanionic and

more likely to get attacked by electrophiles. On the other hand, the metal centre is more likely to get attacked by nucleophiles. The metal centre generally has vacant orbitals, which accept the electrons from nucleophiles, and by doing so it stabilizes an unstable transition state of organometallic compounds during the reaction course. While, organic compounds have bond polarity $M^{\delta-}$-$C^{\delta+}$. Generally, non-metallic elements (whose electronegativity is greater than carbon atom), like Cl, Br, F, O, and N, are used, while carbon containing moieties are cationic.[5]

The metal atoms present in the organometallic compounds are either main-group metal atoms or transition metal atoms. The *s*-block metal atoms from groups 1 and 2, and the *p*-block heavier elements from group 13 to 15 in the periodic table are the main-group metal atoms, which can be used as metal atoms in the formation of organometallic compounds. The metalloids from *p*-block, like boron, silicon, germanium, arsenic, etc. can also be used for that matter. For example, the main-group organometallic compounds like *n*-BuLi or $PhB(OH)_2$ are vastly used vastly in organic synthesis. While, the elements from *d*- and *f*-blocks in the periodic table are the transition metal atoms that can be used as metal atoms in the formation of organometallic compounds. For example, ferrocene or Zeise's salt are used extensively in chemistry.[6]

Classification of organometallic compounds

Depending on the type of metal-carbon bonding, the organometallic compounds can be divided into five different types. The electronegativity of carbon is 2.5, so it can form ionic bonds with the electropositive elements, while with several main-group and transition elements it can form covalent bonds.

(a) Metal-carbon ionic bonds: Generally, the elements which have less electronegativity than carbon readily forms metal-carbon ionic bonds. For the generation of ionic compounds, the stability of their hydrocarbon anion is very important. In anions of aromatic and unsaturated systems, the negative charge is delocalized over the entire ring or unsaturated organic groups, and therefore, their anions are very stable. For this reason, the aromatic or unsaturated systems are preferred in formation of ionic organometallic compounds. For example, in $Na^+C_5H_5^-$ salt, a stable $C_5H_5^-$ anion is generated when the $C_5H_5^{\cdot}$ radical accepts electron from the sodium atom. The six π-electrons in $C_5H_5^-$ anion forms a delocalized aromatic ring, like benzene ring system.[5]

(b) Metal-carbon bridge bonding: Generally, the cations of light electropositive elements (e.g., Al, Be, Li, and Mg) are too strongly polarized with the carbanions in ionic compounds. Such elements forms organometallic compounds like CH_3Li, $(CH_3)_2Mg$, and Ph_3Al, which do not exist as monomers rather form oligomers or polymers, viz., $(CH_3Li)_4$, $((CH_3)_2Mg)_n$, $(Ph_3Al)_2$ through bridging by alkyl or aryl groups. This bridge formation is similar to that observed in boranes.[5]

(c) Metal-carbon two electron covalent bond: The metal-carbon (M-C) two electron covalent bonds can be formed by the elements of main-group, when these elements form binary alkyls or aryls, MR_n. Depending on the differences in electronegativity of these elements, their M-C bond polarity can be varied. Lesser the electronegativity difference, lesser is the bond polarity. For example, between $(CH_3)_3B$ and the monomeric form of $(CH_3)_3Al$, the B-C bond shows less polarity than the Al-C bond, because the electronegativity difference of $(CH_3)_3B$ (X_C-X_B = 2.5 - 2.1 = 0.4) is lesser than that of $(CH_3)_3Al$ (X_C-X_{Al} = 2.5 – 1.6 = 0.9). It is observed that with the increase in atomic number of main-group elements, their M-C bond strength decreases. M-C bond also exists in transition metals with alkyl and aryl derivatives, for example, $(CH_3)_4Ti$,

$(C_2H_5)_4Ti$, $(CH_3)_6W$, $(C_2H_5)_2Ni$, etc. In contrast to what was observed in main-group elements, the M-C bond strength of such transition elements increases with increase in atomic number. [5]

(d) Metal-carbon multiple bonds: It is not common to find the metal-carbon multiple bonds in organometallic compounds with main-group elements and carbon, except for multiple bonds of C with O, N and C itself. However, the metal-carbon multiple bonds are observed in organometallic compounds with elements such as P and Si, for example, $Ph_3P{=}CH_2$ (phosphorous ylide) or $R_2C{=}SiR_2$' (silaethenes). Organometallic compounds with transition elements involving metal-carbon multiple bonds are commonly observed, for example, $(Bu^tO)_3W{\equiv}CC_2H_5$, $(OC)_5W{=}C(OCH_3)CH_3$, etc. Such M-C multiple bonds formation in organometallic compounds with transition elements involves overlapping between *2p* orbitals of carbon and *d* orbitals of metal for π-overlap. [5]

(e) Metal-carbon π-bonds with complexes of unsaturated hydrocarbons: Large number of organometallic compounds involving *d*-block transition elements and unsaturated hydrocarbons with metal-carbon π-bonds are observed in organometallic chemistry, for example, Zeise's salt or ferrocene (Figure 5). Predominantly, such bonding interactions are covalent in nature, which can be caused by the interaction between valence orbitals of metal and organic ligand's empty π*orbitals. Very small number of organometallic compounds of unsaturated hydrocarbons with main-group elements involving metal-carbon π-bonds are observed. The bonds involved in such compounds are ionic in nature. Also, large number of organometallic compounds involving lanthanides or actinides and unsaturated hydrocarbons with metal-carbon π-bonds are observed. The bonds involved in such compounds are strongly polar in nature. The unsaturated hydrocarbons involved in such organometallic compounds are mainly cyclopentadienyls, allys and cyclooctatetraene.[5]

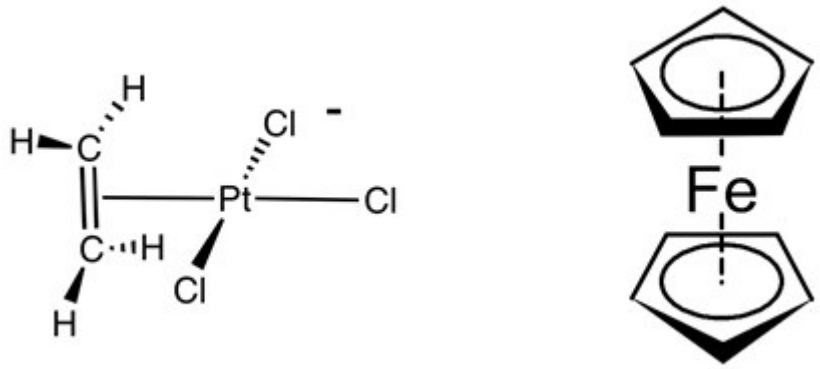


Figure 5. Structures of (a) Zeise's salt and (b) Ferrocene.

Properties of organometallic compounds

Organometallic compounds have different chemical and physical properties. The physical properties of large number of organometallic compounds are more similar to the physical properties of the organic compounds than the physical properties of the inorganic compounds. At normal temperature, a large number of organometallic compounds exists as gases, liquids or low melting crystals, their distinct structure is the reason behind it. Normally, the organometallic compounds are soluble in organic solvents with weak polarity, like, ethers, toluene, etc. Strikingly, the chemical composition can greatly affect the thermal stability of such compounds. For example, at ordinary temperature, $(CH_3)_4Ti$ decomposes very quickly, while at 500 °C, $(CH_3)_4Si$ does not show any changes for several days. Kinetic stability of organometallic compounds to the oxygen varies greatly. For example, oxygen does not attack

compounds like $FeCp_2$, $Hg(CH_3)_2$, $(CH_3)_4Si$, etc., at normal temperature, while compounds like $CoCp_2$, $Zn(CH_3)_2$, $B(CH_3)_3$, etc. are highly inflammable. A large number of organometallic compounds are highly toxic in nature, notably the ones who are volatile.[5]

So far, we have got to know about exactly what is organometallic chemistry and organometallic compounds, bond polarity of M-C bonds involved in such compounds, classification of organometallic compounds depending on the type of M-C bonds involved in them, and properties of such compounds as well. However, it is interesting to find out when, where and how all of this started? To find out that let's have a quick look at the chronicle of organometallic chemistry (Figure 6).

1.2.2 A chronicle of Organometallic Chemistry.

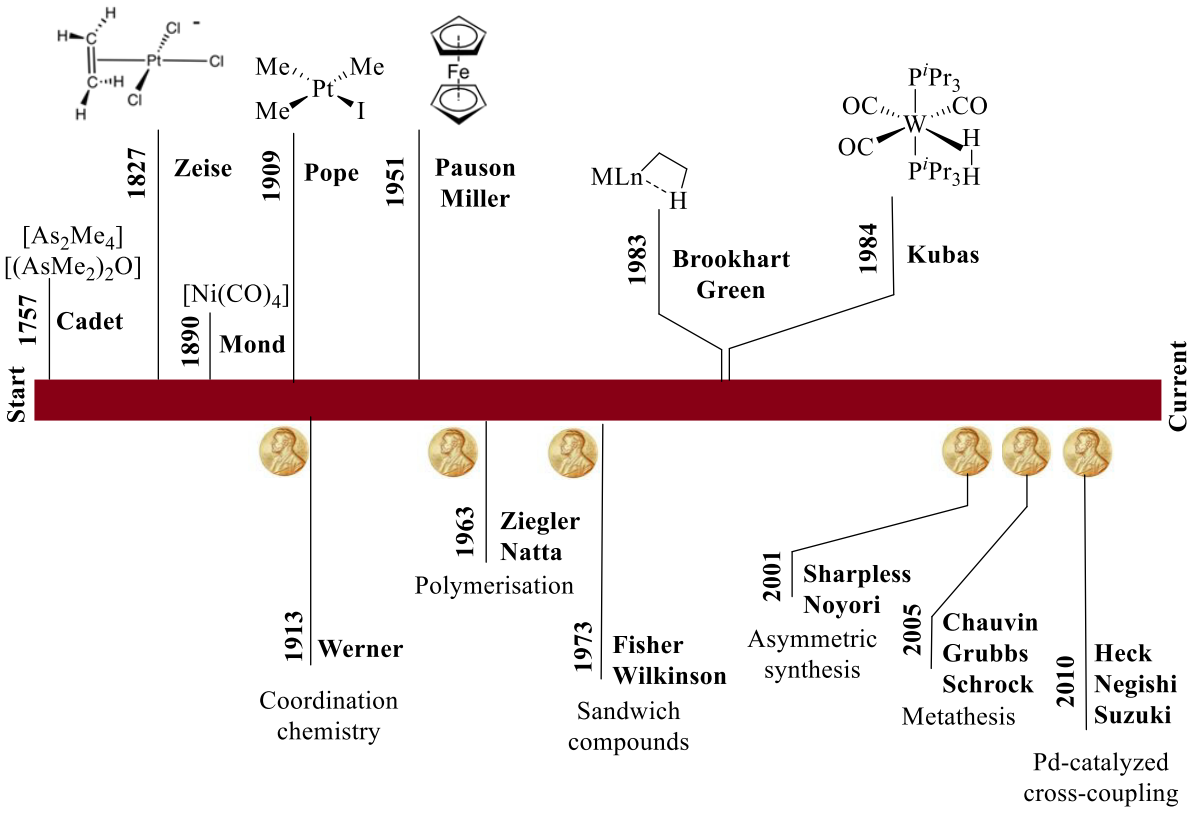


Figure 6. Timeline of organometallic chemistry.

- In 1757, the first organometallic[7] compounds were synthesised when **Louis Claude Cadet de Gassicourt**[8] accidently obtained a mixture of organoarsenic compounds while investigating cobalt containing inks. That mixture of organoarsenic compounds was called as Cadet's fuming liquid. In late 1830s, **Robert Bunsen** characterised Cadet's fuming liquid and identified them as tetramethyldiarsane-$[As_2(CH_3)_4]$ and cacadoyl oxide-$[(As(CH_3)_2)_2O]$, this discovery nearly cost him his life.[7]
- One of the most important discoveries in the 19th century was the discovery of the Zeise's salt, a π-complex $K[PtCl_3(C_2H_4)]$ (Figure 7). It was synthesised by the Danish pharmacist **William C. Zeise** in 1827. It was the first synthetic organometallic compound involving transition metal atom, Pt.[4,7]

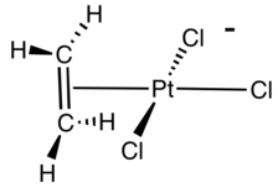


Figure 7. Structure of Zeise's salt.

- In the mid-1850s, the British chemist **Edward Frankland** discovered several air sensitive metal alkyl species of zinc [$Zn(C_2H_5)_2$], mercury [$Hg(C_2H_5)_2$], boron [$B(CH_3)_3$] and tin [$Sn(C_2H_5)_4$], while he was working on the preparation of methyl and ethyl radicals in Robert Bunsen's laboratory.[4,7] Diethylzinc (DEZ)[9] is highly useful as doping agent and for corrosion protection in nuclear reactor. Many other organometallic complexes consisting main-group elements were synthesized by utilizing the zinc and mercury metal alkyl complexes. For example, in 1863, **C. Friedel** and **J. M. Crafts** used ZnR_2, a metal alkyl, as alkyl transfer reagents, for the synthesis of organochlorsilanes R_nSiCl_{4-n}. This discovery set the groundwork for industrial silicon chemistry.[4,7]
- In 1870, first metal carbonyl complexes, such as [$Pt(CO)_2Cl_2$] and [$Pt(CO)Cl_2]_2$, were synthesized by **Schützenberger**. In 1890, the British industrial chemist **Ludwig Mond** reported the synthesis of first binary metal carbonyl compounds, such as tetracarbonylnickel, [$Ni(CO)_4$] and pentacarbonyl iron, [$Fe(CO)_5$]. This laid the foundation for the synthesis of many other metal carbonyl compounds, such as $Cr(CO)_6$ (Job and Cassal-1927), $Fe(CO)_4H_2$ (1st organometallic hydride complex by W. Heiber, in 1931), etc.[4,7]
- The research work of the French chemist **Phillipe Barbier's** on the preparation of organomagnesium compounds was the highlight of the end of the 19th century, which laid the foundation for his then doctorate student **Victor Grignard's** discovery of the well-know **"Grignard reagents"**, RMgX. Grignard's reagents are vastly used in the formation of C-C bond with carbonyl groups in aldehyde or ketone. In that period, the introduction of Grignard's reagent in chemistry not only had a huge impact on transition-metal organometallic chemistry, but also it greatly boosted the progress of organic chemistry.[4,7]
- One of the most important highlights of the first half of 20th century was the dawn of catalysis in chemistry. The French chemist **Paul Sabatier** was the first to distinguish between heterogeneous and homogenous catalysis. He reported the heterogeneous hydrogenation of olefins to saturated hydrocarbons using nickel. For his work in catalysis, he received 1912s Nobel Prize in Chemistry along with **Grignard** (for the discovery of Grignard's reagents).[4,7]
- Organometallic chemistry boomed in the 1950s, due to various significant discoveries such as structure determination of the first bio-organometallic compound, vitamin B_{12} coenzyme or the synthesis and structure determination of sandwich complexes, like ferrocene. Ferrocene was accidently synthesized by three different groups of researchers, independently, during 1940s-1951. First, by some anonymous chemists at Union Carbide, in 1940. Second, by S. Miller *et al.* at British Oxygen, around 1950 and third, by Pauson[10] and Kealy at Duquesne University, in 1951. All these researchers failed to determine the structure of this mystery compound. In 1951, German theoretical chemist **Ernst Otto Fischer** and British chemist **Sir Geoffrey Wilkinson** independently discovered the sandwich structure[11] of the compound ferrocene,[12] [$Fe(C_5H_5)_2$], which is commonly known as sandwich complex (Figure 8).

The discovery of ferrocene opened the gates for the study of other new π-complexes with poly-hapto ligands or one can say study of complexes involving hydrocarbons and *d*-block metals and thus, many other metallocenes were prepared after that. The impact of this discovery was such that Fischer and Wilkinson was awarded 1973s Nobel Prize in chemistry.[4,7]

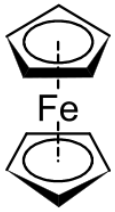


Figure 8. Structure of Ferrocene.

- The British chemist **Dorothy Crawfoot Hodgkin** determined the X-ray crystal structure of first bio-organometallic compound, vitamin B_{12} coenzyme, in 1956, which contains the M-C bond. For this discovery she received the Nobel Prize in 1964. From 1961-1972, **Robert B. Woodward** and his other 99 co-workers managed to perform the total synthesis of this very same coenzyme in total 70 steps.[4]
- In the 1950s, the German chemist **Karl Ziegler** developed a catalyst for ethylene polymerization based on a catalyst formed by the reaction of $TiCl_4$ with $Al(C_2H_5)_3$. Very soon after that, the Italian chemist **Giulio Natta** made use of this type of catalyst for the polymerization of propylene to produce polymers with highly regular structures. In 1963, the Noble prize in Chemistry was awarded to them for this discovery.
- In 1983, the concept of agostic interaction or intramolecular agostic C-H bond in complexes involving Lewis acidic transition metal centre was introduced by **Brookhart**[13] and **Green**[14]. In such metal complexes, the C-H bonds can play role of ligands through an intramolecular interaction involving two-electron, three-centre species.
- In 1984, **Gregory Kubas** reported the transition metal complexes involving a coordinated dihydrogen molecule, where the transition metal has poor electron density. The poor electron density of the transition metal aids to avoid oxidative and the formation of metal dihydride, which in turn gives the stable and isolable dihydrogen transition metal complexes.[4]
- Since the start of 1980s, researchers all over the world started to show interest in finding industrial applications by using the concepts of organometallic chemistry. The effort and impact were so significant that just from 2001-2010 three Nobel Prizes were awarded to three groups of organometallic chemists from all over the world.
- In 2001, **William Standish Knowles** shared half of the Nobel Prize in Chemistry in 2001 with **Ryōji Noyori** for "their work on chirally catalysed hydrogenation reactions". The other half of the prize was awarded to **K. Barry Sharpless** for the development of a range of catalytic asymmetric oxidations.
- In 2005, **Yves Chauvin, Robert H. Grubbs and Richard R. Schrock** were collectively awarded the Nobel Prize in Chemistry, for their elucidation of the reaction mechanism and their discovery of a variety of highly active catalysts in Olefin metathesis (Figure 9).

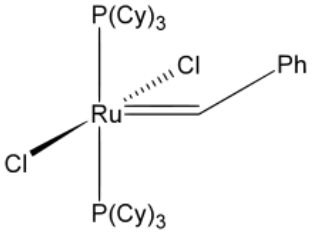


Figure 9. Structure of Gubbs catalyst.

- In 2010, an American chemist **Richard Frederick Heck** was awarded the Nobel Prize in Chemistry for his work on palladium-catalyzed cross-coupling reactions in organic synthesis, which he shared it with the Japanese chemists **Ei-ichi Negishi** and **Akira Suzuki**. Suzuki first published the Suzuki reaction, the organic reaction of an aryl- or vinyl-boronic acid with an aryl- or vinyl-halide catalyzed by a Pd(0) complex, in 1979. Negishi published the Negishi reaction, the reaction couples organic halides or triflates with organozinc compounds, forming carbon-carbon bonds (C-C) in the process.

From left: Suzuki, Negishi, and Heck (2010)

1.2.3 Why so much emphasis on use of Organometallic Chemistry in industries?

The boom in the organometallic chemistry took place in the 1950s, in terms of new research and applications, especially with industrial processes in pharmaceutical, fine chemical or agriculture industries. Since then, organometallic chemistry came out from the shadows of coordination, inorganic and organic chemistry to a very important branch of chemistry in its own right. The applications of organometallic compounds as stoichiometric reagents or catalysts greatly affected organic synthesis of molecules and has revolutionized the manufacturing of organic compounds in many industrial areas. However, all these things did not happen in one day, but the transformation took place gradually but firmly, starting from synthesis of first synthetic organometallic compound involving transition metal atom, Zeise's salt, to the revolutionary discovery of Grignard's reagent, and to the highly useful cross-coupling reactions like, Suzuki, Heck or Sonogashira, etc. Organometallic chemistry's rise has provided synthesis and understanding of many interesting structures, like ferrocene, new significant conceptual perceptions, and effective organometallic catalysts for the processes used in many industrial areas. Due to their unique structures, properties and high reactivities, the organometallic compounds became so crucial in industrial processes.[3,15]

Many organometallic catalysts are proficient in selectively introducing asymmetric centres in organic compounds while carrying out their asymmetric synthesis and they have been greatly used in the asymmetric synthesis of one preferred enantiomer of a chiral compound. It has been discovered that the enzymes, like acetyl CoA synthase, can carry out organometallic catalysis. Such association of organometallic chemistry with biochemistry is proving to be pivotal in mankind's pursuit of finding applications of organometallic catalysis in industries. New conceptual ideas from organometallic chemistry have been applied to understand the chemistry of metal and metal oxide surfaces, which found to be of significant importance in the area of heterogeneous catalysis. Recently, the association of organometallic chemistry and material science shown much usefulness. By the method of thermal decomposition of the metal substrates, organometallic compounds have been preferentially used as the starting materials to deposit materials on different kind of substances.[15]

Organometallic compounds can be used as precursors for synthesis of nanoparticles and by doing so they are greatly transforming the fields of nanotechnology and nanoscience.[16] Such nanoparticles with metals have unique properties and found many valuable applications in solar cells, optical, electronic, magnetic or light-emitting devices, and also in sensors[17]. Recently, nanoparticle catalysis became an emerging field. Many organometallic compounds are also present in biological systems, for example, the chlorin ring in chlorophyll contains magnesium at the centre or porphyrin ring in myoglobin and haemoglobin has iron at the centre. Nowadays, the synthesis of most of the natural products and medicines of pharmaceutical industries include at least one or more than one catalytic reaction which involves organometallic compounds, for example, methanol carbonylation, hydrogenation, hydrosilylation, hydroformylation, hydrocyanation, olefin metathesis, alkene polymerization, alkene oligomerization, hydrocarboxylation, etc. In the past couple of decades, global warming causes by pollution became a serious threat to the well-being of our planet earth and mankind as well.[15,18]

Along with the governments all over the world, the researchers are trying to come up with the solutions to deal with those threats. Green chemistry is the branch of chemistry, which is

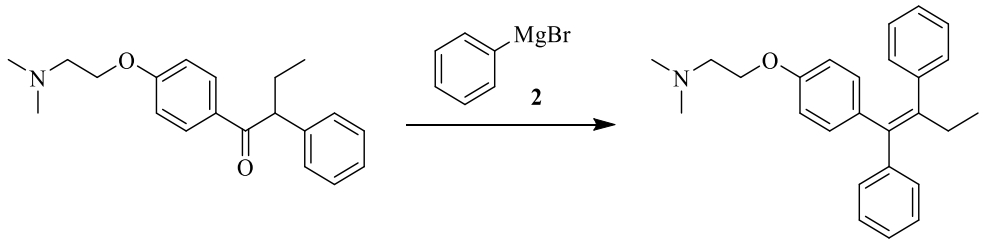
dedicated to solving those problems, which are man-made only. Many industrial processes cause a tremendous amount of pollution in terms of toxicity, by releasing toxic green-house gases like CO, CO_2, SO_2, etc., and solvent or chemical wastes, like by-products of chemical reactions. So, it became very crucial to create more efficient, greener or cleaner and economical industrial processes to tackle these problems. To solve these problems, atom economy came up with a satisfactory solution. By controlling the atom economy of the industrial processes, the solvent/chemical waste, by-product formation can be reduced, along with the minimizations of presence of starting materials which remained unreacted during the reaction course. Catalysts involving organometallic compounds has a huge arsenal to solve these problems. They are being used to eliminate the above-mentioned problems and improve the atom economy of the industrial processes. For example, no notable by-products are formed during the Cativa and Monsanto processes, which are the processes used to convert the methanol and carbon monoxide to acetic acid by using iridium and rhodium-based catalysts, respectively. Recovery and re-use of catalysts has become an important factor in industrial processes as well, which can help to tackle the economic and ecological challenges faced by industries. Catalysts involving organometallic compounds comes handy for that reason and very crucial in that direction.[15,18]

So now what's next for this amazing branch of chemistry, organometallic chemistry? Organometallic chemistry's future looks quite bright, and it will be a branch of chemistry which will be pursued by many researchers, for sure. The chemistry related to the organometallic compounds is precious, exclusive and irreplaceable, therefore, there are and will be many researchers studying and exploring the interesting chemistry of organometallic compounds.

1.2.4 Some important industrial applications of organometallic chemistry.

So far, we got to know about organometallic chemistry, its history and some reasons answering why it is very useful in industries. Here, we will have a look at some important industrial applications of organometallic chemistry.

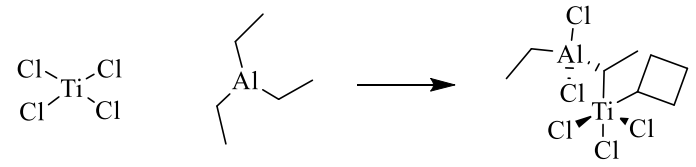
The Grignard reagents (organomagnesium halides) are used widely in industrial processes involving organic synthesis. If you've ever known anyone who's had breast cancer, you may remember that they were taking the drug Tamoxifen **3**.[19] Did you know that during the synthesis of Tamoxifen, an organometallic compound is used? Its phenylmagnesium bromide **2** and it is used to add a benzene group to the compound **1** (eq 1). The Grignard reagent is special in the chemistry world because it creates a new bond between two carbons. Here's the important thing to remember, there aren't many reactions that do this!



(1)

1 Tamoxifen **3**

Alkylaluminum compounds are also used in industrial processes involving organic synthesis. Used with titanium salts, they form important catalysts called Ziegler-Natta catalyst (eq 2), which can be used in the polymerization of unsaturated hydrocarbons, like propylene and ethylene **7** to form polymers such as polypropylene and polyethylene (eq 3), respectively. The polymerization process by using Ziegler-Natta catalyst has been used in industries all over the globe and it provides polyethylene and polypropylene supply to almost entire world. Unlike thermal polymerization, which requires drastic reaction conditions (200 °C and 1000 atm.), polymerization using Ziegler-Natta catalyst requires mild condition (25 °C and 1 atm.). Another benefit of polymerization using this catalyst is that the obtained product has less branching than the one using thermal method. Polymers obtained by using this method are used in so many things, like, trays, drums, milk/fruit juice bottles, garbage containers, toys, fishing nets, ropes, etc.[20,21]

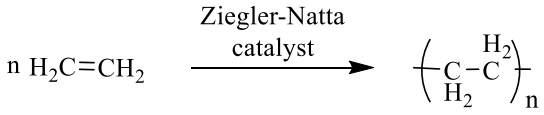


(2)

4 Titanium tetrachloride

5 Triethyl aluminium

6 Ziegler-Natta catalyst

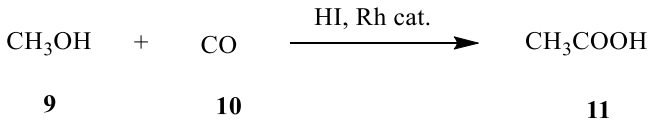


(3)

7 Ethene

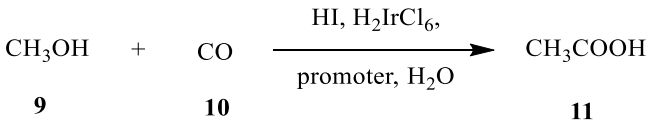
8 Polythene

Large scale carbonylation (addition of CO **10**) of MeOH **9** to acetic acid **11** using transition metal catalysts is successfully used in various industries across the world. The Monsanto process (eq 4) uses an anionic Rh carbonyl catalyst, while Cativa process (eq 5) uses similar iridium-based catalyst. Cativa process is more environmentally friendly and economical than the Monsanto process. Acetic acid prepared by these processes have been used mainly as an acylating agent in the synthesis of aspirin, as a solvent for the synthesis of esters, etc.[22,23]



(4)

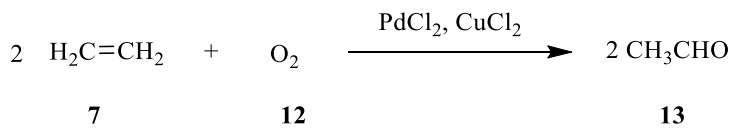
9 **10** **11**



(5)

9 **10** **11**

Hydroformylation or *oxo* process, discovered by Otto Roelen in late 1930s, is the addition reaction of carbon monoxide and hydrogen, syngas, to an alkene using $Co_2(CO)_8$ as a catalyst to form an aldehyde, which contains one extra carbon atom than the starting alkene. Large scale industrial production of synthetic aldehyde from alkene has been achieved globally by this process using Co or Rh catalytic system. This transition metal catalysed reaction has been used in the petrochemical industry, in the synthesis of fragrances, medicines, etc. Similarly, in the Wacker process, acetaldehyde **13** can be prepared by the oxidation of ethylene **7** using palladium(II) chloride as a catalyst (eq 6). This process is also used on an industrial scale for the production of synthetic aldehyde. The aldehydes synthesized by these processes can be reduced to alcohols, which has applications as plasticizers, as solvents, and in the synthesis of various pharmaceutical agents and detergents.[24,25]



(6)

7 **12** **13**

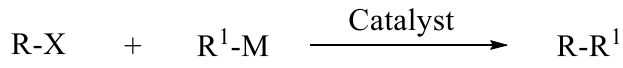
1.3 Cross-coupling reactions.

In 1941, nearly 40 years after the discovery of Grignard's reagent, an Ukrainian organic chemist Morris Selig Kharasch carried out the first systematic carbon (sp^2) - carbon (sp^2) coupling reaction, while he was analysing the behaviour of homocoupling of Grignard's reagents.[26,27] In 1943, he reported the earliest C-C bond forming cross-coupling reaction involving transition metal catalyst, where a vinyl bromide and an aryl Grignard reagent were coupled using a cobalt-based catalyst.[28] His studies on the behaviour of Grignard's reagents laid the foundation for cross-coupling reaction, which made him the father of cross-coupling reactions.

The cross-coupling reactions involving transition-metal catalysts represent a class of synthetic transformations which consists of organometallic reagents (mostly main group metal atom) and organic electrophiles, like alkyl or aryl halides, to form a C-C, C-O, C-N, C-S, C-H or C-P bond. These type of reactions have surfaced as a synthetic tool of great importance and their recent developments has provided a vast array of efficient coupling partners to for the synthetic purposes.[29,30,31] In the past five decades, the scientists all over the world have carried out a tremendous amount of research and developments on the transition-metal catalyzed cross-coupling reactions and were able to synthesize and study the compounds with complex structures and interesting diverse applications. The compounds prepared by using such cross-coupling reactions have applications in many fields, such as, polymers, nanotechnology, chemical biology, agrochemical industries, synthesis of natural products and pharmaceutical agents, etc. Recently many developments have been carried out in the field of cross-coupling reactions to provide a variety of organometallic reagents used in these kinds of reactions and to expand the scope of functional groups, which can be used along with those organometallic reagents.[32,33,34,35,36] The cross-coupling reactions have been very popular among scientific community due to such synthetic diversity and a vast array of applications of the compounds prepared by using them. The impact and importance of cross-coupling reactions was so huge that, in 2010, Richard Heck, Ei-ichi Negishi and Akira Suzuki received the Nobel Prize in chemistry for their contribution on Pd-catalyzed cross-coupling reactions in organic synthesis.[37,38]

Since 1970s, many cross-coupling reactions have been emerged as a powerful tool for C-C bond formation in organic synthesis, which involved different kinds of organic electrophiles and organometallic reagents (R^1-M), like, organotin, organozinc, organoboron, organosilicon, etc. (Scheme 1). For example, the Migita-Kosugi-Stille cross-coupling reaction involves organostannanes,[39] the Suzuki-Miyaura cross-coupling reaction encompasses organoboranes,[40,41] the Kumada reaction consists of organomagnesium compounds (Grignard's reagent),[42] and the Negishi reaction profits from organozinc compounds,[43] etc. Nowadays, many industrial processes successfully use the cross-coupling reactions involving organometallic reagents and a great number of important synthetic compounds are prepared by using them.

General reaction for all cross-coupling reactions is as follows,



M = Li (Murahashi),
Mg (Kumada-Tamao, Corriu),
B (Suzuki-Miyaura),
Al (Nozaki-Oshima, Negishi),
Si (Tamao-Kumada, Hiyama-Hatanaka),
Zn (Negishi),
Cu (Normant),
Sn (Migita-Kosugi-Stille), etc.

Catalyst = Rh, Ni, Cu, Pd, Fe, etc.

X= I, Br, Cl, OTf

Scheme 1. General reaction for all cross-coupling reactions.

The reaction mechanism of cross-coupling reactions may vary depending on the type of organometallic reagent and the organic halide used. In general, the sequential steps by which a cross-coupling reaction occurs proceeds through the following catalytic cycle, which is shown below (Figure 10).

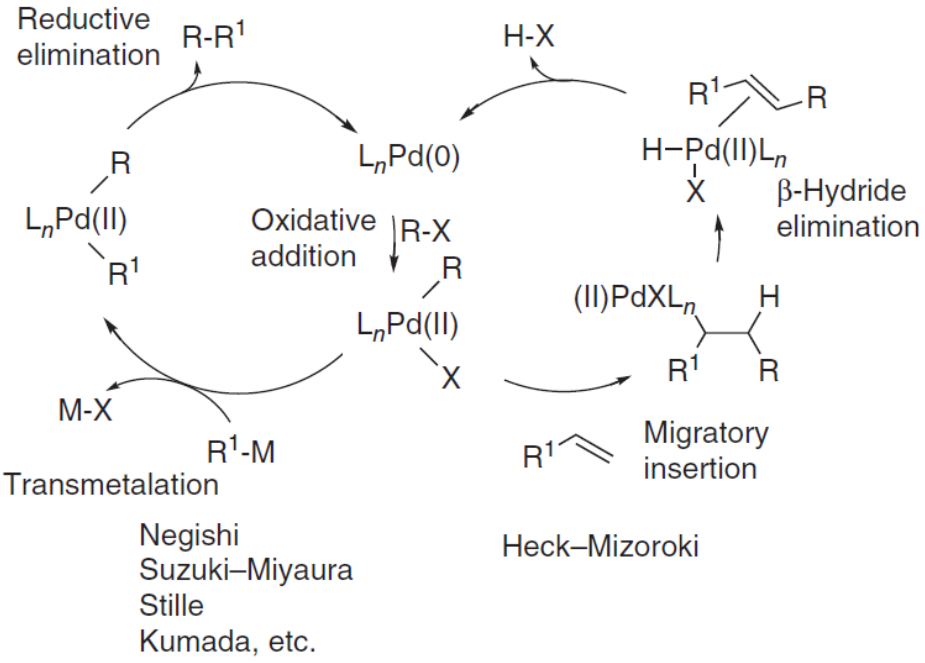


Figure 10. General catalytic cycle of cross-coupling reactions.[37]

The general catalytic cycle for cross-coupling reactions consists of three main steps in the following order: (i) oxidative addition, (ii) transmetalation (organometallic substitution), and (iii) reductive elimination. The first step involves the oxidative addition of the organic halide (organic electrophile), R-X, to the Pd(0) catalyst, which generates the [Pd(II)(R)(X)] species, where palladium is oxidized from 0 to +2 oxidation state. Generally, this step is considered as the rate determining step in the cross-coupling reactions. Additionally, the C-X bond strength

is very crucial as well for this oxidative addition step. Depending on the bond dissociation energies of C-X bond, the reactivity usually decreases in the following order: I > Br > Cl. This step can be improved by increasing the stability and activity of catalytic systems by using efficient supporting ligands, like, X-phos, S-phos, $P(Cy)_3$, PPh_3, etc. The 2nd step is termed as transmetalation step, where the R^1 group from R^1M is transferred from M (one metal) to Pd (another one) which results in the formation of [Pd(II)(R)(R^1)] species. The last step is the reductive elimination step, where, reductive elimination of the R and R^1 groups of [Pd(II)(R)(R^1)] species takes place and palladium is reduced back to 0 from +2 oxidation state, here, the desired product R-R^1 is formed and the Pd(0) catalyst is regenerated and recovered.

In the pursuit of understanding the exact nature of mechanism of the above-mentioned steps, many researchers all over the world carried out several studies. Various research groups, like, Hartwig *et al.*, Lloyd-Jones *et al.* and Denmark *et al.*, have independently carried out studies regarding the transmetalation step of the Suzuki-Miyaura cross-coupling reactions.[44,45,46] Generally, Cu-catalyst is used in stoichiometric amount as a co-catalyst in Sonogashira cross-coupling reaction.[47] However, several recent studies of this reaction have reported that on careful selection of reaction conditions and palladium catalyst, the use of Cu co-catalyst can be avoided.[48,49,50]

1.3.1 Palladium Metal Catalysts for Cross-Coupling reactions.

The organometallic chemistry of palladium is one of the most extensive and varied fields of transition metal organometallic chemistry. In many respects, the chemistry of palladium parallels that of platinum, as one would expect from its place in the periodic table. However, where a given compound might be a stable species in platinum chemistry, it will often be a reactive intermediate in some palladium catalyzed process. Many of the more than 1000 research articles that are published each year in organopalladium chemistry deal with applications of palladium complexes in organic synthesis. These applications arise because palladium complexes readily form reactive adducts with many common, inexpensive classes of organic molecules, such as alkenes, alkynes, dienes, CO, and alkyl, aryl, and vinyl halides. The resulting compounds, in turn, can be used to introduce new functional groups into organic molecules or change the framework of the organic moiety through carbon–carbon bond formation.[51]

In organometallic chemistry, palladium exists in four different oxidation states, viz., Pd(II), Pd(0), Pd(IV), and Pd(I). Palladium metal can change its reactivity from electrophile to nucleophile by reducing palladium Pd(II) to Pd(0). However, unlike main group nucleophiles such as thiolates or cyanide, Pd(0) complexes react with both alkyl halides and aryl or vinyl halides. Reactions of Pd(0) complexes with these latter sp^2 halides generate new Pd(II) aryl or vinyl bonds through the process of oxidative addition. Derivatives of Pd(II) are normally prepared from $PdCl_2$. This salt is insoluble in organic solvents, and nearly so in water. Thus, it is normally used in a solubilized form. Addition of MCl to $PdCl_2$, where M= Li, Na, or K, gives M_2PdCl_4, which is soluble in water and low-molecular weight alcohols. The Li salt is also soluble in many organic solvents.[52]

The more electrophilic reagent $Pd(OAc)_2$ is another useful reagent in organopalladium chemistry. It is monomeric in benzene at 80 °C but is trimeric at room temperature in benzene. For even greater reactivity, $Pd(O_2CCF_3)_2$ can be used. Both the acetate and trifluoroacetate are soluble in organic solvents. Reaction of palladium acetate with acetylacetone produces $Pd(acac)_2$. This acetylacetonate and especially the hexafluoroacetylacetonate, $Pd(hfac)_2$, are useful as volatile sources of palladium in metalorganic chemical vapor deposition.[53] With proper optimization of reaction conditions, these catalysts can be more efficient than the stoichiometric catalysts or co-catalysts in many aspects, like, high tolerance of functional groups, high selectivity, preventing the use of protecting groups, mild reaction conditions, low loadings, etc.

The discovery of the Pd-catalyzed cross-coupling was more subtle and evolutionary. Thus, Pd catalyst have been used vastly in the past four decades in organic synthesis including method developments and synthesis of natural products. The cross-coupling reactions involving Pd catalysts, such as Suzuki, Tsuji-Trost, Negishi, Stille, Heck, Kumada and Sonogashira reactions, have been vastly used not only academic research but also in industries.

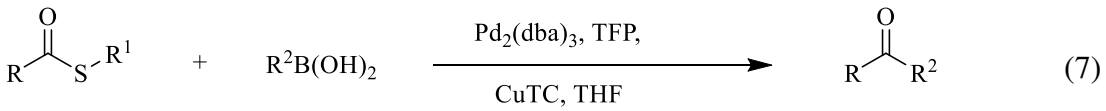
1.3.2 Liebeskind-Srogl cross-coupling reaction.

A great number of uniquely selective, efficient, reliable, and highly studied C-C bond forming cross-coupling reactions are well reported in the past five decades. However, researchers all over the world are curious and interested in finding out new and unique reaction protocols which can come up with different or orthogonal reactivity to that of the available protocols. In addition to that, many of the organic halides or triflates used in those cross-coupling reactions as electrophiles are unstable and not easily available. Furthermore, many of these cross-coupling reactions are carried out using basic conditions, and it can be a huge challenge and drawback when reactions consist of substrates which are highly sensitive to base. For such reasons, the researchers are in the pursuit of finding substitute electrophiles to organic halides or triflates for cross-coupling reactions. For that matter, electrophiles consisting of sulphur has attracted a lot of attention in past couple of decades, because of their high availability in medicines, bio-molecules and naturals products.[54,55,56,57]

In 2000, Lanny S. Liebeskind and Jiri Srogl reported a new and unique cross-coupling reaction between thioesters as organic electrophiles and boronic acids to synthesize ketones under neutral conditions using palladium as a catalyst, Cu-carboxylate as a co-catalyst.[58,59,60] This reaction involves a reaction mechanism which was never seen before in any other cross-coupling reactions. This C-C bond forming cross-coupling reaction involves palladium(0) as a catalyst, stoichiometric amount of copper(I) as a co-catalyst, and it can be used for wide array of organometallic reagents and organosulfur derivatives. In recent times, this reaction is widely used as a synthetic tool for the formation of C-C bonds, due to the easy access of the starting materials and neutral conditions needed for the reaction, especially in those cases where conventional reactions were not successful. Ever since its first report in 2000, this cross-coupling reaction has been the recipient of attention from the scientific community across the globe.

The key feature of this method is the requirement of a stoichiometric amount of a copper(I) carboxylate species, such as copper(I) thiophene-2-carboxylate (CuTC), as a thiophilic metal co-metal catalyst. Since the year 2000, the scope of this intriguing C-C bond forming process has been extended considerably to enable successful cross-coupling reactions between a variety of organosulfur and organometallic reagents.

The overall reaction is shown below (eq 7).



14 **15** **16** (7)

dba= dibenzylideneacetone, TFP= tri(2-furyl)phosphine. R, R^1= alkyl, aryl and R^3= aryl, styryl.

Generally, thioether or thioester as organic electrophile and boronic acid or stannane as organometallic reagent have been used. However, other reactive organic electrophiles can be used, for example, thioamides, thiocyanates, (hetereo)aryl thioethers, and thioalkynes.[61]

The proposed reaction mechanism for the Cu(I) mediated, Pd(0) catalyzed coupling is shown in Figure 11.

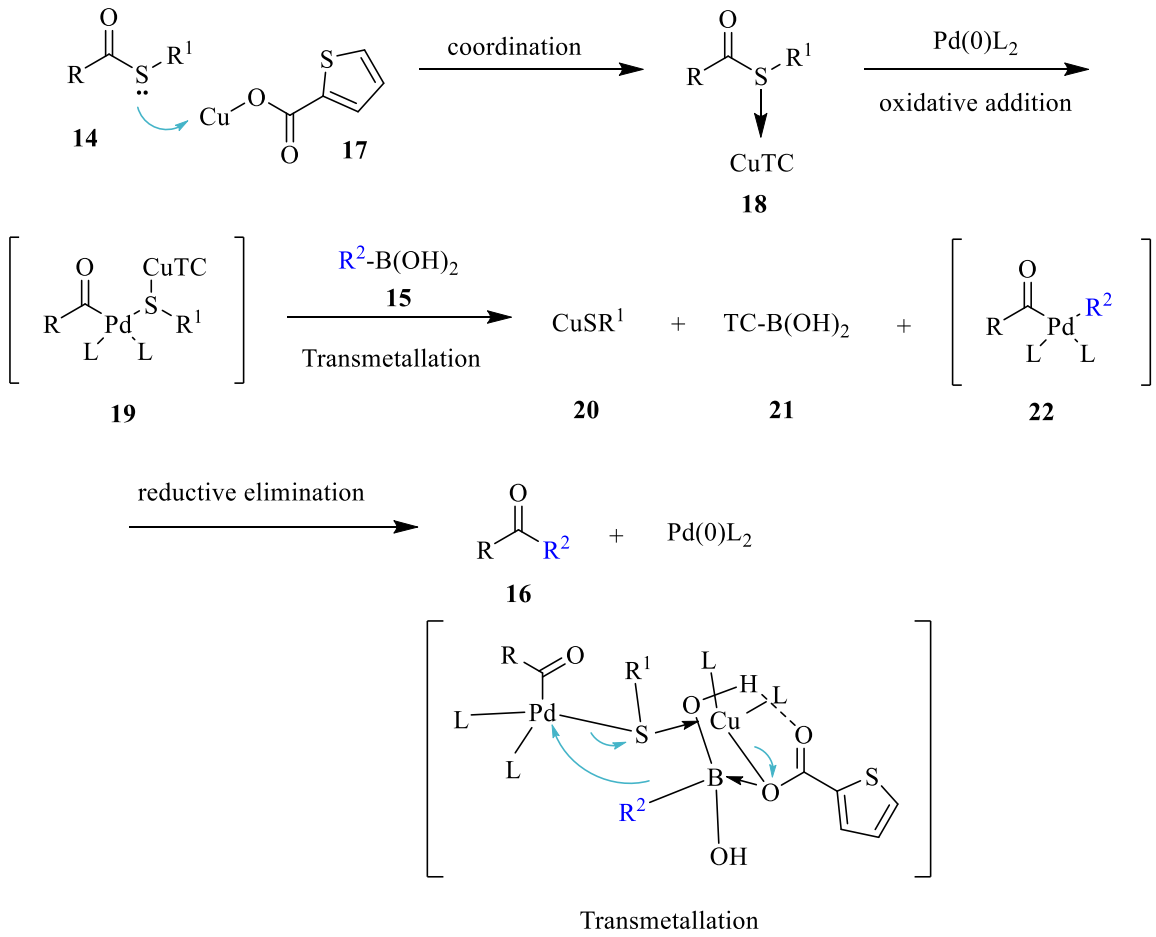


Figure 11. Proposed mechanism for the Liebeskind–Srogl reaction. L= ligand.

The thioester **14** complexes with copper complex (CuTC) **17** to form compound **18**. With the oxidative addition of palladium into the carbon–sulfur bond, compound **19** is formed, and with transmetalation, organopalladium species **22** is formed. The transmetalation proceeds via the transfer of R^2 to the palladium metal centre with concomitant transfer of the sulfur atom to the copper complex. Reductive elimination gives ketone **16** with the regeneration of the active catalyst.

A full equivalent of the Cu(I) additive is required because of the need to scavenge the released thiolate as the reaction proceeds. Any readily available copper(I) carboxylate should be suitable for this coupling reaction. The choice of CuTC or, in subsequent studies, copper(I) 3-methylsalicylate (CuMeSal) or copper(I) diphenylphosphinate (CuDPP), all of which are now commercially available, was explained by Liebeskind and Srogl in terms of a combination of low cost and relative air stability.[62,63] To avoid any undesired oxidation of the Cu(I) co-catalyst to a Cu(II) species, the reaction generally must be performed under an inert atmosphere.

Whereas the presence of a base is essential in the traditional Suzuki–Miyaura cross-coupling of boronic acids and organic halides,[64] an oxygen base was found to be deleterious to the Liebeskind–Srogl reaction.[65] This observation and the much greater reactivity of boronic acids

relative to boronates led to the proposal of a hydrogen bonded, ternary complex as the reactive intermediate (Figure 12).[55] A low-energy reaction pathway via this ternary complex would most likely be sensitive to steric effects and would depend on the presence of hydrogen bonds from the boronic acid to the carboxylate counter ion.[55]

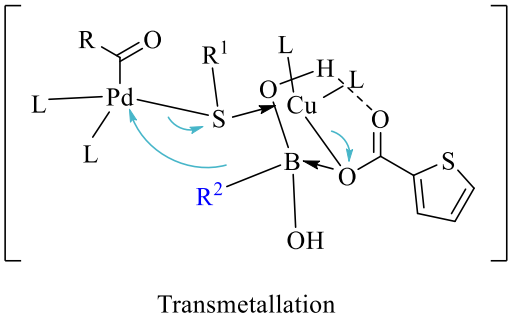
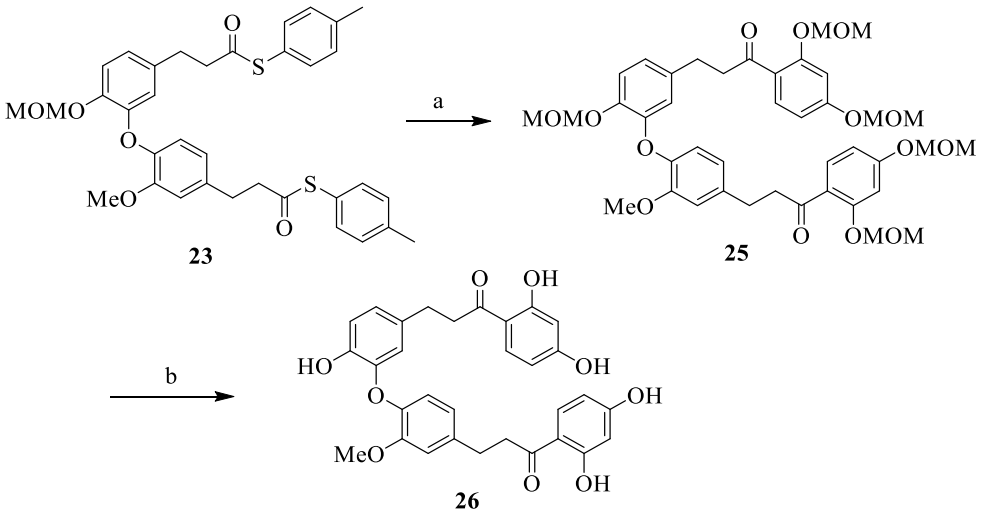


Figure 12. Proposed formation of a ternary complex.

The intermediacy of such a ternary complex was confirmed during the development of a Pd-catalyzed coupling of thioesters with aliphatic boron reagents.[55] In fact, alkyl boronic acids prove to be problematic in the traditional Suzuki cross-coupling and generally result in comparatively low product yields.[54] Similar low reactivity was observed in the Liebeskind–Srogl coupling of thioorganics. As in the case of the Suzuki transformation, this difficulty could be overcome by using, for example, a B-alkyl 9-BBN reagent (9-BBN= 9-borabicyclo[3.3.1]nonane).[55] Initially, B-alkyl 9- BBN reagents participated only sluggishly in the Liebeskind–Srogl coupling under nonbasic conditions. As observed with boronates, the greater steric demand of the B-alkyl 9- BBN reagents prevented dual activation by the copper(I) reagent and the formation of the ternary complex. Therefore, a base (Cs_2CO_3) was required to activate the boron reagent in this particular case to give moderate to excellent yields.

There are plenty of excellent applications underline the utility and potential of Liebeskind-Srogl cross-coupling reaction in organic synthesis, natural product synthesis and pharmaceutical industries as well. Here, few of them are mentioned.

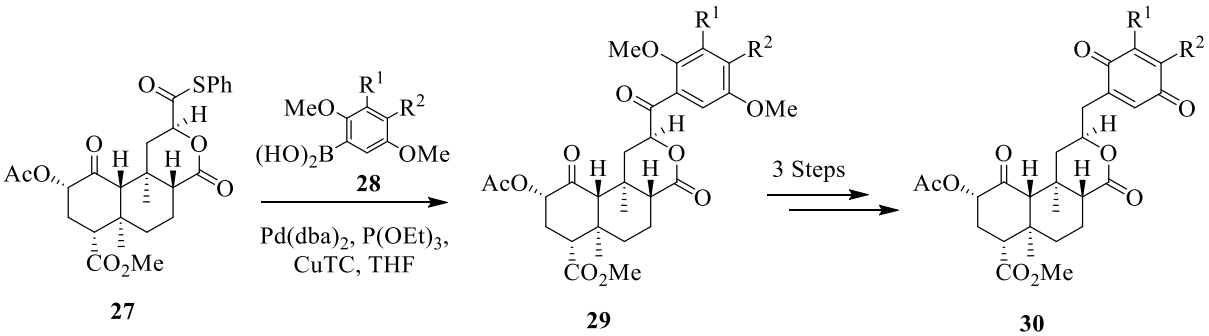
Dandepally *et al.*, in 2010, reported an easily adoptable and scalable total synthesis of verbenachalcone, which has a biaryl ether subunit in its structure. The synthesis was carried out in 8 steps, starting from 3-(4-hydroxyphenyl)propanoic acid (Scheme 2).[66] The Liebeskind-Srogl cross-coupling reaction was a crucial step for the synthesis to complete. The dithioester **23** and 2,4-bis(methoxymethoxy)phenylboronic acid **24** under Liebeskind-Srogl reaction conditions formed ketone **25** in 73% yield, which on PTSA hydrolysis synthesized verbenachalcone **26** and completed the total synthesis.



23 **25** **26**

Scheme 2. Reagents and conditions for the synthesis of verbenachalcone: (a) 2,4-bis(methoxymethoxy)phenylboronic acid **24** (3 equiv), CuTC (3 equiv), $Pd(PPh_3)_4$ (2 mol%), THF, 60 °C, 1 h, 73%; (b) PTSA, MeOH, 50 °C, 3 h, 96%.

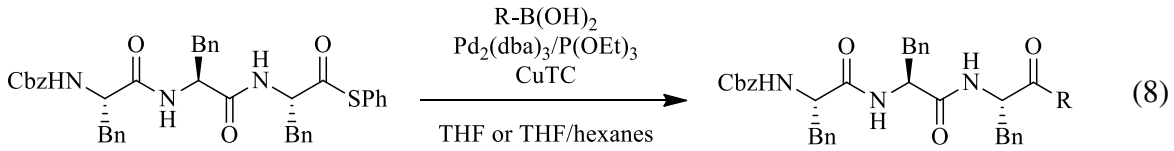
Prisinzano *et al.*, in 2014, reported total synthesis of new analogues of salvinorin A **30** by using the Liebeskind-Srogl cross-coupling reaction. They used this efficient C-C bond forming reaction to attach the nakijiquinone *p*-quinoid moiety with the salvinorin A nucleus under neutral conditions (Scheme 3).[67] Against the MCF3 breast cancer cells, these analogues of salvinorin A **30** exhibited antiproliferative activity.



27 **29** **30**

Scheme 3. Synthesis of quinone-containing salvinorin A analogues **30**.

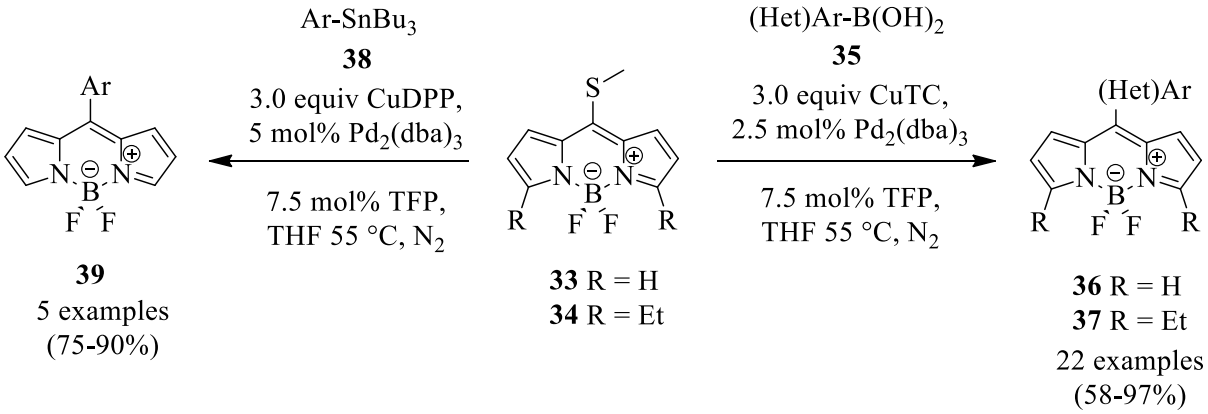
In peptide chemistry, an ongoing challenge is the development of new synthetic pathways for the formation of enantiomerically pure *N*-protected a-amino ketones and peptidyl ketones. Recently, by using Liebeskind-Srogl reaction, the synthesis of pH-sensitive peptidyl ketones from mono-, di-, and tripeptidyl thioesters and boronic acids has been carried out. The *N*-protected peptidyl ketones were prepared in good to excellent yield with high diastereomeric purity (eq 8).



31
R= styryl, 4-$MeOC_6H_4$

32
2 examples
(80, 85%)

Nearly for the past two decades, Peña-Cabrera *et al.* did a pioneering work in the investigation of applications of Liebeskind-Srogl cross-coupling reaction for the synthesis of different kinds of BODIPY derivatives using modified synthetic methods.[68] They reported the C-C bond formation between 8-thiomethylBODIPY **33** and/or **34** and different aryl[68a,68b,68d] and alkenyl boronic acids[68c] using the Liebeskind-Srogl cross-coupling reaction conditions thereby synthesizing a variety of BODIPY derivatives (Scheme 4). They also reported the use of arylstannanes instead of boronic acids for the synthesis of variety of BODIPY derivatives using Liebeskind-Srogl cross-coupling reaction.[68d]



39
5 examples
(75-90%)

33 R = H
34 R = Et

36 R = H
37 R = Et
22 examples
(58-97%)

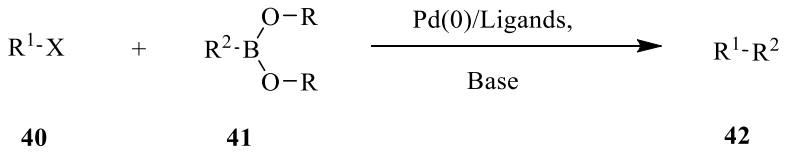
Scheme 4. Synthesis of *meso*-substituted BODIPY derivatives using Liebeskind-Srogl cross-coupling reaction.

1.3.3 Suzuki-Miyaura cross-coupling reaction.

Suzuki-Miyaura (S-M) reaction is a type of organic reaction, which belongs to a class of cross-coupling reactions involving C-C bond formation. It is widely used in organic synthesis and one of the most efficient reaction available in modern day chemistry. This reaction involves Pd-catalyzed C-C bond forming cross-coupling between organoboron reagents, such as, aryl, heteroaryl or vinyl boronic acid or boronic esters and organic electrophiles, such as, aryl, heteroaryl or vinyl halides, pseudo halides, etc., under basic conditions.[69,70,71] It was first reported by N. Miyaura and Akira Suzuki in 1979. It is vastly used for the synthesis of polyolefins, styrenes, and substituted biphenyls. It is undoubtedly the most intensively investigated C-C coupling reaction, particularly in the 21st century.[29,72] Although, there are many other cross-coupling reactions, like, Negishi, Kumada, Stille reactions, etc., available for the synthesis of C-C bonds, Suzuki reaction has been the most popular one and widely used. This is not an accident or biasness for the reaction. Suzuki reaction has key advantages over those other reactions, like mild reaction conditions, easy availability of boronic acids at affordable costs. Additionally, the boronic acids that are used in the reaction are non-toxic, air and moisture tolerant, so basically, they are easy to handle, and their by-products can be easily removed. This proves to be highly useful in large-scale industrial processes. Water can be used as a solvent in Suzuki reaction,[73] which makes this reaction more economical, eco-friendly, and practical to use with different kind of reagents which are water-soluble. This is of great importance in pharmaceutical industry.

One of the most important advantage provided by Suzuki reaction is that it has a high tolerance for the functional groups used in the organoboron reagents, unlike Kumada and Negishi reactions, which uses highly reactive Grignard reagent and organozinc reagents, respectively. The organoboranes have poor nucleophilicity and that can limit the transmetalation step, which is the transfer of the organic groups from boron to the Pd-metal centre. However, the transmetalation between Pd-metal centre and organoboranes can be increased by the addition of a base to the reaction system. Sodium carbonate, Na_2CO_3, has been the most commonly used base in Suzuki reaction. However, when substrates with steric hindrance are employed, it was not effective enough. For substrates like that, potassium phosphate, K_3PO_4, or barium hydroxide, $Ba(OH)_2$, were found to be efficient. Bases like, Cs_2CO_3, K_2CO_3, KF and NaOH are other types of bases which are commonly used in Suzuki reaction. The applications of Suzuki reaction have been found in many fields, such as synthesis of pharmaceutical agents, intermediates of fine chemicals, total synthesis of natural products, etc. Suzuki received the 2010 Nobel Prize in Chemistry along with Richard F. Heck and Ei-ichi Negishi for their important contribution in the discovery and development of palladium-catalyzed cross couplings in organic synthesis.

The Suzuki reaction's general scheme is shown below (eq 9), which is a palladium catalyst cross-coupling reaction between an organohalide **40** and an organoboron species **41** under basic conditions to form a C-C single bond.



40 **41** **42** (9)

R^1= aryl, alkenyl, alkyl
X= Cl, Br, I, OTf, etc.

R^2= aryl, alkenyl, alkyl, allyl
R= alkyl, H

Like other cross-coupling reactions, this reaction typically proceeds through (i) oxidative addition of aryl or alkyl halides to a low-valent palladium complex, Pd(0); (ii) transmetalation with the organoboranes; and (iii) reductive elimination to give the cross-coupling product and the Pd-catalyst is regenerated which can be used in the next catalytic cycle. The general reaction mechanism is shown in Figure 13.[74]

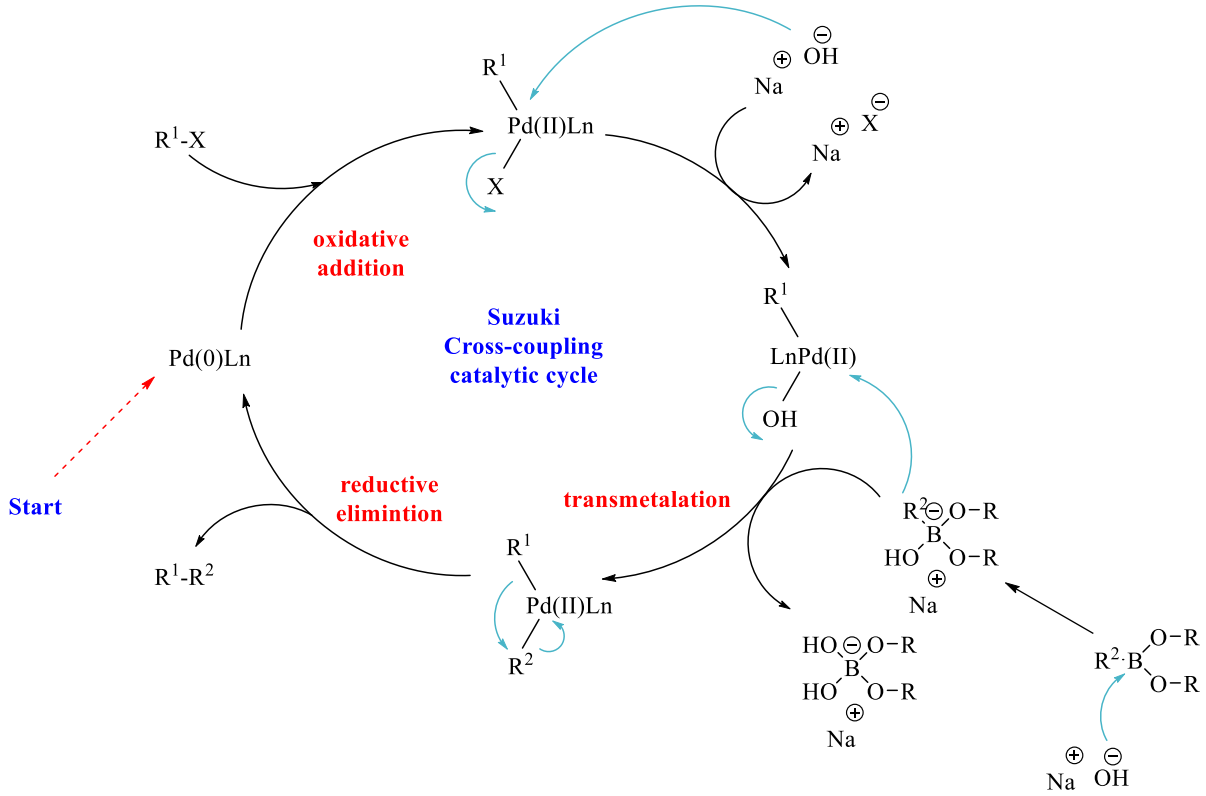


Figure 13. General reaction mechanism for Suzuki-Miyuara cross-coupling reaction.

In most cases, oxidative addition is the rate determining step. The electronic character of the aryl groups and the nature of the halide or pseudohalide greatly influences the rate of oxidative addition. Fu and coworkers have shown that the relative rate of oxidative addition of the electrophile is in the order I >> Br > OTf >> Cl.[75] In oxidative addition step, the Pd-catalyst is oxidized from Pd(0) to Pd(II). The palladium catalyst Sis coupled with the alkyl halide to yield an organopalladium complex. As shown in the Figure 14, the oxidative addition step breaks the carbon-halogen bond where the palladium is now bound to both the halogen and the R^1 group. The oxidative addition initially forms the *cis*-palladium complex, which rapidly isomerizes to the *trans*-complex.

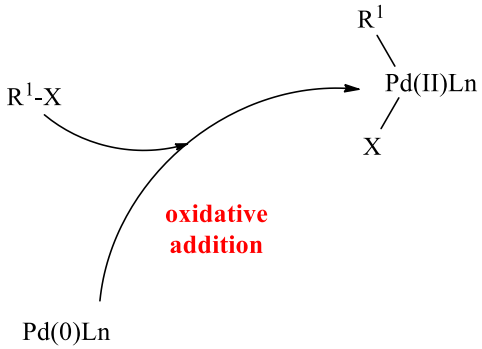


Figure 14. Oxidative addition step.

In the second step of the Suzuki reaction, the halide (X) from the Pd(II) complex is gets exchanged with the hydroxide (OH) (Figure 15). This exchange of ligands between the reacting chemical species that concludes in a similar interaction in the products as in the reactants is called metathesis.

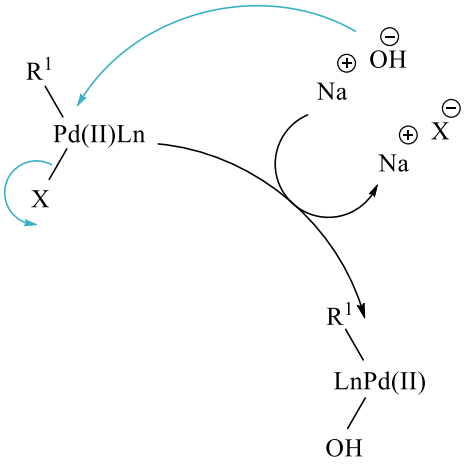


Figure 15. Ligand exchange step.

In organometallic cross-coupling reactions, transmetalation involves the transfer of ligands from one species to another. In Suzuki cross-coupling reaction, the transfer of ligands takes place from organoboron species to Pd(II) complex. In this step, the exchange of the hydroxide (base), which was added in the previous ligand exchange step, with the R^2 substituent of the organoboron species takes place to form the new Pd(II) complex (Figure 16). The organoboranes have poor nucleophilicity and that can limit the transmetalation step. However, the transmetalation between Pd-metal centre and organoboranes can be increased by the addition of a base to the reaction system and thus, the presence of base is highly necessary for the transmetalation step. In this way, the base plays the role of the organoboron compound activator and facilitate the generation of R^1-Pd(II)-OH complex from R^1-Pd(II)-X complex. However, the exact mechanism of transmetalation for the Suzuki coupling remains to be discovered and has been the subject of debate among the scientific community.

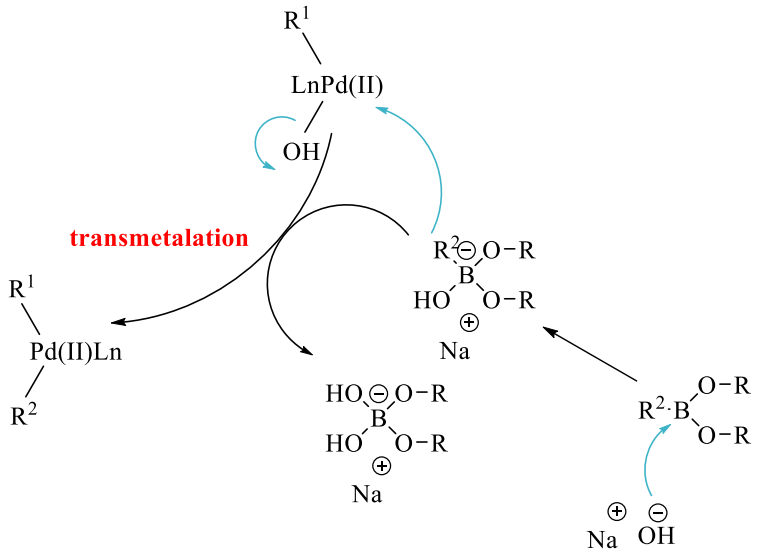


Figure 16. Transmetalation step.

Transmetalation is the exchange of ligands between two metal centres. However, the definition of transmetalation will probably leave us wondering where the second "metal" is. In this difficulty, there is an opportunity to discuss how boron acts "metal like". Boron is a metalloid with an empty *p*-orbital. This empty *p*-orbital allows it to exchange ligands with organometallics, similar to the exchange metals do with empty *d*-orbitals. Transmetalation in the Suzuki reaction occurs through a four-atom cycle transition state. This transition state is formed while the electrons from the boron-carbon sigma bond are attacking the empty *d*-orbital on the palladium and the electrons from the oxygen palladium single bond are attacking an empty *p*-orbital on the boron.

Reductive elimination is the final step in the catalytic cycle of Suzuki reaction (Figure 17), where the Pd(II) complex eliminates the product and regenerates the Pd(0) catalyst. In this step, before the reductive elimination can take pace, the isomerization of *trans*-Pd(II) complex to the *cis*-Pd(II)complex, its *cis*-isomer, is necessary. The relative rates of reductive elimination of different alkyl or aryl groups from Pd(II) complexes are as follows:

aryl–aryl > alkyl–aryl > n-propyl–n-propyl > ethyl–ethyl > methyl–methyl

Reductive elimination, the inverse of oxidative addition, occurs when the Pd-metal is reduced from the +2 to the 0 oxidation state. However, it is particularly important to discuss that because the reductive elimination in the Suzuki reaction not only forms the product but also regenerates the catalyst.

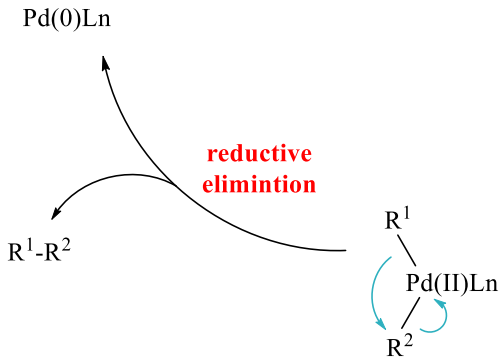
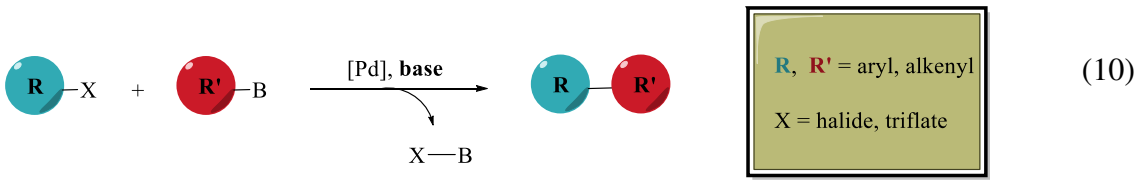


Figure 17. Reductive elimination step.

Two different possible reaction mechanisms in Suzuki reaction:

For the transmetalation step, two different reaction mechanisms have been suggested depending on what role the base (here, hydroxide) plays in this step (Figure 18).[76] For this purpose consider the general reaction shown in eq 10.



(10)

As mentioned earlier, the organoboranes have poor nucleophilicity, which can be increased by using a base. In **path A**, the boronate mechanism, the boronate species **A** is generated by the nucleophilic attack of hydroxide (OH) on the boron atom of the boronic acid and by doing so, the nucleophilicity of boronate species is increased, which is highly necessary for the transmetalation to take place. The generated boronate species **A** then displaces the halide from the R-Pd(II)-X complex and undergoes transmetalation to generate R-Pd(II)-R' (Figure 18).

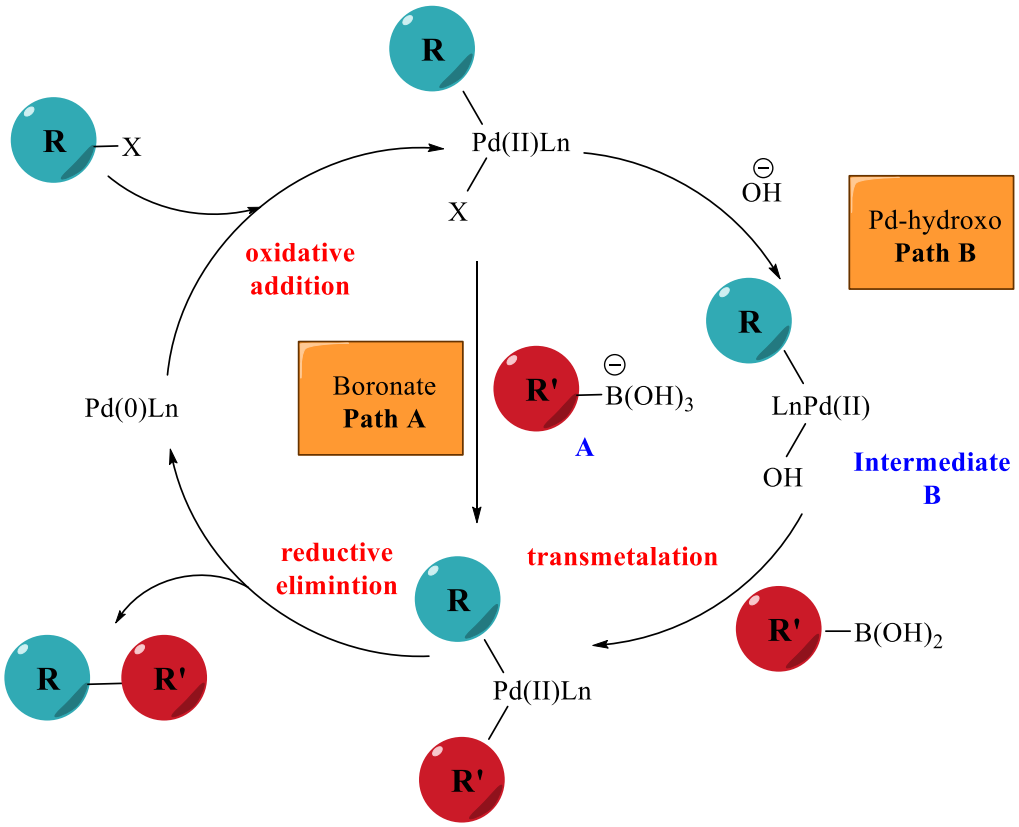
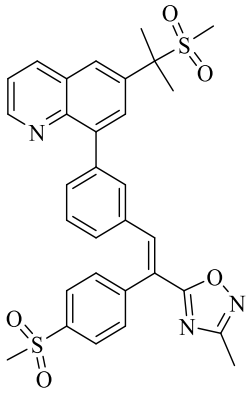


Figure 18. Two possible pathways in Suzuki reaction mechanism.

In **path B**, the Pd-hydroxo mechanism, the intermediate **B**, R-Pd(II)-OH, is generated when the hydroxide (OH) displaces halide from the R-Pd(II)-X complex and coordinates itself to Pd-metal. Then, the intermediate **B** further reacts with boronic acid (neutral) to complete the transmetalation. Interestingly, many groups came up with the experimental and theoretical studies backing both mechanistic pathways, however, the firm reaction mechanism for transmetalation step is still unclear.[77]

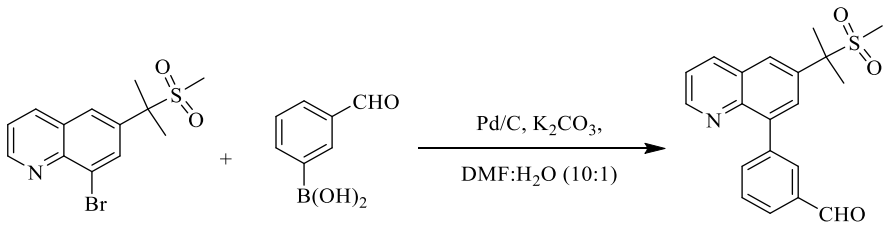
In recent years, Suzuki cross-coupling reaction have been used extensively in the total synthesis of complex natural products. High functional group tolerance, mild coupling conditions, and the ability to utilized novel disconnections have made Suzuki cross-coupling reaction a mainstream coupling reaction in chemistry.

Merck Research Laboratories and Merck Frosst Therapeutic Research Center have come up with a kilogram scale synthetic route for the synthesis of compound **43**, which is a PDE4 inhibitor and can be used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma (Figure 19).[78,79] The synthesis of compound **43** involves the synthesis of phenylquinoline intermediate **46**, which was achieved by a Suzuki reaction involving compound **44** and boronic acid **45** (eq 11).



43

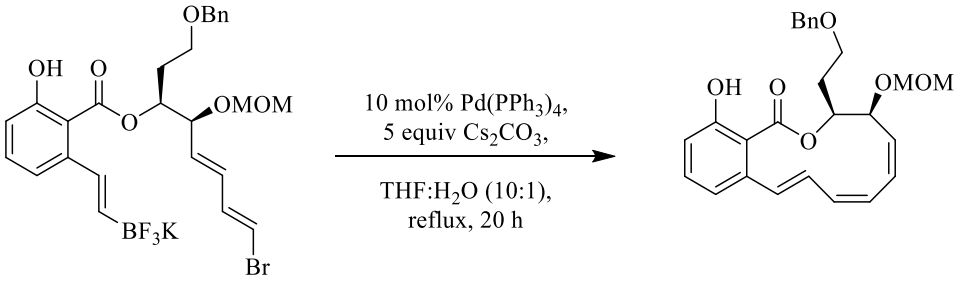
Figure 19. Structure of PDE4 inhibitor.



44 **45** **46**

(11)

In 2004, Molander[80] *et al*. published a formal total synthesis of Oximidine II **48** via a Suzuki type cross-coupling macrocyclization (eq 12). Oximidine II is highly biologically active. It exhibits selective cytotoxicity at ng/mL levels for oncogene transformed cells.



47 **48**

(12)

1.3.4 Stille cross-coupling reaction (*Kosugi-Migita-Stille coupling*).

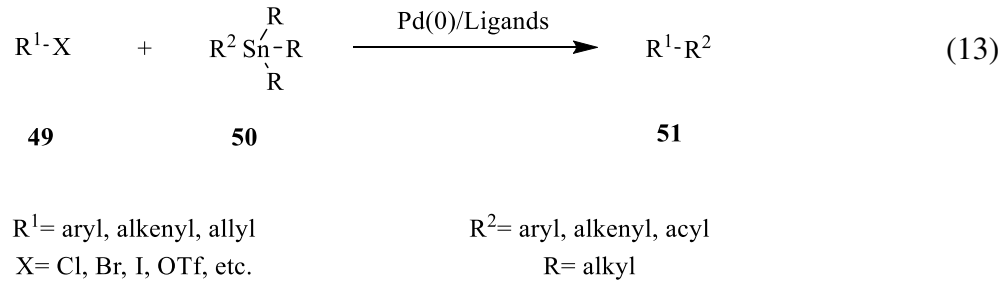
Stille reaction is a type of organic reaction, which belongs to a class of cross-coupling reactions involving C-C bond formation. This reaction involves Pd-catalyzed C-C bond forming cross-coupling between organostannane reagents, such as, aryl, heteroaryl, benzyl, or allyl and organic electrophiles, such as, aryl, heteroaryl, alkenyl or allyl halides, pseudo halides, etc. This reaction was first reported by Kosugi *et al.* in 1977[81] and subsequently by Stille *et al.* in 1978[82], therefore it is also known as Migita-Kosugi-Stille coupling. This reaction involves C-C bond formation between organostannanes and organic electrophiles, organic halides, which do not have a sp^3-hybridized β-hydrogen atom. The C-Sn bond in organostannanes is relatively inert and because of that this versatile reaction shows high chemoselectivity. Sometimes, drastic reaction conditions are needed for the C-C bond formation in this reaction, which also supports the above statement, the C-Sn bond being relatively inert. Organostannanes are toxic in nature and thus, their use in large-scale industrial processes makes them less attractive. This is a drawback of this reaction. A much higher toxicity is observed with organostannanes containing high number of alkyl group and smaller number of carbon atoms. However, this is a limited drawback, owing to the reports about the use of non-polluting polymer supported organostannanes with less toxicity in organic synthesis.[83] Recently, the organostannanes are becoming easily available, they are moisture and air stable, and have high tolerance towards many functional groups, owing to those features Stille reaction proved to be effective for the synthesis of polymers,[84] macrocycles[85] and molecules with complex structures and unique functional groups,[86,87]

The organotin regents, generally, consists of one migratory group, such as aryl, vinyl, allyl or benzyl, and three non-transferable alkyl groups, such as methyl or butyl.[88] The organostannane with three butyl groups on the Sn atom has lesser toxicity and lesser mobility of the butyl groups as compared to that of the organostannane with three methyl groups. The migratory group of the organostannanes can significantly affect the reactivity of the organotributyltins. Their relative reactivity is in the following order:

alkynyl > alkenyl > aryl > allyl ~ benzyl > alkyl.[89]

One of the most striking features of the Stille reaction is that, in this reaction, the aryl chlorides can easily form C-C bond with an organostannane, unlike Suzuki reaction. In 2002, Fu *et al.* reported that Pd/$P(tBu)_3$ catalyzed Stille reaction of aryl chlorides and bromides with a wide range of organostannanes, including $SnBu_4$.[90] Excellent yields were obtained, when instead of Pd/$P(tBu)_3$, $Pd(P(tBu)_3)_2$ was employed.

The general reaction scheme for Stille cross-coupling reaction is shown below (eq 13).



(13)

Generally, CuI and a phosphorus ligand are necessary for the Stille reaction. The rate of reaction can be increased by using ligands with lower donicity. On replacing the traditional PPh_3 with TFP, tri(2-furyl)phosphine, or $AsPh_3$, rate enhancement of 10^2-10^3 was observed due

to the enhanced electrophilicity and reactivity of Pd(II) intermediate toward the organostannanes.[91] Additionally, the presence of free ligand in the reaction system can actually inhibit the Stille coupling,[87,92] especially the ligands with high donicities. CuI can be employed to scavenge the free ligands present in the reaction system, which in turn can increase the reaction rate as well as selectivity,[87,88,93] due to the formation of a more reactive organometallic species (i.e., organocopper). Other salts that have a function similar to CuI to form a bimetallic catalyst include silver salt[94] and LiCl.[95] In addition, a hypervalent tin complex can be formed between organotin compound and fluoride, with which transmetalation can happen rapidly. Furthermore, fluoride ions can act as scavengers for tin by-products, making them easier to remove via filtration.[96]

The Stille reaction's mechanism has been widely studied.[97,98] The oxidative addition is the first step, where the oxidative addition of an organic electrophile, organohalide, to the Pd-catalyst, Pd(0), takes place to form a R^1-Pd(II)-X complex. It is a *cis*-complex which rapidly isomerizes to the *trans*-complex.[99] Then, the transmetalation takes place between R^1-Pd(II)-X complex and the organotin reagent, where the R^2 group of the organotin reagent replaces the halide anion on the R^1-Pd(II)-X complex to generate R^1-Pd(II)-R^2 complex. Transmetalation is the rate limiting step in Stille reaction. Reductive elimination of R^1-Pd(II)-R^2 complex forms the desired product and the Pd-catalyst is regenerated and can be reused (Figure 20).

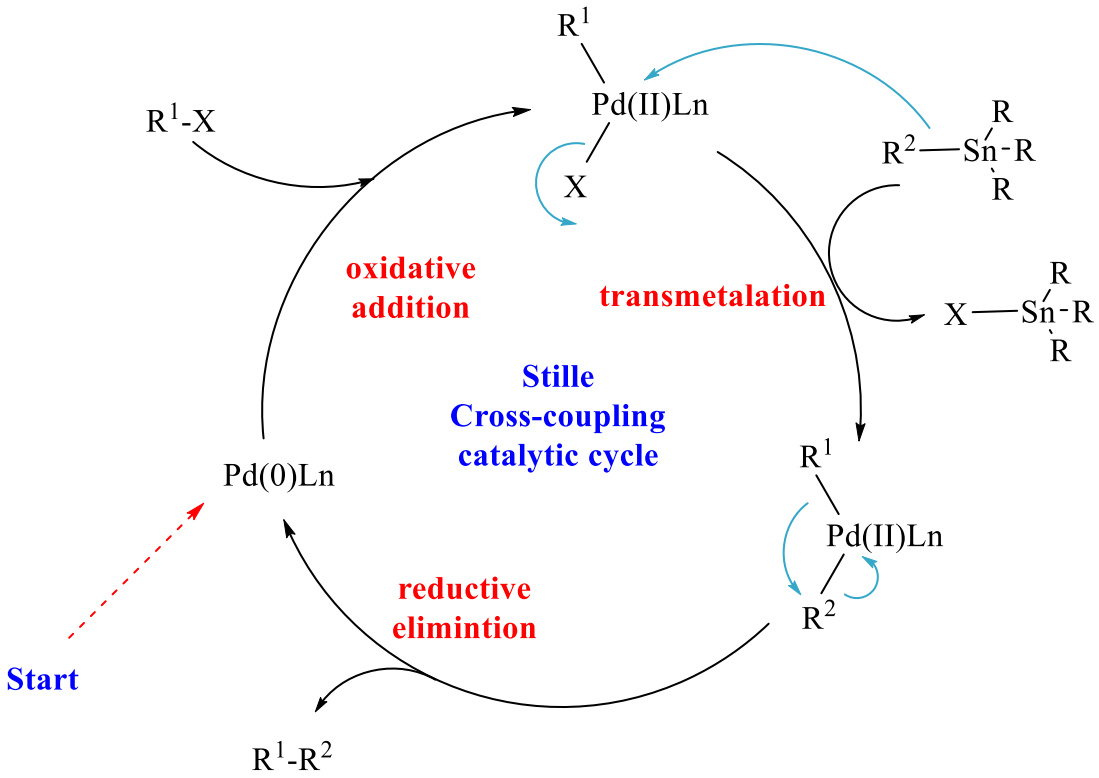
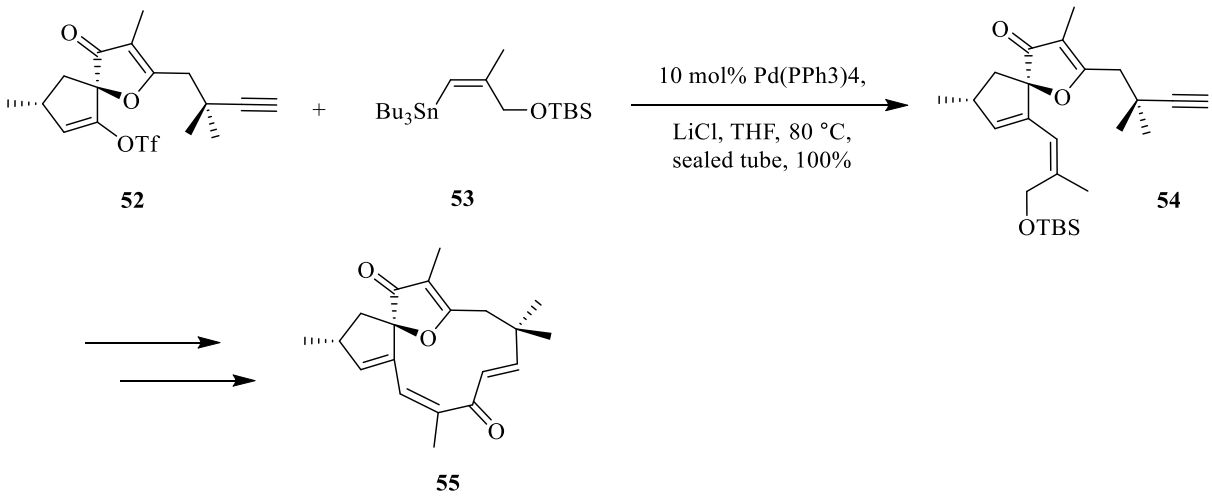


Figure 20. General reaction mechanism for Stille cross-coupling reaction.

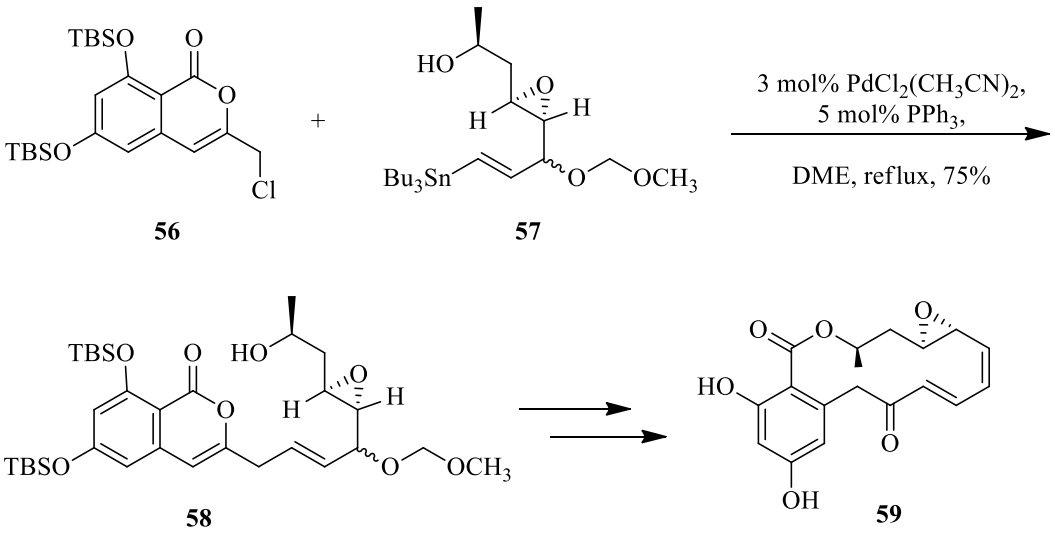
A wide range of polymers have been synthesized using the Stille reaction.[100,101,102] However, the Stille reaction is vastly employed in synthesis of organic molecules, and precisely, in synthesis of natural products, such as amphidinolide A,[103] dysidiolide,[104] callipeltoside A,[105] guanacastepene A,[106] maitotoxine,[107] manzamine,[108] pumiliotoxin B,[109] sanglifehrin A,[110] strychnine,[111] Jatrophone[112] and zearolone.[113]

In 1992, Wiemer *et al.* were the first to provide the optically active natural product, (+)-Jatrophone **55**. It is the macrocyclic diterpenoid, which shows significant antileukemic activity. They used the Stille cross-coupling reaction to synthesize one of the intermediates, which after few more steps gave the final product, (+)-Jatrophone **55** (Scheme 5).



Scheme 5. Use of the Stille cross-coupling reaction in the total synthesis of (+)-Jatrophone **55**.

In 1992, Robert Lett *et al.* did the first total synthesis of antifungal resorcyclic macrolides Monocillin I **59**, which was achieved by convergent stereospecific route. They used the Stille cross-coupling reaction to synthesis one of the intermediate **58**, which after few more steps gave the final product, Monocillin I (Scheme 6).



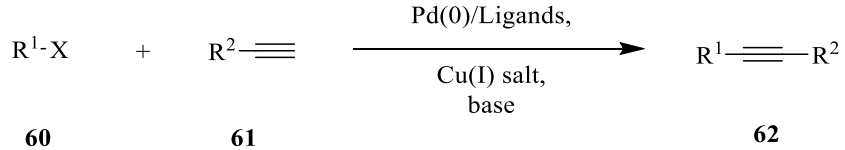
Scheme 6. Use of the Stille cross-coupling reaction in the total synthesis of Monocillin I **59**.

1.3.5 Sonogashira cross-coupling reaction.

The Sonogashira cross-coupling reaction is a type of organic reaction, which belongs to a class of cross-coupling reactions involving C-C bond formation. This reaction involves Pd-catalyzed C-C bond forming cross-coupling between terminal alkynes and organic electrophiles, such as, aryl, heteroaryl, alkenyl, alkyl, benzyl or vinyl halides, pseudo halides, etc. in the presence of Cu(I) salts, like CuI, as a co-catalyst and a base. This reaction involves coupling between a sp^2 hybridized carbon of an organic halide and a terminal sp carbon of an alkyne. In 1975, it was first reported by Sonogashira *et al.*, where they carried out the reaction at normal temperature using $PdCl_2(PPh_3)_2$ as a catalyst, CuI as a co-catalyst and amine as a base and solvent (eq 14).[114] Few months before this discovery, Cassar[115] and Heck *et al.*[116] reported similar reaction, without using Cu-cocatalyst or base, at high temperature by employing Pd-catalyst only. Sonogashira *et al.* employed Cu-mediated transmetalation of alkynes with Pd-catalyst and by doing so they came up with a robust procedure which can operate at low temperatures, unlike procedure reported by Heck *et al.* Use of Cu-cocatalyst increases the reactivity of the catalytic system and thus, increases the reaction rate of Sonogashira reaction. However, the main drawback of use of Cu-cocatalyst is its sensitivity towards oxygen. The oxygen must not be present in the reaction system, its presence can generate the unwanted alkyne homocoupled by-product by Cu-mediated Hay/Glaser reaction.[117] This drawback can be avoided by avoiding the use of Cu-cocatalyst, which makes it Cu-free Sonogashira cross-coupling reaction. By doing so, the reaction could be simply called as Heck-Cassar coupling or Sonogashira- Heck-Cassar reaction or Heck alkynylation.

The general features of this reaction include: 1) the reaction can be conducted at room temperature; 2) the reaction system does not need to be rigorously dried; 3) the copper acetylides are generated *in situ* by using the catalytic amounts of Cu salt and terminal acetylenes under the action of base, which avoids handling the equivalent amounts of the shock-sensitive/explosive copper acetylides; 4) this reaction is suitable for both small and large scale production; 5) the good functional group compatibility makes it feasible to use this reaction with complex substrates, even in the late stages of a multistep synthetic sequence. These advantages can be mostly attributed to the combined use of the palladium and copper catalysis, which has greatly inspired chemists to apply this concept to other challenging chemical transformations. Thus, making this reaction very important in the synthesis of natural products, dyes, sensors, biologically active molecules, heterocycles, and conjugated polymers or nanostructures.[118,119]

The general reaction scheme for Sonogashira cross-coupling reaction is shown below (eq 14).



(14)

60 **61** **62**

R^1= aryl, alkenyl, alkyl
X= Cl, Br, I, OTf

R^2= H, aryl, alkenyl, alkyl

Many studies have been carried out to understand the exact mechanism of Sonogashira reaction and search new efficient catalysts, additives and ligands, which can improve the reaction rates

and yields of the desired products.[120,121,122,123] However, despite those studies, the mechanistic pathway of Sonogashira reaction is not fully understood. Several studies proposed that the mechanistic pathway is in fact the amalgamation of Pd-catalyzed cycle and Cu-catalyzed cycle (Figure 21). The first step in the Pd-catalyzed cycle is the oxidative addition of R^1-X to the Pd(0) catalyst to form [R^1-Pd(II)-X] complex. Here, the Pd-metal got oxidized from 0 oxidation state to +2. The electronic properties of R^1-X bond and reactivity of halide dictates the rate of oxidative addition of R^1-X. The reactivity of halide is in the order of I ≥ OTf ≥ Br > Cl. If the electron withdrawing functional groups are present in R^1 then they can decrease the electron density of the R^1-X bond and in turn activates it. Transmetalation is the next step in the catalytic cycle, in which transmetalation takes place between [R^1-Pd(II)-X] complex and organocopper reagent. The alkynyl anion displaces the halide (X) of the [R^1-Pd(II)-X] complex and forms [R^1-Pd(II)-C≡C-R^2] complex, with regeneration of Cu-cocatalyst. The organocopper reagent is generated *in situ* through Cu-catalyzed cycle. It is obtained from Cu-catalyst and the terminal alkyne in the presence of base, like triethylamine. The last step in the catalytic cycle is the reductive elimination step, where the reductive elimination of [R^1-Pd(II)-C≡C-R^2] complex gives the desired product with Pd(0) catalyst is regenerated and can be reused in the catalytic cycle.

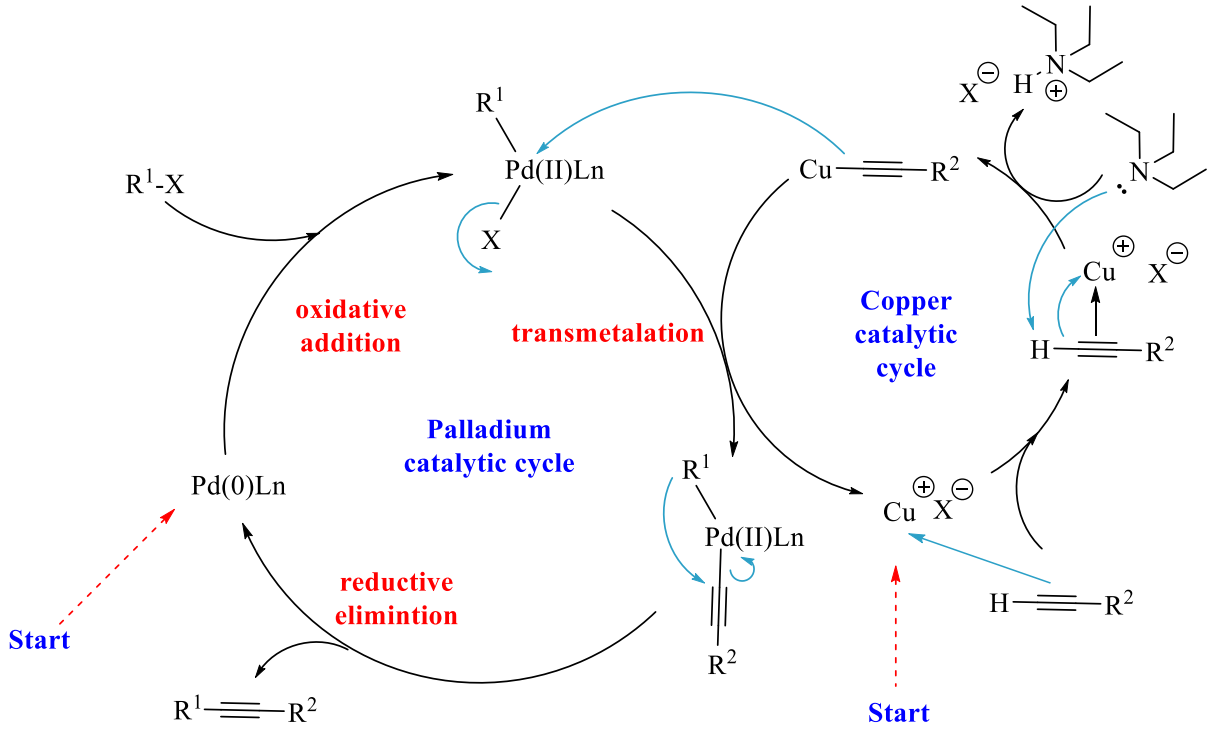
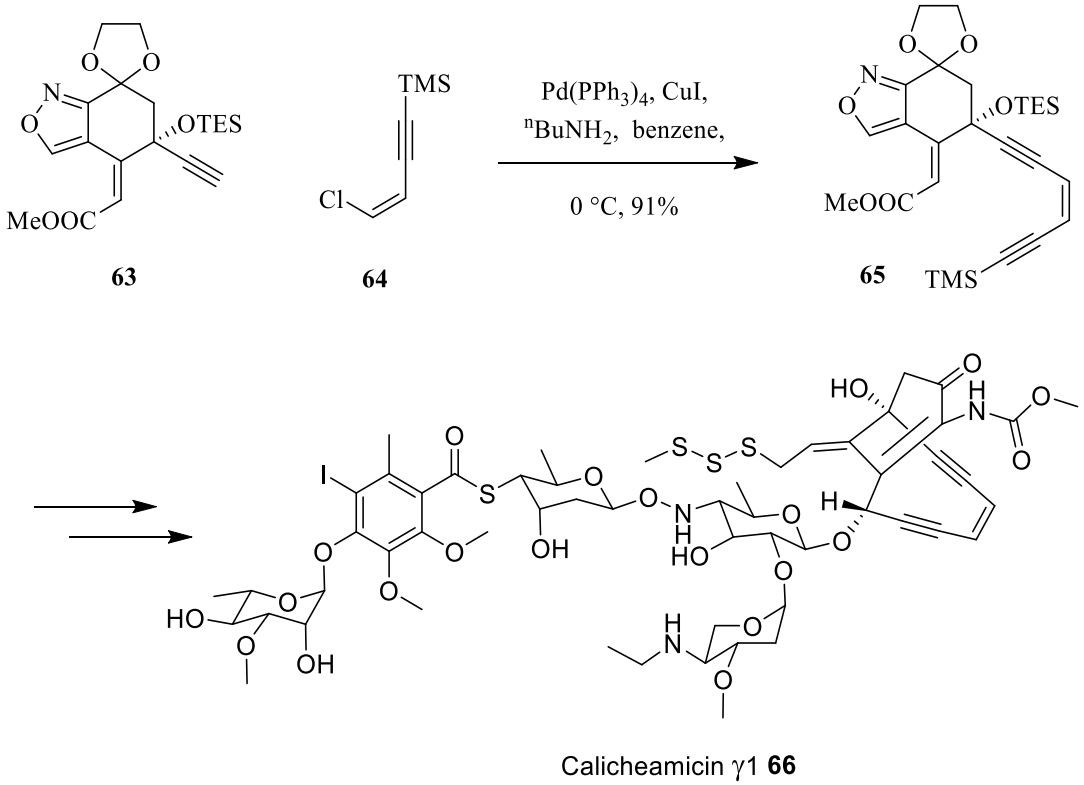


Figure 21. General reaction mechanism for Sonogashira cross-coupling reaction.

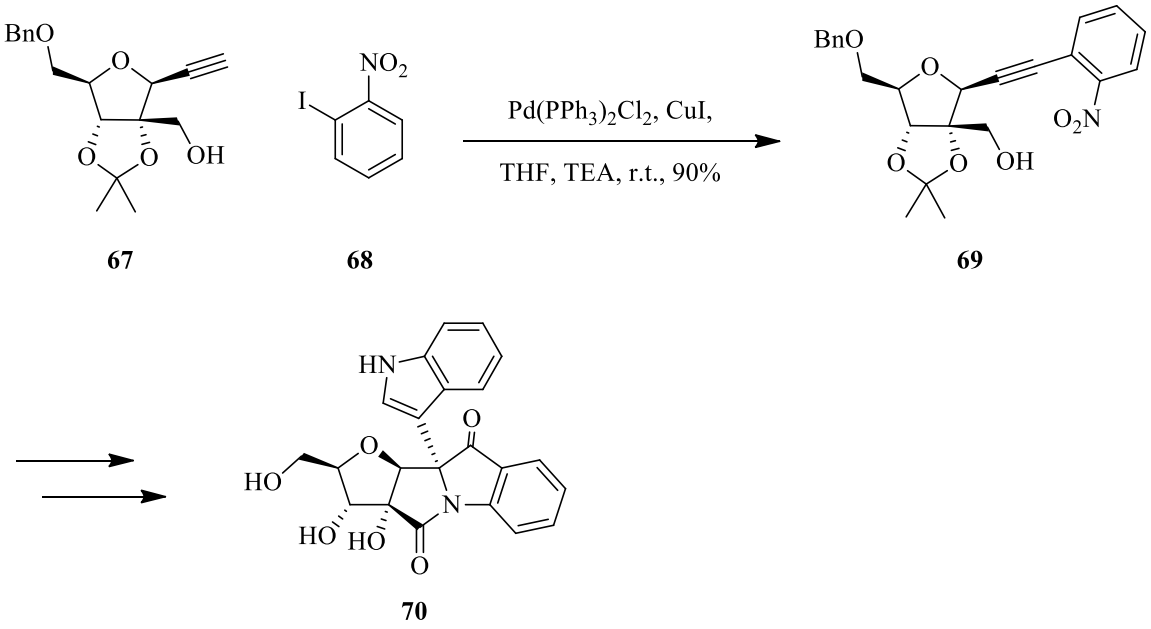
The Sonogashira reaction is used in the synthesis of various organic compounds and in the production of natural products, pharmaceuticals agents, and agricultural chemicals. The researchers all over the world have been very much interested in conjugated enediynes or enynes containing natural products. Such natural products have interesting complex structural motifs, and they can be employed in chemical biology studies as starting material or bioactive compounds.[124,125,126,127,128] The complex structural motifs, consisting conjugated enediynes and enynes, of such natural products makes their total synthesis highly. Intra- or intermolecular Sonogashira reactions have been very resourceful for that matter.

In 1992, Nicolaou *et al.* reported the total synthesis of calicheamicin γ_1 **66** by employing Sonogashira reaction.[124] The Pd/Cu-cocatalyzed coupling of alkyne **63** with vinyl chloride **64** gave the enediyne product **65** in 91% yield, which after few more steps gave the final product, calicheamicin γ_1 **66** (Scheme 7).



Scheme 7. The use of Sonogashira cross-coupling reaction in the total synthesis of calicheamicin γ_1 **66.**

In 2012, Ramana *et al.* demonstrated the use of Sonogashira cross-coupling reaction in the total synthesis of (−)-isatisine A **70**[129]. The Pd/Cu-cocatalyzed coupling of **67** with 2-iodonitrobenzene **68** under standard conditions furnished the nitroalkyne **69** in 90% yield, which after few more steps gave the final product, (−)-isatisine A **70** (Scheme 8).



67 **68** **69** **70**

Scheme 8. Use of Sonogashira cross-coupling reaction in the total synthesis of (−)-isatisine A **70**.

1.4 BODIPY Chemistry.

1.4.1 Introduction to BODIPY fluorophores.

The fluorescent dyes are highly convenient, essential, and widely employed molecular tools for bioimaging in vivo and vitro,[130,131,132] owing to their capability to compile and restrain at the subcellular levels and to deal with the biological barriers. Therefore, organic chemists and biologists across the world have carried out so many studies to find out a large number of significant fluorescent probes for bioimaging in wide range of targets.[133,134,135,136] Fluorescent dyes are also known as fluorophores or reactive dyes. Fluorescent dyes have low cost, simplicity for implementation, and great sensitivity, which makes them suitable candidates in the areas like imaging, detecting and sensing applications. Boron-dipyrromethenes/BF_2-dipyrrins (BODIPYs), coumarin, rhodamine, fluorescein and cyanine dyes are the examples of fluorescent dyes which are greatly used for imaging purposes. Among them, BODIPY dyes have emerged as one of the most important fluorescent dye in the development of fluorescent probes. It is a widely used fluorophore owing to its intriguing features such as sharp absorption and emission in the visible and near-IR region depending on substituents, high fluorescence quantum yields, sharp absorption and emission peaks, large absorption coefficients, small Stokes shift, high stability at different pH value, insensitivity to polarity of solvents, reasonably long singlet state lifetimes, easy synthesis, thermal, chemical, and photostability. Because of all these excellent features, in addition to their use as fluorescent probes, BODIPY dyes have been vastly employed as laser dyes, drug delivery agents, light harvesters, cation/anion sensors, fluorescent switches, sensitizers in solar cells, and electroluminescent films.[137,138,139,140,141] Their photophysical properties can be altered by making changes in the conjugation length, using different kinds of electron donating/or withdrawing substituents or making chemical modifications at different positions.[142]

1.4.2 Structure of BODIPY.

The IUPAC name of the BODIPY dye is 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene, which is very much alike to *s*-indacene, its tricyclic analogue and its simplest unsubstituted structure is shown in Figure 22 (right). The numbering in BODIPY dyes is also very much alike to indacene. The second, first/third and eighth position of BODIPY dyes are often termed as α, β and *meso*, respectively. BODIPY dyes have delocalization of π-electron system in their backbone (Figure 22, left).

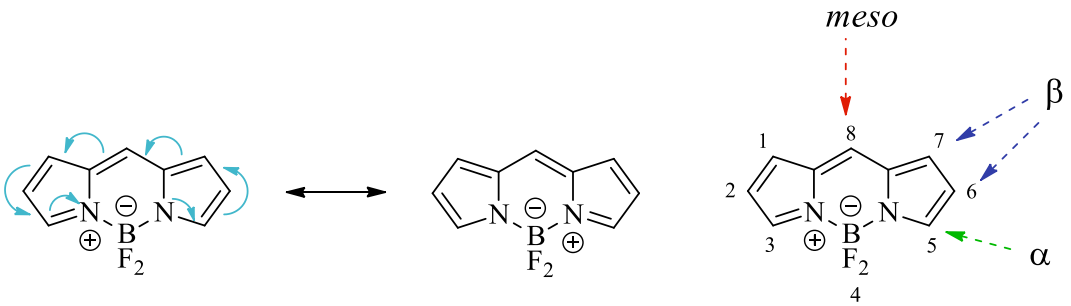


Figure 22. The delocalized structures of BODIPY (left) and its simplest unsubstituted structure, parent BODIPY, (right).

There is a correlation among structures of BODIPYs and cyanines (Figure 23). One can say that BODIPYs are monomethine cyanine dyes with rigid conformation, where BF_2 unit holds

both chain ends together.[143] The sharp emission bands and high fluorescence quantum yields of BODIPY dyes are due to the flexibility restriction in dipyrromethene backbone.

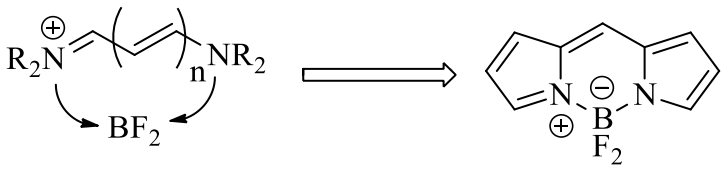


Figure 23. The correlation among structures of BODIPYs and cyanines.

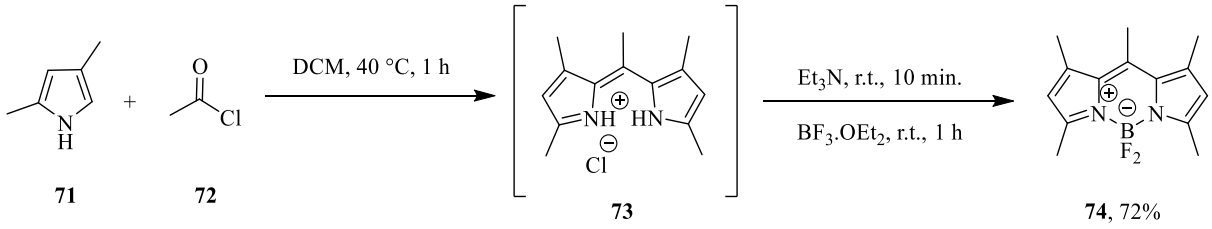
Functionalization can take place at all the possible positions of BODIPY dyes. Upon functionalization BODIPY dyes becomes highly useful synthons, which can be employed for the synthesis of wide range of BODIPY derivatives consisting of unique photophysical properties. Addition of different kinds of functional groups can be carried out at α, β and *meso* positions, and at boron centre as well.

1.4.3 Synthesis of BODIPYs and its derivatives using different kinds of reactions (mostly cross-coupling reactions).

In 1968, Treibs and Kreuzer reported the earliest synthesis of BODIPY derivatives.[144] Since then, then many research groups have carried out studies towards the synthesis and development of a great number of different kinds of BODIPY derivatives. For a long time, researchers across the globe failed to synthesize the parent BODIPY, a simplest unsubstituted BODIPY. However, in late 2010s, research groups like Peña-Cabrera *et al.*, [145] Jung *et al.*, [146] Bruce *et al.*, [147] Thompson *et al.*[148] were able to successfully synthesize it. The parent BODIPY is highly sensitive towards the electrophilic attack which makes it less stable and less accessible as well. Peña-Cabrera *et al.* were the first group to successfully report the easy and systematic synthesis and optical properties of that parent BODIPY system.[144]

Synthetic approaches to the difluoroboron dipyrromethene core are largely based on chemistry well known from porphyrin research, leading to the parent BODIPY chromophore.[149] Many synthetic procedures have been reported for the synthesis of BODIPY derivatives. The basic synthetic procedure involves the condensation reaction between a pyrrole and carbonyl compound with high electrophilicity, such as acyl chloride, aldehyde, or acid anhydride. Among all the reported methods, BODIPY derivatives can be synthesized using three widely employed routes, first route involves pyrroles and acyl chlorides, second route involves pyrroles and pyrrole aldehydes or ketopyrroles, and third route involves Lindsay's approach.

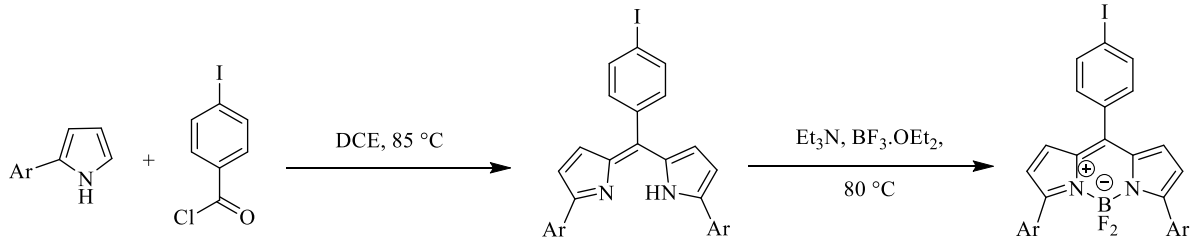
In the first route, the condensation of pyrrole and acyl chloride generates the dipyrromethene hydrochloride salt as an intermediate, which has the dipyrrin core of dipyrromethenes. Generally, the obtained intermediate is directly employed in the next step without isolation or any kind of purification. Then $BF_3.OEt_2$ was added subsequently under basic condition to the obtained intermediate to generate the final desired BODIPY derivative (Scheme 9).[150,151] Alkyl or aryl groups can be added at the *meso*-position by using this synthetic route. Apart from of acid chloride, several different kinds of acid anhydride[152] or orthoester[153] can be also employed in this route. The single step formation of the dipyrromethene is an appealing feature of this route. Additionally, this route is useful for the synthesis of symmetrically substituted BODIPY derivatives. However, the main drawback of this route is that the starting materials are not always totally consumed, which can make purification complicated.



71 72 73 74, 72%

Scheme 9. Condensation of 2,4-dimethyl pyrrole with acetyl chloride to form 1,3,5,7-pentamethyl BODIPY **74**.[150]

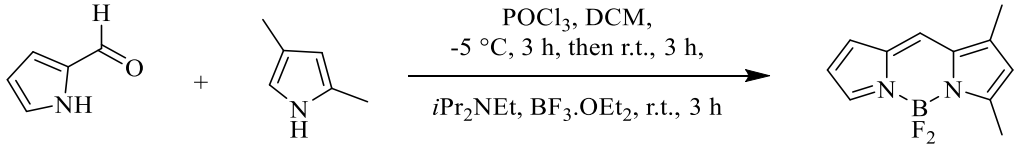
In addition, this route can be used for the synthesis of 3,5-diaryl BODIPY derivatives. Burgess *et al*. have synthesized 3,5-diaryl BODIPY derivatives by employing this route (Scheme 10).[154] They used 2-arylpyrrole with 4-iodobenzoyl chloride for that purpose, which on condensation gives diarylpyrromethenes, to which $BF_3.OEt_2$ was added subsequently under basic condition to form desired BODIPY derivatives.



75 76 77 78

Scheme 10. Synthesis of 3,5-diaryl BODIPY derivatives.[153]

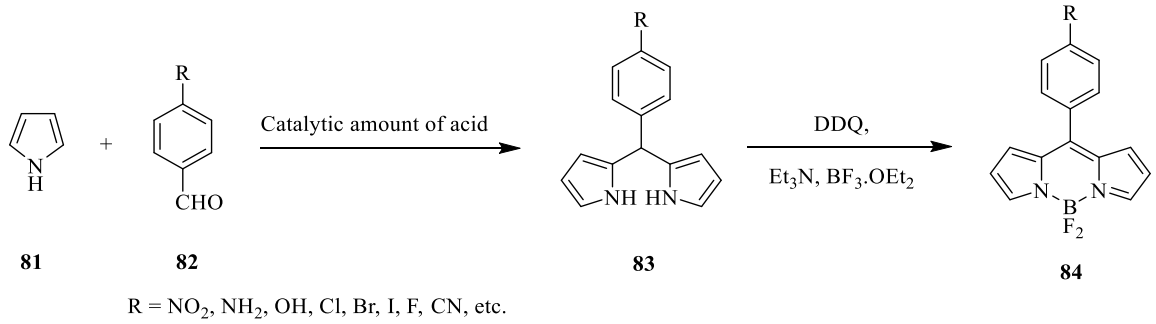
The first route has another drawback, it cannot used for the synthesis of non-symmetrically substituted BODIPY derivatives. It could be achieved through the second route, which involves the condensation of pyrrole aldehyde or ketopyrrole with the 2nd pyrrole unit. Their condensation in the presence of Lewis acid generates the dipyrromethene intermediate, which on subsequent $BF_3.OEt_2$ addition under basic conditions gives a non-symmetrically substituted BODIPY derivative. In 2009, Young-Tae Chang *et al*.[155] have used this approach to synthesize non-symmetrical BODIPY (eq 15).



79 71 **80,** 51% (15)

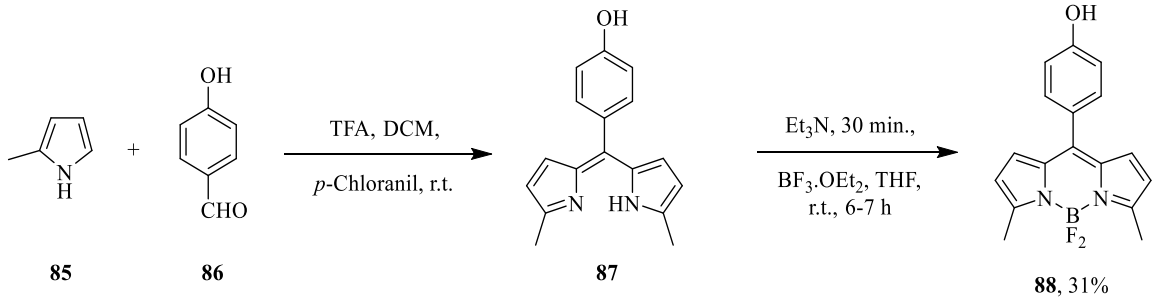
The condensation reaction between α-free pyrroles or 2-substituted pyrroles and aromatic aldehydes is the third route of synthesis for the derivatives of BODIPY, which often called as Lindsay's method. In this route, the Brønsted acid catalyzed condensation of α-free pyrrole with aldehydes consisting functionalized aryl group gives dipyrromethane, its subsequent DDQ oxidation forms dipyrromethene intermediate. The BF_2 complexation of that dipyrromethene intermediate by employing $BF_3{\cdot}OEt_2$ in the presence of base gives *meso*-aryl derivatives of BODIPY (Scheme 11).[156] BODIPY derivatives without α- or β-substituents can be synthesized

by this route. However, since the pyrrole used in this route has α-free position, this route has one limitation, to restrain porphyrin formation and/or polymerization the pyrrole must be used in excess amount.[157,158]



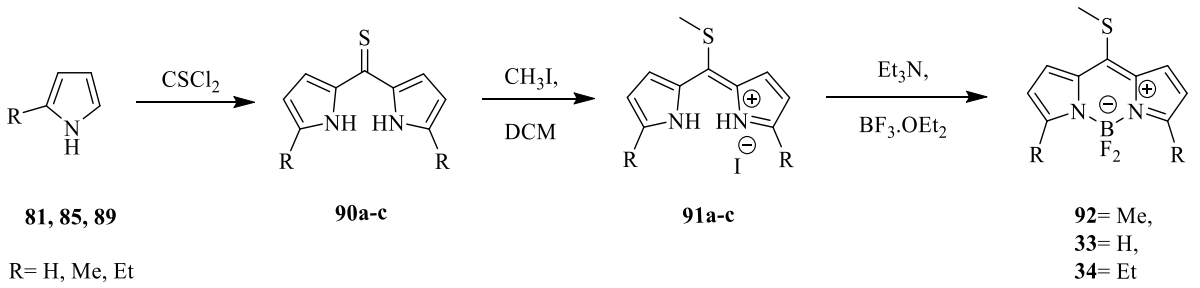
Scheme 11. Synthesis of *meso*-aryl BODIPY derivatives **84** using Lindsay's approach.

Like α-free pyrrole route, the condensation reaction between 2-substituted pyrrole and aldehyde in the presence of Brønsted acid, like TFA, as a catalyst forms dipyrromethane, which on subsequent oxidation using *p*-chloranil generates dipyrromethene intermediate. The BF_2 complexation of that dipyrromethene intermediate by employing $BF_3{\cdot}OEt_2$ in the presence of base gives *meso*-aryl derivatives of BODIPY.[156] Baruah and coworkers reported the synthesis of *meso*-phenolic BODIPY **88** by using this synthetic route. Here, only 2 equivalents of 2-methylpyrrole were used, unlike *α*-free pyrrole route (Scheme 12).[159]



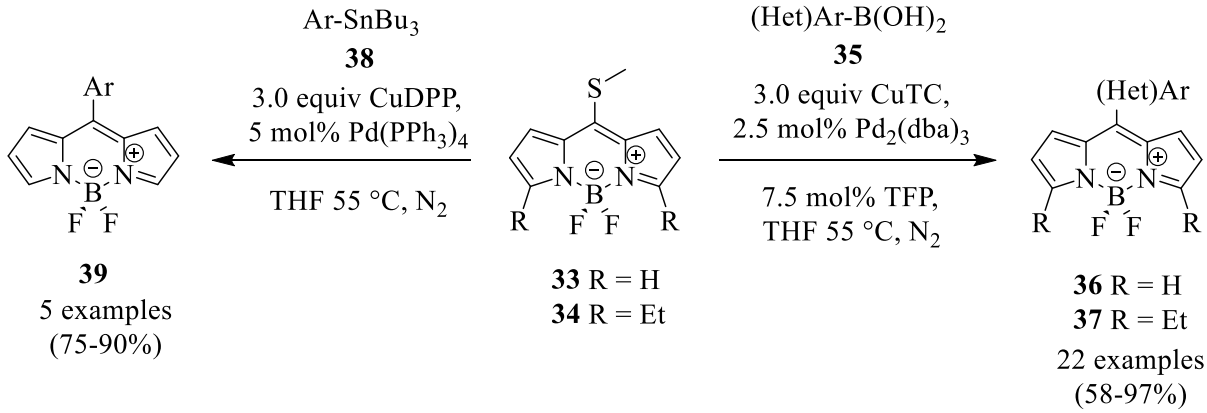
Scheme 12. Synthesis of *meso*-phenolic BODIPY **88** using second route.

However, synthesis of BODIPY derivatives by Lindsey's method is demanding and have some drawbacks, like, tedious purifications, aryl aldehyde's functional groups showing sensitivity towards oxidising agents and Lewis acids used in the reaction, and synthesis of aryl aldehydes (starting material) if they are costly or commercially unavailable. To overcome those limitations researchers made efforts to come up with better route to synthesize derivatives of *meso*-substituted BODIPY. Biellmann and coworkers, [160] in 2006, synthesized a new synthon, 8-methylthio BODIPY **92** or Biellmann BODIPY, which proved to be revolutionary in the synthesis of wide range of derivatives of *meso*-substituted BODIPY by using different methods like aromatic nucleophilic substitution (S_NAr) reaction, Liebeskind-Srogl reaction,[161] etc.



Scheme 13. Synthesis of the Biellmann BODIPY.

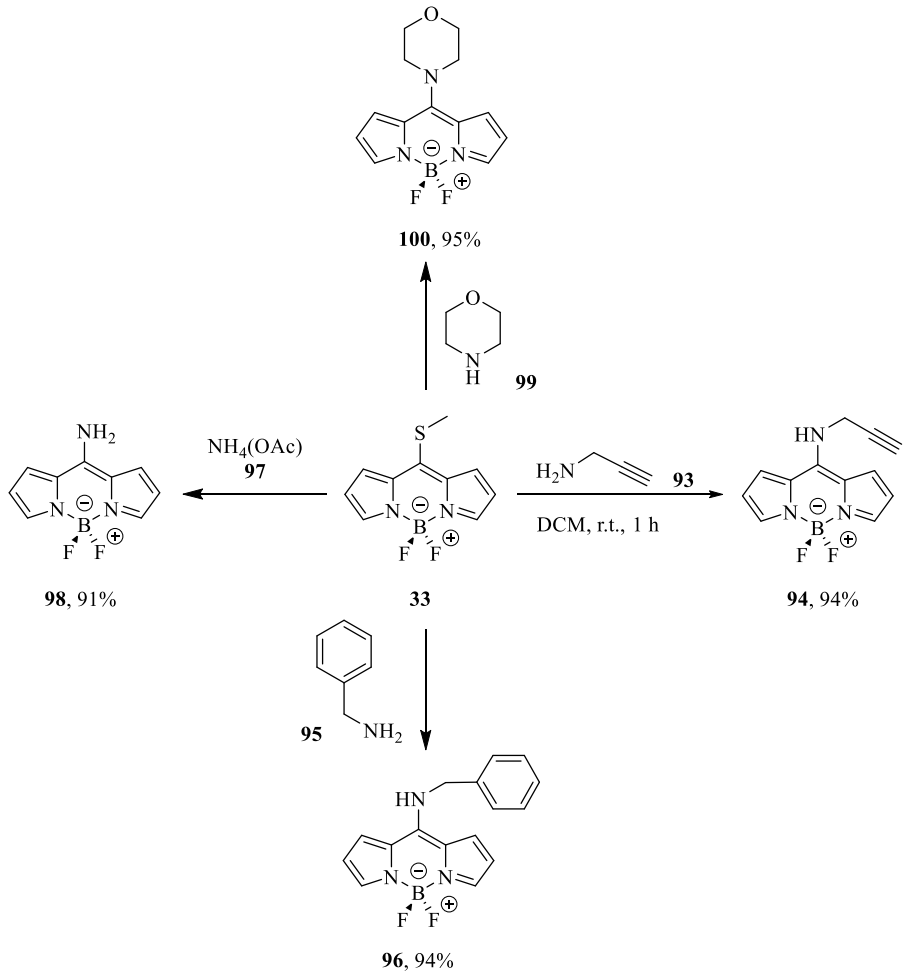
The Biellmann BODIPY can be synthesized in overall two steps. The 1st step involves the reaction of pyrrole with thiophosgene, $CSCl_2$, generating a thioketone **90a-c**. The 2nd step involves the reaction of the obtained thioketone with methyl iodide, CH_3I, to generate the dipyrromethene salt **91a-c**, which on subsequent BF_2 complexation using $BF_3{\cdot}OEt_2$ under basic condition, TEA, gives Biellmann BODIPYs, 8-methylthio BODIPY **34, 35** and **92** (Scheme 13). Peña-Cabrera *et al.*[68a,d-h] reported the synthesis of a wide range of derivatives of *meso*-substituted BODIPY by employing conditions of Liebeskind-Srogl reaction to **34** and **35**. Reaction of **34** and **35** with aryl, alkenyl, heteroaryl and organometallic boronic acids in the presence of $Pd_2(dba)_3$/TFP as a catalytic system and CuTC as a co-catalyst (stoichiometric amount) gives the *meso*-substituted BODIPYs **36–37** (22 examples 58-97%) (Scheme 4).[68g] The reaction also works efficiently if organostannanes were used instead of boronic acids using $Pd(PPh_3)_4$ as catalyst and CuDPP as a co-catalyst (5 examples 75-90%) (Scheme 4).[68g]



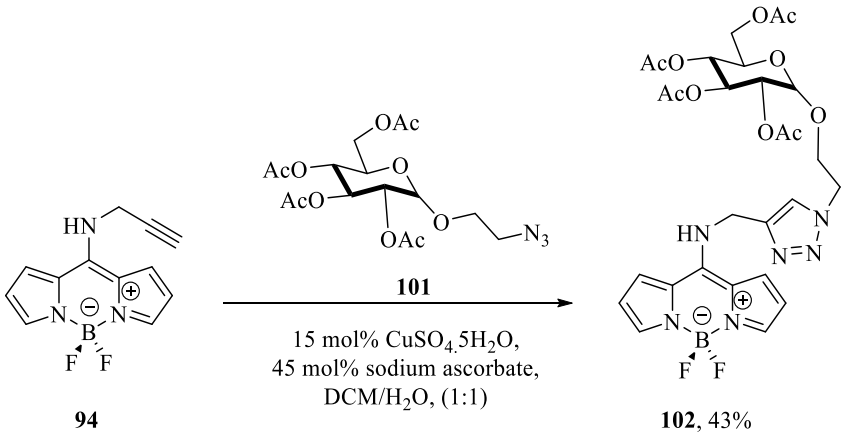
Scheme 4. Synthesis of *meso*-substituted BODIPY derivatives using Liebeskind-Srogl cross coupling reaction.

In addition to the exceptional reactivity of thiomethyl group present at the *meso*-position in Biellmann BODIPY, the thiomethyl group can also serve as a good leaving group during the synthesis of BODIPYs with O- or N- based nucleophiles (e.g., -OH or $-NH_2$) substituted at the *meso*-position. Thus, *meso*-amino or *meso* -alkoxy or *meso* -aryloxy BODIPYs can be prepared by using S_NAr type reaction. Peña-Cabrera *et al.* did pioneer work in such chemistry. They prepared several *meso*-substituted amino BODIPYs (14 examples, 35-96% yield) by treating **33** with various substituted amines.[162,163,164,165] The *meso*-amino BODIPY **98** was prepared by treating **33** with ammonium acetate. The other *meso*-amino substituted BODIPYs **94**, **96** and **100** were prepared by treating **33** with propargylamine **93**, benzylamine **95** and morpholine **99**, respectively (14 such examples, 35-96% yield) (Scheme 14). Furthermore, the amino-BODIPYs could be used for further functionalization, e.g., reaction between 8-

(propargylamino) BODIPY **94** and azido-carbohydrates using conditions of click reaction generated BODIPY-carbohydrate hybrid **102** (8 such examples, 24-80% yield) (eq 16).[68f]



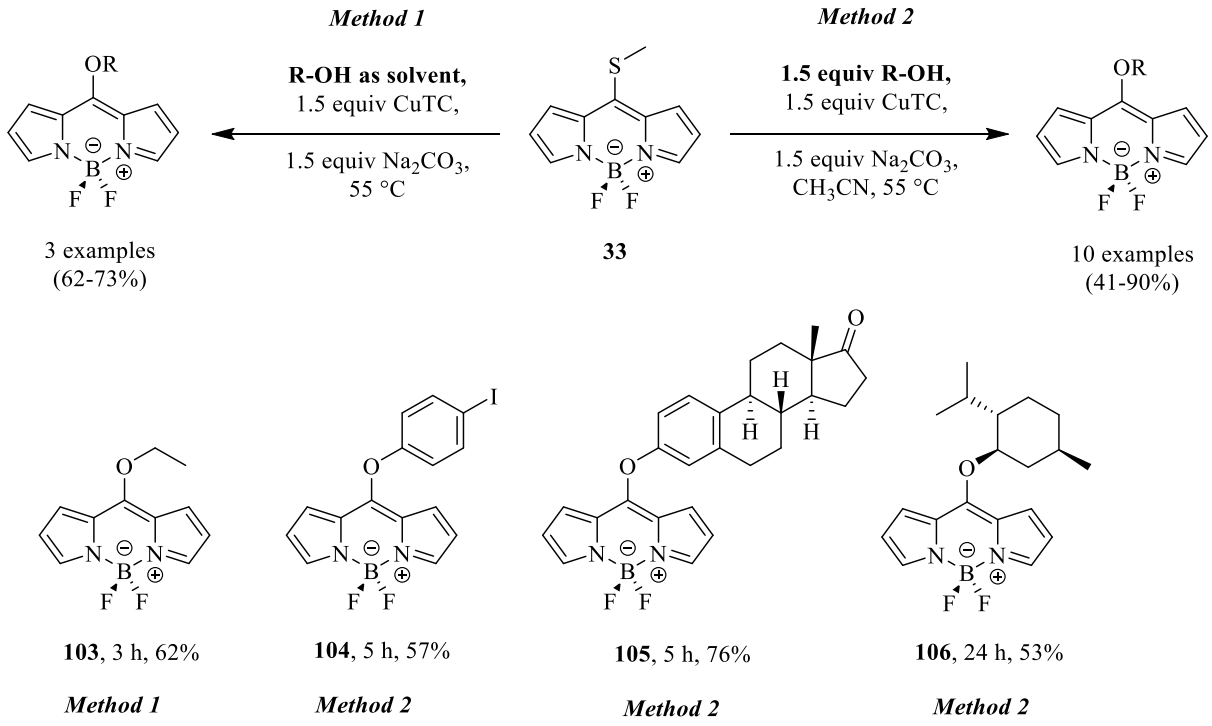
Scheme 14. Synthesis of various types of *meso*-substituted BODIPYs derived from *meso*-(thiomethyl) BODIPY **33** by S_NAr reaction.



(16)

Also, Peña-Cabrera *et al.* effectively used the *meso*-(thiomethyl) BODIPY **33** to prepare *meso*-alkoxy and *meso*-aryloxy BODIPYs by treating it with corresponding alcohols in the presence of a base and Cu(I) additive (Scheme 15).[166,167] They employed two methods for that purpose

(Method-1 and Method-2). Besides using simple alcohols, they also reported similar reactions using natural products, like, estrone **105**, menthol **106**, eugenol and cholesterol (Scheme 15).[165]



Scheme 15. Synthesis of various types of *meso*-alkoxy or *meso*-aryloxy BODIPYs synthesized from **33** using S_NAr reaction.

Thus, a wide range of BODIPY derivatives, involving -O, -N, and -C based nucleophiles substituted at the *meso*-position, can be prepared from **33** by using S_NAr type reaction and the Liebeskind-Srogl reaction. Based on the type of substituent present at the *meso*-position, all those BODIPY derivatives can show absorption and fluorescence bands from the blue region to near-IR region (Figure 24).

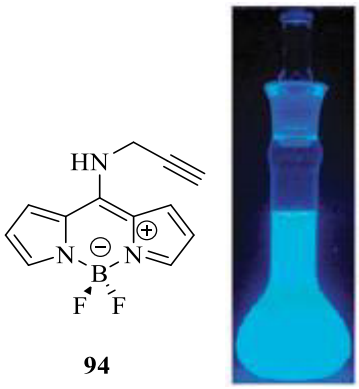
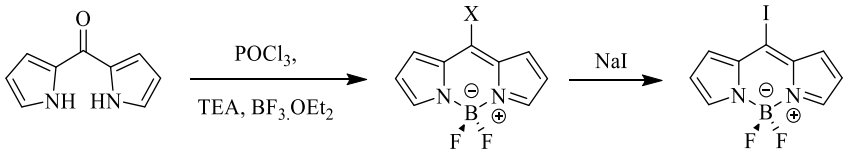


Figure 24. Left: Structure of meso-(propargylamino) BODIPY **94** Right: visual blue emission of **94** under UV light.

The *meso*-halo substituted derivatives of BODIPY can also be used for the synthesis of the *meso*-substituted derivatives of BODIPY. Wim Dehaen and coworkers[168] synthesized the *meso*-halo substituted derivatives of BODIPY and used them in the preparation of different

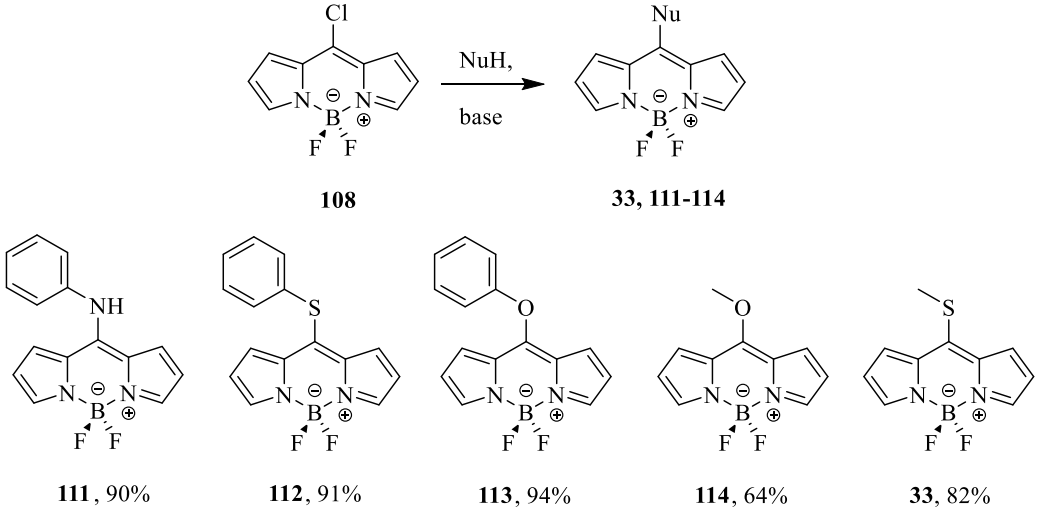
meso-substituted derivatives of BODIPY by employing Pd-catalyzed Sonogashira, Suzuki and Stille reactions and S_NAr reactions. In the synthesis of *meso*-halo substituted derivatives of BODIPY, halogen is added at the *meso*-position of dipyrrylketone **107** by using deoxygenative substitution reaction with $POCl_3$ or $POBr_3$, which leads to the immediate generation of the intermediate, dipyrrinium salt. The dipyrrinium salt on subsequent BF_2 complexation using $BF_3{\cdot}OEt_2$ in the presence of a base, TEA, formed 8-chloro BODIPY **108** (59% yield) or 8-bromo BODIPY (68% yield). 8-iodo BODIPY **110** could not be prepared by using this method. It was synthesized from **108** by using modified Finkelstein method (Scheme 16).



107 **108**, X= Cl, 59 % **109**, X= Br, 68% **110**, 66%

Scheme 16. Synthesis of meso-halo substituted BODIPYs.

Additionally, Wim Dehaen and coworkers[178] reported the use of *meso*-halo substituted derivatives of BODIPY for the synthesis of various BODIPYs with O-, S- or N- based nucleophiles (e.g. –O CH_3, -SCH_3 or -NHPh) substituted at the *meso*-position through S_NAr reaction (Scheme 17) and for the synthesis of *meso*-substituted derivatives of BODIPY through C-C forming Pd-catalyzed cross-coupling reactions, like, Suzuki, Stille and Sonogashira, as shown in Table 1.

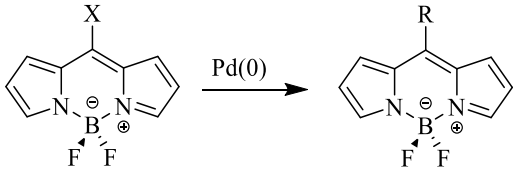


108 **33, 111-114**

111, 90% **112**, 91% **113**, 94% **114**, 64% **33**, 82%

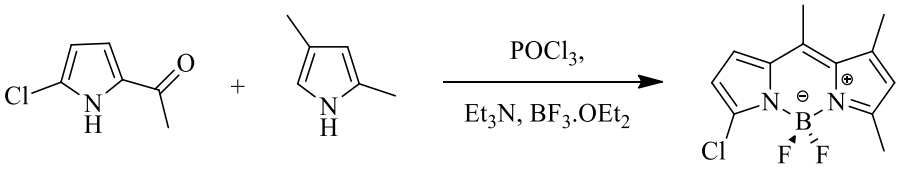
Scheme 17. Use of 8-halo BODIPYs for the synthesis of various BODIPYs with O-, S- or N-based nucleophiles substituted at the *meso*-position through S_NAr reaction.

Table 1 Pd-catalyzed cross-coupling reactions of 8-HaloBODIPYs (**108-110**).

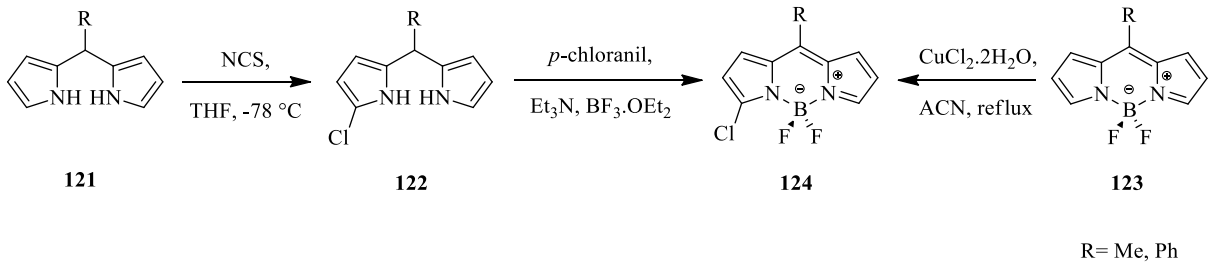


Product	X	Reaction type	R	Yield (%)
115	Cl	Suzuki	Ph	36
115	Br	Suzuki	Ph	53
115	I	Suzuki	Ph	75
116	I	Suzuki	4-MeO-Ph	58
115	Br	Stille	Ph	73
117	Br	Stille	2-thienyl	61
118	Cl	Sonogashira	C≡CPh	76

Furthermore, functionalization at α-position of BODIPY backbone can be achieved through different methods, reactions of α-halo substituted derivatives of BODIPY at α-position are one of them. [169] The required α-halo substituted derivatives of BODIPY can be synthesized by three different methods. The first method includes reaction between α-halogenated pyrroles **119** and another unit of pyrrole **71** (eq 17).[170] The second method includes halogenation at α-position of the dipyrromethane intermediate **121**, which on further BF_2 complexation gives the desired α-halo substituted derivatives of BODIPY, like **124**.[171,172] The third method includes direct halogenation at the α-position of BODIPY core to form α-halo substituted derivatives of BODIPY, like **124**[173] (Scheme 18).



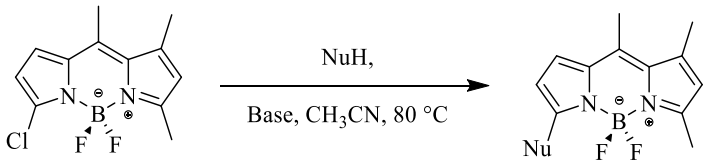
(17)



Scheme 18. Two different routes for the synthesis of α-chloro-BODIPY.

The halogen substituents at the 3,5-positions of BODIPY core are greatly susceptible towards the Pd-catalyzed cross-coupling reactions or S_NAr reactions, owing to the electron deficiency at those positions.

The electron deficiency at the 3,5-positions provides halogen substituents at these positions a high reactivity towards nucleophilic aromatic substitution (S_NAr) and palladium-catalyzed cross coupling. The S_NAr reaction of derivatives of 3-chloro BODIPY, like **120**, can be easily achieved at room temperature (Scheme 19), similar to that of 8-chloro derivatives of BODIPY.[174,175,176] For disubstitution at 3,5-positions, longer reaction times and/or higher temperatures are necessary.



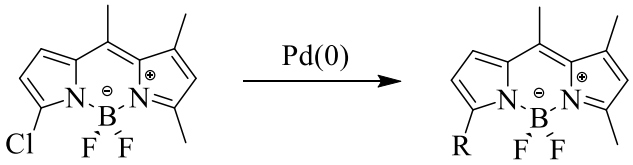
120 **124a-d**

a= PhS- (97%)
b= BuS- (92%)
c= BuNH- (77%)
d= PhO- (43%)

Scheme 19. The S_NAr reaction of derivatives of 3-chloro BODIPY.

Additionally, 3-chloro-BODIPY **120** can easily undergo Pd-catalyzed cross-coupling reactions like, Suzuki, Sonogashira, Stille, and Heck as shown in Table 2.[169]

Table 2 Pd-catalyzed cross-coupling reactions of 3-chloro-BODIPY **120**.

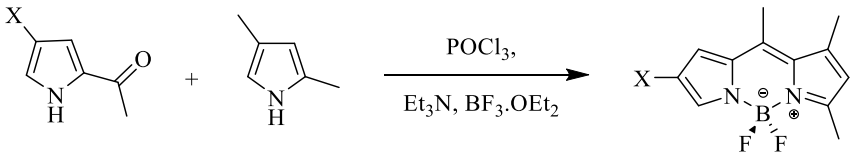


120 **125a-h**

Reaction type	R	*t* (h)	Yield (%)	Compound **125a-h**
Suzuki	Ph	5	75	**125a**
Suzuki	4-MeO-Ph	6	49	**125b**
Stille	2-thienyl	3	66	**125c**
Stille	2-furyl	16	87	**125d**
Heck	Styrene	2	93	**125e**
Heck	butyl acrylate	4	53	**125f**
Sonogashira	PhC≡C	3	46	**125g**
Sonogashira	TMSC≡C	3	48	**125h**

The 2,6-positions of derivatives of BODIPY shows high reactivity towards the electrophilic aromatic substitution reactions (S_EAr) like halogenation, formylation and sulfonation, because those positions have very less positive charge. Two different methods available for the halogenation of BODIPY core at C-2 position. [169,177,178] The first method is the condensation

reaction between 4-halo-2-acylpyrrole and another unit of desired pyrrole using $POCl_3$ to form halogenated dipyrromethene intermediate, which on BF_2 complexation using $BF_3{\cdot}OEt_2$ under basic conditions gives 2-halogenated derivatives of BODIPY **127a-c** 36%–57% yields (eq 19).[169]



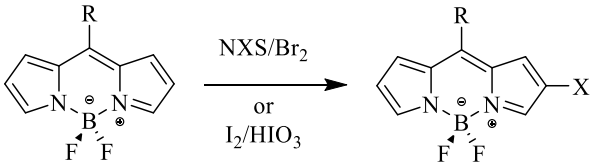
(19)

119, 126a-b
X= Cl, Br, I

71

127a-c, 36-57%

Second route involves the treatment of BODIPY with N-halosuccinimide (NXS) in CH_2Cl_2 to generate 2-halogenated BODIPYs **129a-c** in high yields, since the C-2 position of BODIPY is more prone to electrophilic substitution reactions (eq 20).[176,177] Additionally, brominating agent like, Br_2, and iodinating agent like, I_2/HIO_3, can be used for the synthesis of **129b** and **129c**, respectively.

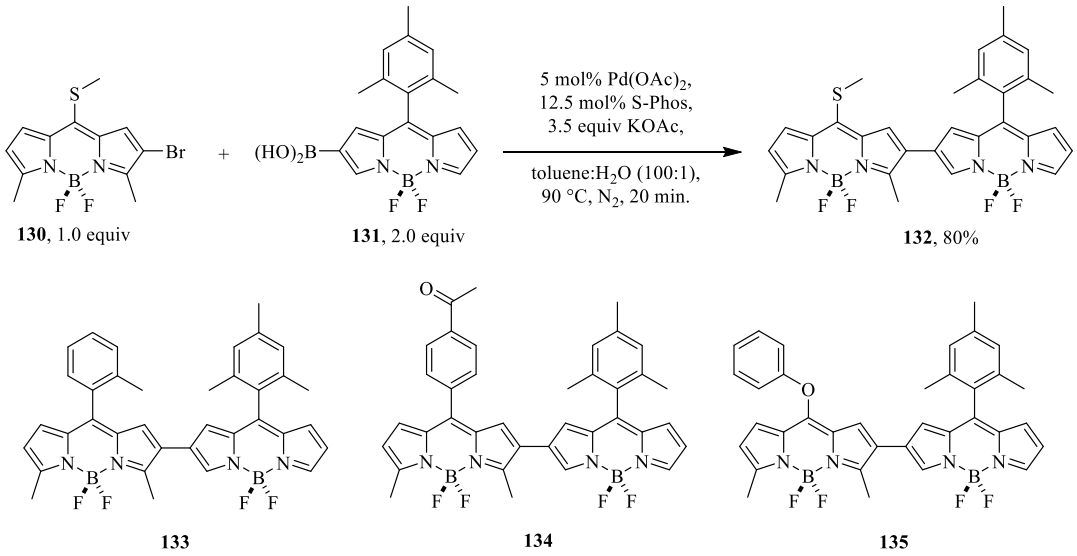


(20)

128
R= Me, aryl

129a-c
a, X= Cl,
b, X= Br,
c, X= I

There are several applications of 2-halogenated BODIPYs in organic synthesis, such as cross-coupling reactions like Suzuki and Sonogashira reactions. Also, these 2-halogenated BODIPYs can used to synthesize the dimers of BODIPY. Recently, in 2018, Peña-Cabrera *et al.* did a pioneering work in the synthesis of fully functionalizable *β,β′*-BODIPY dimers (Scheme 19). First, they performed the Suzuki cross-coupling reaction between **130** and freshly prepared **131** to obtain BODIPY dimer **132**, which upon Liebeskind-Srogl cross-coupling reaction or S_NAr reaction (Scheme 20) gives several BODIPY dimers (16 examples, 25-96%).[179]



Scheme 20. Synthesis of BODIPY-dimers **132-135**.

1.5 Summary and Outlook.

In this chapter, we had a glance over the history of chemistry, along with the meticulous knowledge about the chronicles of organometallic chemistry, starting from the synthesis of very first organometallic species by Louis Claude Cadet de Gassicourt to the recent, 2010, Noble Prize in chemistry to Richard Frederick Heck, Ei-ichi Negishi and Akira Suzuki for their work in palladium-catalyzed cross-coupling reactions and organic synthesis. Also, an emphasis on the use of organometallic chemistry in industries as well as its industrial applications has been provided. To have the better understanding of the upcoming chapters which includes the actual research conducted in this doctorate course, an indispensable basis of cross-coupling reactions as well as use of palladium metal catalysts in cross-coupling reactions has been provided. During this Ph.D. research, cross-coupling reactions like Liebeskind-Srogl, Suzuki, Stille and Sonogashira has been used. Hence, the comprehensive information about these reactions including their mechanisms and applications, has been provided. Finally, in order to understand the colossal field of BODIPY chemistry, the profound knowledge about its synthetic pathways and use of cross-coupling reactions to synthesize its derivatives has been explained here.

In the second chapter of the thesis, three different strategies are discussed. The first strategy is the functionalization of cyclobutendione oligothiophenes by means of cross-coupling reactions. In that strategy, three different types of cross-coupling reactions, viz., Liebeskind-Srogl, Suzuki and Stille were used. The second strategy is the synthesis of bis-thienyl-substituted cyclobutenedione *via* the Liebeskind-Srogl and Stille cross-coupling reactions. In this strategy, the synthesis of the 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione (bis-thienyl-substituted cyclobutenedione) **192** is demonstrated, which on photochemical air oxidation gave the 2,3-bis(5-[2,2']-bithien-5-yl) maleic anhydride **193**. The third strategy involves the functionalization of phenyl containing cyclobutenediones by means of cross-coupling reactions. This strategy involves Liebeskind-Srogl and Stille cross-coupling reactions. In this strategy, 3,4-bis(4-bromophenyl)cyclobut-3-ene-1,2-dione **195** was synthesized by using Liebeskind-Srogl cross-coupling reaction. The functionalization of **195** was achieved by its Suzuki cross-coupling reaction with several boronic acids.

In the third chapter of the thesis, three different strategies are discussed for the synthesis of porphyrin-BODIPY hybrids. The first strategy involves the Liebeskind-Srogl cross-coupling between the boronic acid of porphyrin **262** and the brominated methylthio-BODIPY derivative **263** to give the *meso-meso* linked porphyrin-BODIPY hybrid **264**, which on Suzuki cross-coupling reaction with wide range of boronic acids can give *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** with different functionalities. The second strategy involves synthesis of *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** through series of Suzuki, bromination and Suzuki reactions. First, 8-chloro BODIPY **108** or 8-iodo BODIPY **110** on Suzuki coupling with porphyrin boronic ester **261** can generate *meso-meso* linked porphyrin-BODIPY hybrid **266**, which can give **264** on its bromination at the BODIPY core. The *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** with different functionalities can be obtained from the Suzuki reaction of **264** with wide range of boronic acids. Further, the third strategy involves the Suzuki coupling between 2-bromo *meso* substituted BODIPY derivatives **267** and the porphyrin boronic ester **261** to generate the *meso-β* linked porphyrin-BODIPY hybrids **268a-e** with different functionalities.

Chapter 2: Functionalization of cyclobutendione oligothiophenes by means of cross-coupling reactions.

2.1 Introduction

For the past five decades, squaric acid **136**, derivatives of cyclobutadienone **137**, squaramides **138**, mixed squaramates **139** and squaric acid esters **140** have been studied vastly and various reports have been published about their remarkable synthetic utility (Figure 25). **136-140** can be used as starting materials for the synthesis of a vast range of compounds with interesting motifs, for example, cyclo[*n*]carbons **141**,[180] unsymmetrical squaraines **142**,[181,182] derivatives of quinone **143**,[183] bisquaryls **144**,[184] squaramides **145**,[185] 2-pyrones **146**,[186] benzocyclobutenediones **147**,[187] and even π-conjugated polymeric motifs **148**[188] (Figure 26). The cyclobutenedione derivatives have been used for the synthesis of organic compounds having applications, like, sensitizers in dye-sensitized solar cells,[189,190] organocatalysts,[191] photoconductors,[180] anion recognition systems,[192] non-linear optical materials,[193] high-affinity ligands for excitatory amino acid receptors,[194] ethanol sensors,[195] chiral auxiliaries,[196] and chemosensors,[197] etc.

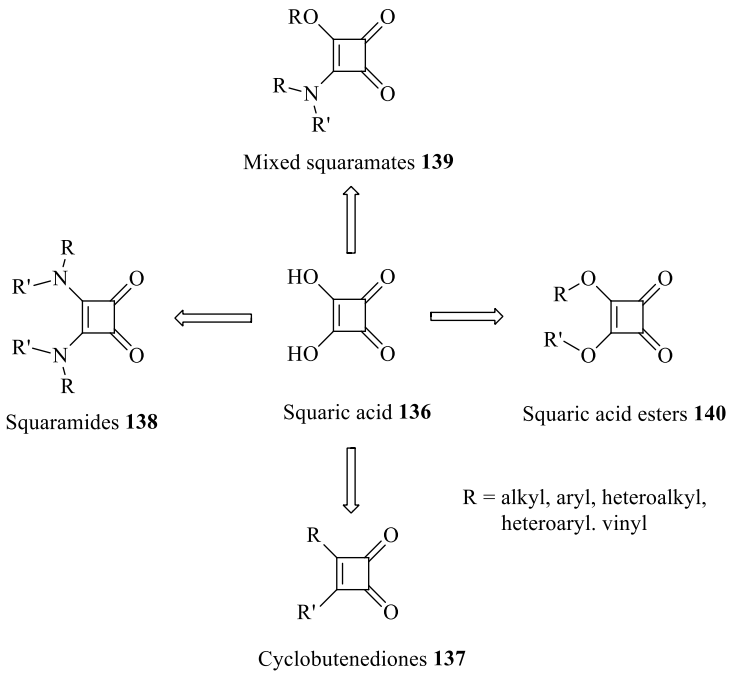


Figure 25. Squaric acid and its analogues.

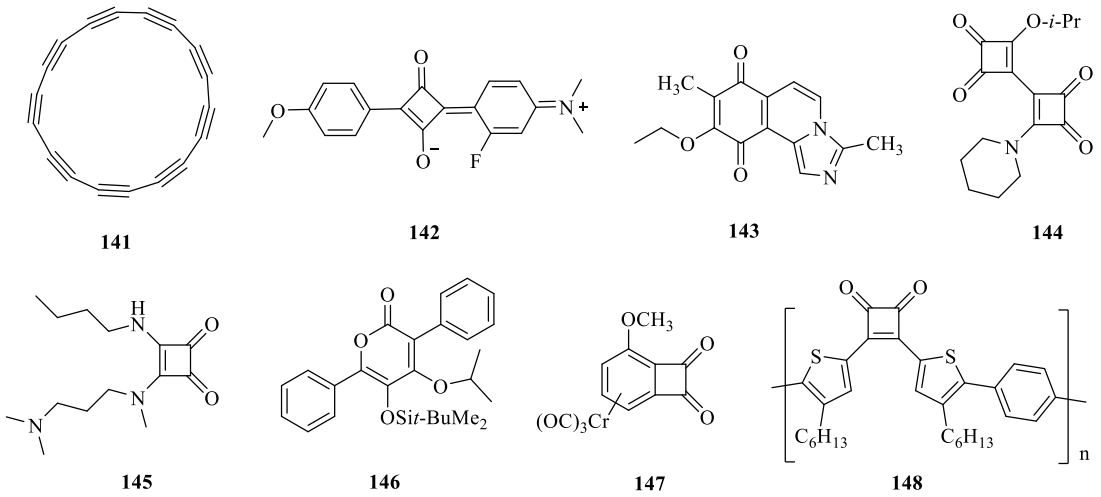


Figure 26. Organic compounds with interesting motifs synthesized from squaric acid and its analogues **136-140**.

Generally, the basic structural core of the cyclobutenedione derivatives is chemically stable in aqueous environment, which those molecules usually come across in the organisms. Therefore, the cyclobutenedione derivatives can be used in the synthesis of organic compounds having biological importance and a wide range of squaric acid analogues have been reported with medicinal properties which are facilitated by the presence of compelling H-bond acceptors and donors.[198] For example, **149** showed moderate to weak antibacterial activity against *Helicobacter pylori*,[199] compound **150** with an *N*-methyl-3-(*R*)-aminotetrahydrofuranyl squaramide moiety used as a HIV-1 protease inhibitor and thus showed an antiviral activity,[200] cyclobutenedione derivative **151** showed a high cytotoxicity against *HeLa* cervical cancer cells or compound **152**, containing cyclobutenedione core with fluorophore, showed a good cytotoxicity and can be potentially useful for the studies in cell imaging,[201] etc. (Figure 27).

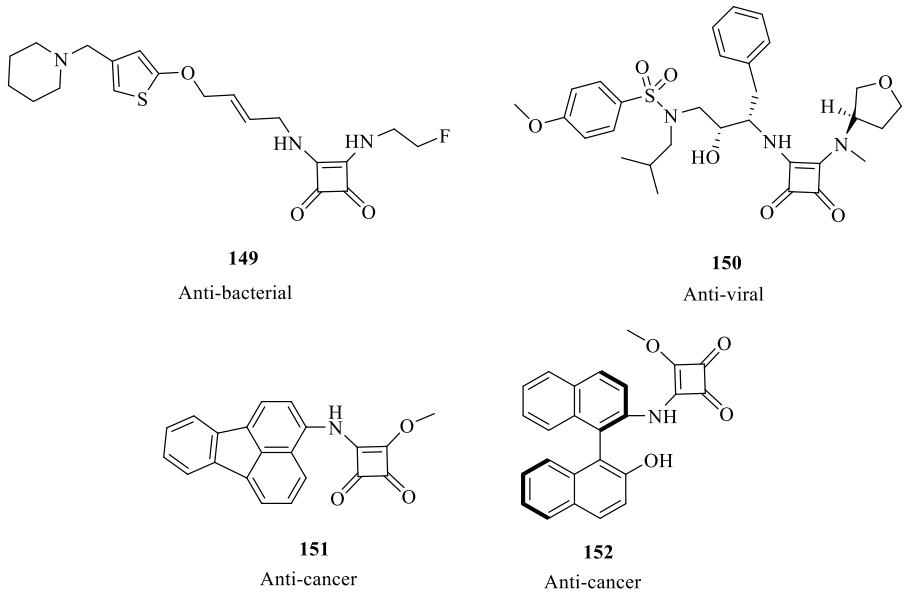
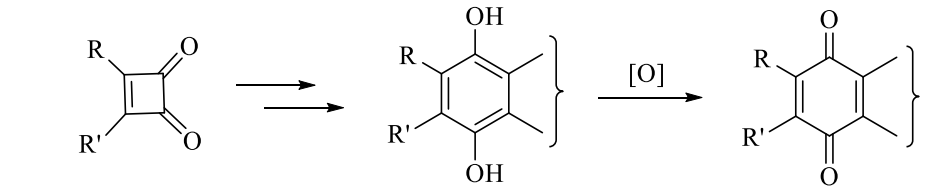


Figure 27. Squaric acid analogues with medicinal properties.

In addition, 4-membered ring core is one of the important features of the derivatives of cyclobutenedione **137**, which is a hidden aromatic moiety **153** or quinone moiety **154** with different substituents at 3 and 4-positions of **1** (Figure 28). Thus, **137** can easily transformed from an electronically poor moiety to an electronically rich fragment **153**.[202] By doing so, they can be used as stating materials for the synthesis of tri- (or oligo-) arylenes. Compounds containing oligoarylenes motifs showed applications as thin-film transistors[203] and organic light-emitting diodes (OLED's).[204] For example, Khanasa *et al*. reported the synthesis of **155** and its potential application as OLED's.[205] Additionally, the natural products involving quinone frameworks have been reported.[206] For example, Cribrostatin 6[207] **143** and (-)-Elisapterosin B[208] **156** are the natural products containing quinone ring system which are obtained from cyclobutenedione derivatives (Figure 29). Research groups like, Suh *et al.*,[209] Huang *et al*. and Ohishi *et al.*[187] reported the use of cyclobutenedione derivatives for the synthesis of π-conjugated cyclobutenedione polymers, for example compound **148**[187] (Figure 29). Recently, Khopkar *et al*. synthesized biologically active 2,3-dihydro-1H-perimidines by using the squaric acid **136** as an eco-friendly, metal-free and green organocatalyst.[190]



R, R' = aryl, heteroaryl, etc.

137 **153** **154**

Figure 28. Cyclobutenedione derivatives as hidden benzene or quinone moiety.

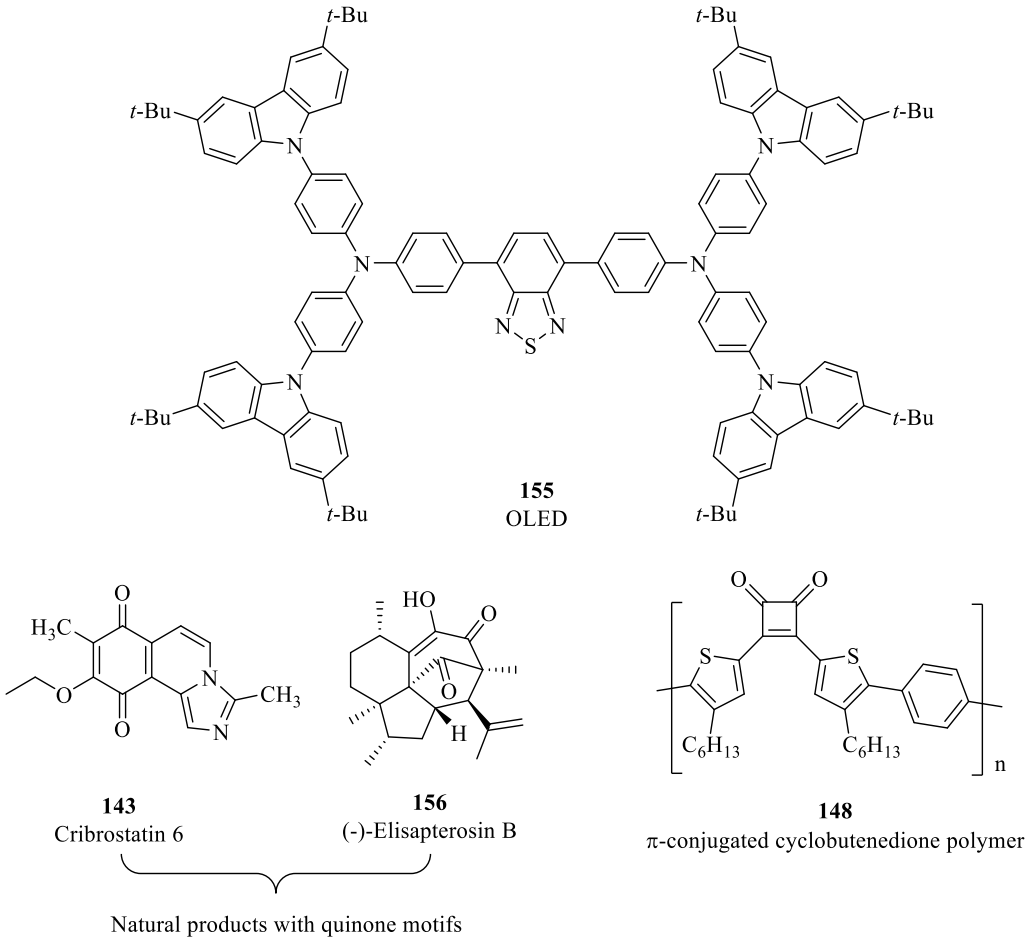


Figure 29. Compound **155** with oligoarylenes motifs having potential applications as OLED, natural products **143** and **156** with quinone motifs synthesized from cyclobutenedione derivatives and a π-conjugated cyclobutenedione polymer **148**.

The unique symmetrical, planar and aromatic structure of squaric acid and its analogues is the reason behind all those significantly important applications. Out of all the reported derivatives of cyclobutenedione, 1,2-dihydroxy-cyclobutene-3,4-dione or squaric acid **136** is very well-know and it was first reported by Cohen and co-workers in 1959.[210] They reported that the squaric acid involves a symmetrical and planar dianionic 4-membered ring system with two carbonyl groups, which has an exclusive 2π-*pseudo*-aromaticity and which in turn makes it a strongly electron-withdrawing molecule. Additionally, they also reported that the dianionic system **158** is resonance stabilized (Figure 30), which makes all 4 oxygen atoms equivalent through resonance. This resonance stabilization of dianionic system is the reason behind the behaviour of squaric acid as a diacidic moiety with *pKa_1 of 0.54 and pKa_2 of 3.58*, which in turn makes it a strong acid.

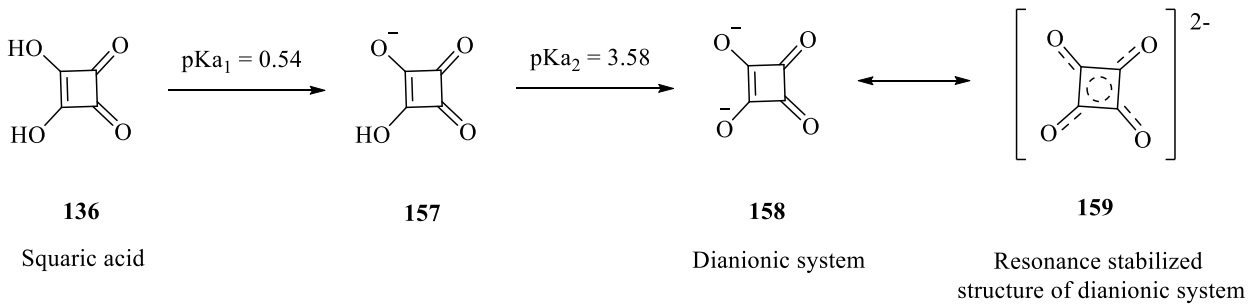


Figure 30. Stabilization of dianionic squaric acid system **158** by resonance.

However, Roberts and co-workers, in 1955, were the earliest to report the first synthesis of a cyclobutenedione derivative, phenylcyclobutenedione **160** and its derivatives **161a-f** (Figure 31).[211]

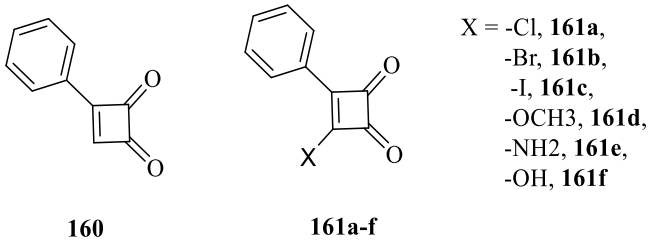


Figure 31. Structure of the first cyclobutenedione derivative, phenylcyclobutenedione **160** and its derivatives **161a-f** reported by Robert *et al*.

Many research groups across the world have been working on the research and development of the diverse synthetic methods and interesting applications of squaric acid and its analogues, in particular, Peña-Cabrera *et al.*,[201,212] Liebeskind *et al.*,[213] Paquette *et al.*,[214] Moore *et al.*,[215] Periasamy *et al.*[216] and Danheiser *et al.*[217] All these groups used squaric acid and its analogues **136-140** for the synthesis of wide range of cyclobutenedione derivatives with many different kinds of functional groups at 3 and/or 4-position of the cyclobutenedione ring core. Functional groups like alkyl, alkenyl, aryl, heteroaryl, vinyl, etc. have been extensively used for such purpose. Generally, the cyclobutenedione derivatives can be synthesized by using highly reactive organolithium species, Grignard reagents or transition metal-catalyzed cross-coupling reactions like, Liebeskind-Srogl, Suzuki, Stille, etc. (Figure 32). However, the use of highly reactive organolithium species and Grignard reagent have a drawback, they are strong bases and thus, they cannot be used as nucleophiles with compounds containing acidic protons, like alcohols and amines. Transition metal-catalyzed cross-coupling reactions using milder conditions can overcome that drawback by synthesizing those compounds which cannot be synthesized or showed complications in synthesis or gives lesser yields by using organolithium species or Grignard reagents.

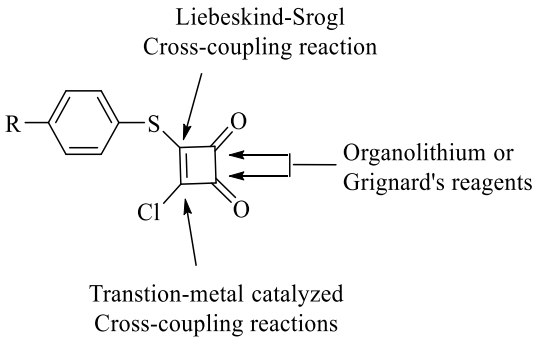
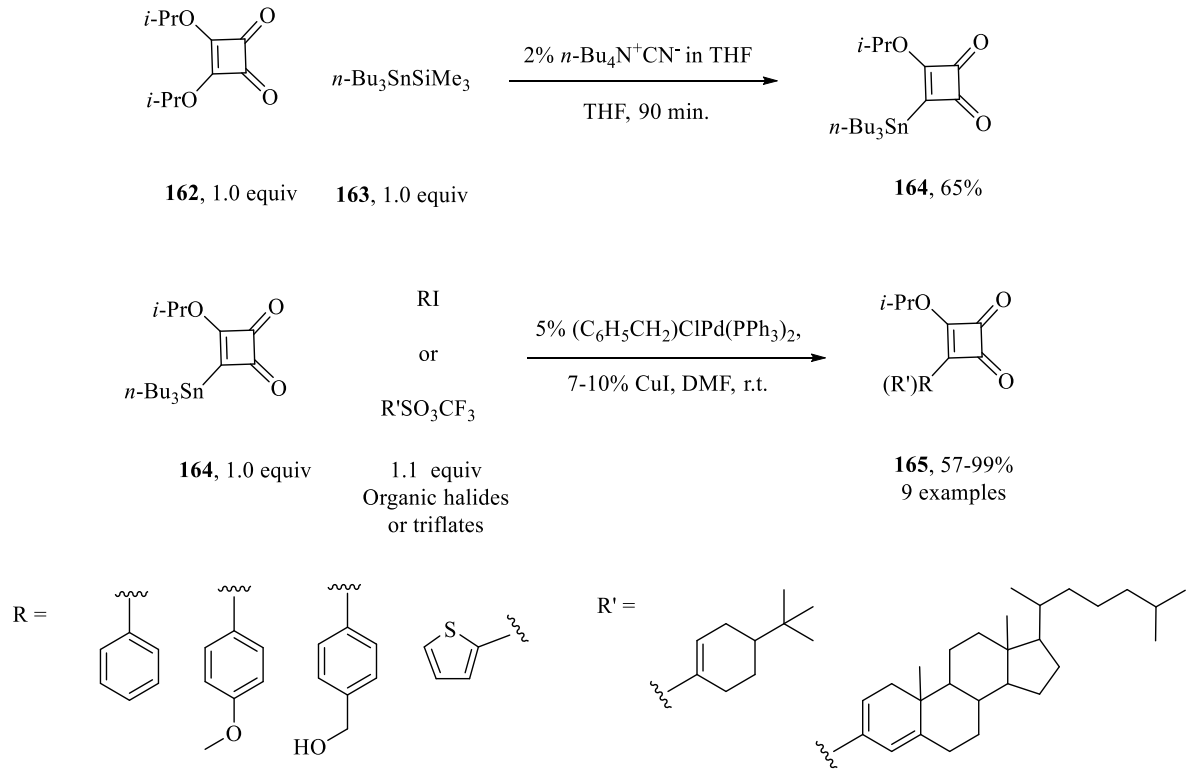


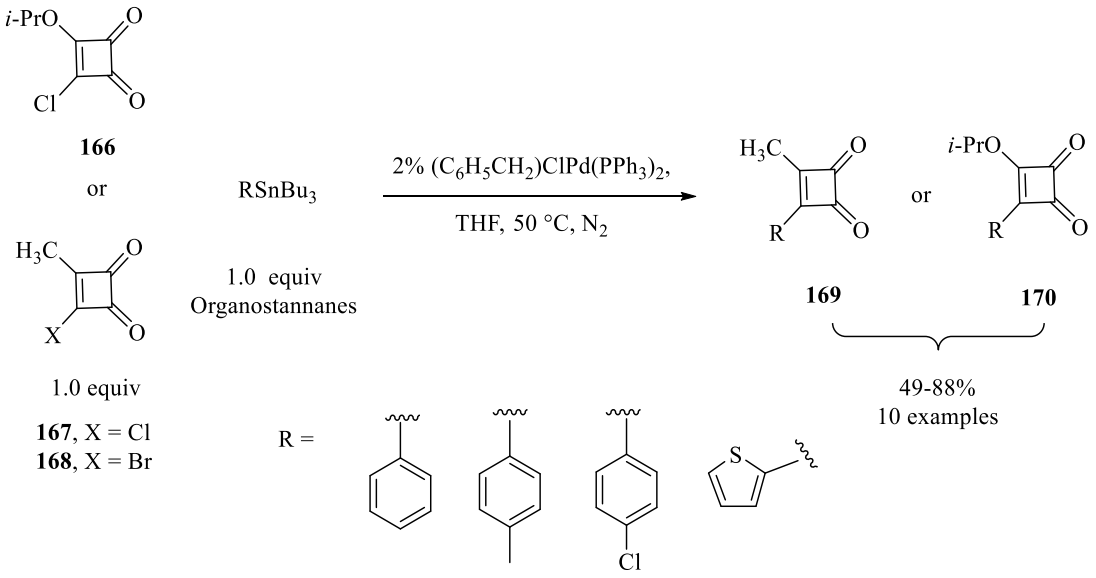
Figure 32. Cyclobutenedione ring core with multiple reaction centres.

During this project, functionalization of cyclobutenedione oligothiophenes by means of cross-coupling reactions, Liebeskind-Srogl, Suzuki and Stille cross-coupling reactions were used for the synthesis of several cyclobutenedione derivatives. Therefore, a quick glance over the past reports of the synthesis of cyclobutenedione derivatives by using cross-coupling reactions will be given here, only few important articles will be discussed. Peña-Cabrera *et al.* and Liebeskind *et al.* did a pioneering work in the application of transition metal catalyzed cross-coupling reactions for the synthesis of cyclobutenedione derivatives. To best of my knowledge, Liebeskind *et al.* were the first to report the synthesis of stannyl derivatives of cyclobutenedione, like, 3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione **164**, from 3,4-diisopropyl squarate **162** and *n*-$Bu_3SnSiMe_3$ **163** and also, the cross-coupling reaction of **164** with different types of organic halides and triflates using 5% $(C_6H_5CH_2)ClPd(PPh_3)_2$ and 7-10% of CuI as a co-catalyst to form several substituted cyclobutenediones (57-99%, 9 examples) (Scheme 21).[218]



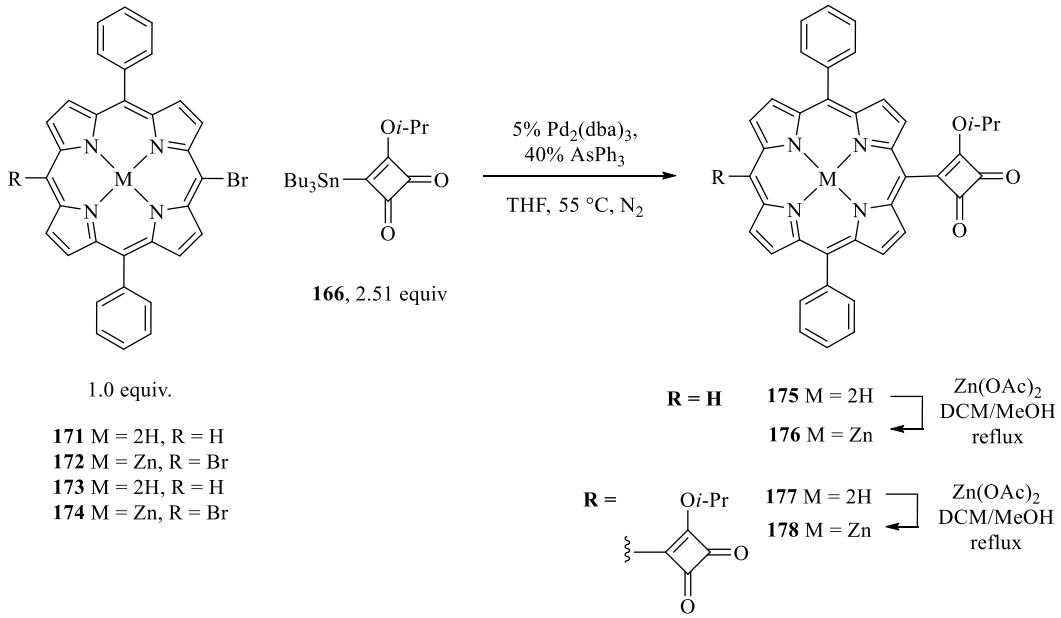
Scheme 21. Synthesis of stannyl derivatives of cyclobutenedione **164** and several substituted cyclobutenediones **165** via Pd-catalyzed cross-coupling reaction.

The same group also reported the Pd-catalyzed cross-coupling reaction of halocyclobutenediones **166-168** with different types of organostannanes for the synthesis of substituted cyclobutenedione derivatives **168-170** (49-88%, 10 examples) (Scheme 22).[219]



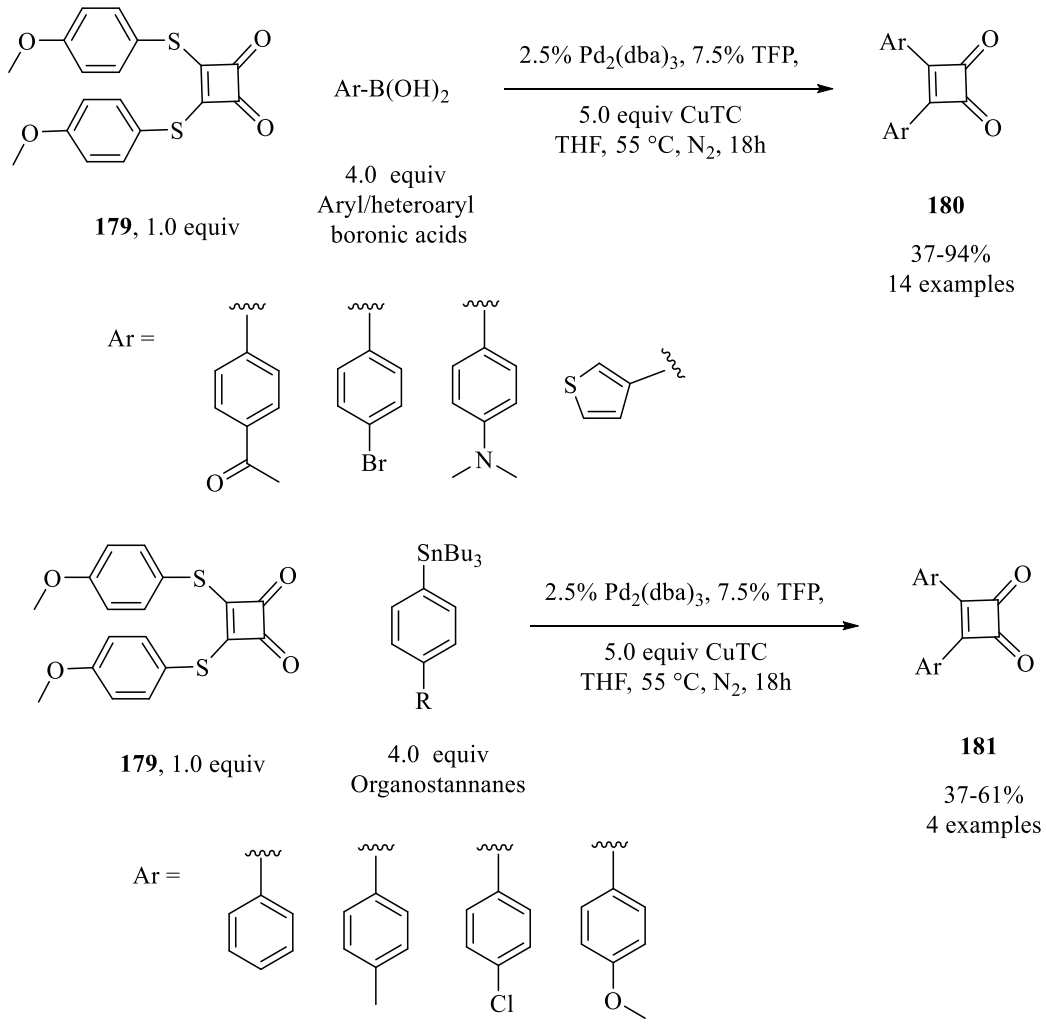
Scheme 22. Pd-catalyzed cross-coupling reactions of halocyclobutenediones **166-168** with different types of organostannanes for the synthesis of substituted cyclobutenedione derivatives **169-170**.

Liebeskind *et al.* also reported a new and efficient preparation of *meso*-linked squarylporphyrins **175-178** by Stille cross-coupling reaction of porphyrins **171-174** with 3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione **164** using 5% $Pd_2(dba)_3$, 40% $AsPh_3$ in THF at 55 °C.[220]



Scheme 23. Synthesis of *meso*-linked squarylporphyrins **175-178** by Stille cross-coupling reaction.

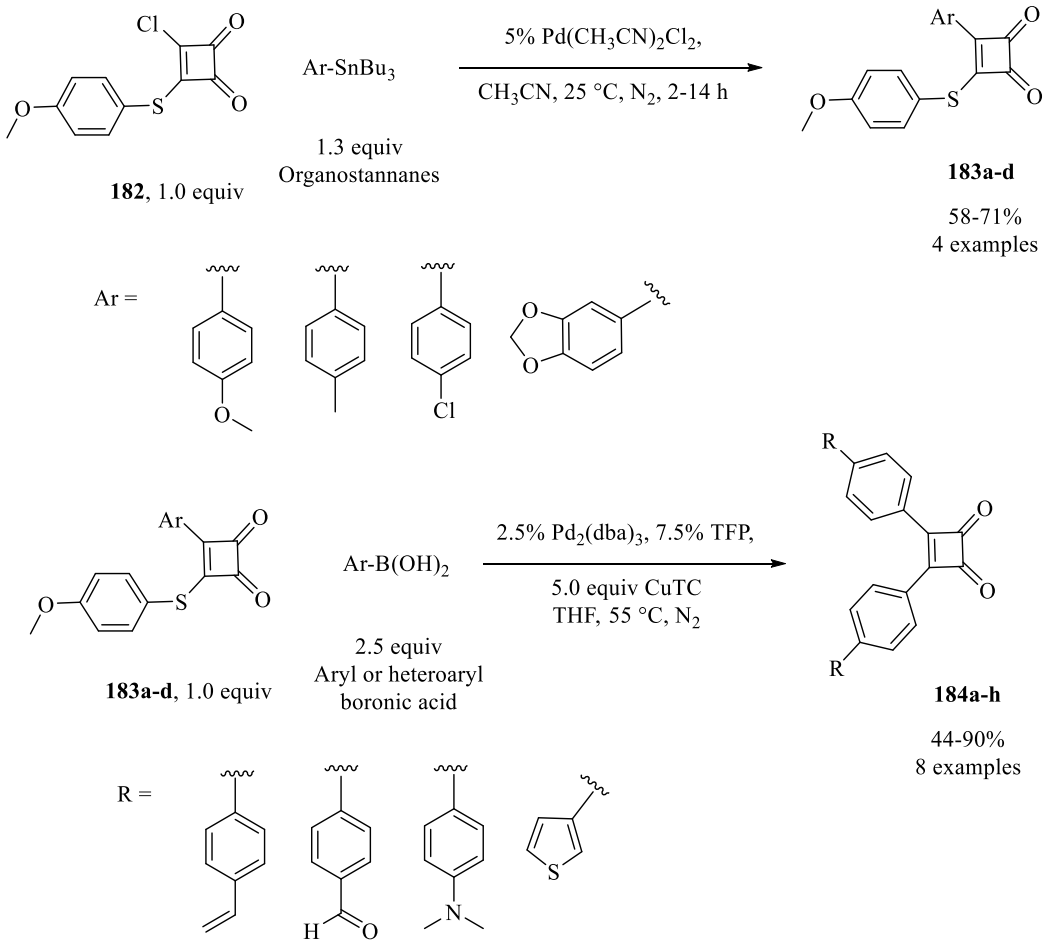
Peña-Cabrera *et al.* were the first to report the application of Liebeskind-Srogl cross-coupling reaction for the synthesis of aryl or heteroaryl substituted cyclobutenedione derivatives at the C-3 and C-4 positions of the 4-membered ring. The Liebeskind-Srogl cross-coupling reaction was carried out using wide range of boronic acids and organostannanes with Pd as a catalyst and Cu as a co-catalyst. They reported the synthesis of 14 aryl and heteroaryl substituted cyclobutenedione derivatives **180** using aryl and heteroaryl boronic acids with yields ranging from 37-94%, while 4 derivatives of aryl substituted cyclobutenedione **181** were reported using organostannanes with yields ranging from 37-61%. All the 18 reported derivatives were symmetrically substituted cyclobutenediones.[211d]



Scheme 24. Synthesis of aryl or heteroaryl substituted cyclobutenedione derivatives **180-181** via Liebeskind-Srogl cross-coupling reaction.

The same group also reported the synthesis of unsymmetrically substituted derivatives of cyclobutenediones via sequential Stille and Liebeskind-Srogl cross-coupling reactions of 3-chloro-4-arylthiocyclobutene-1,2-dione **182**. First, they performed the Stille cross-coupling reaction selectively at the C-3 position of **182** using different organostannanes to obtain **183a-d** with yields ranging from 58-71%. Then the Liebeskind-Srogl cross-coupling reaction of **183a-d** with different aryl and heteroaryl boronic acids generated the unsymmetrically substituted cyclobutenedione derivatives **184a-h** with yields ranging from 44-90% (Scheme

25).[201] This study was one of a kind and was the earliest one to report such unsymmetrically substituted cyclobutenedione derivatives through selective and sequential cross-coupling methods.

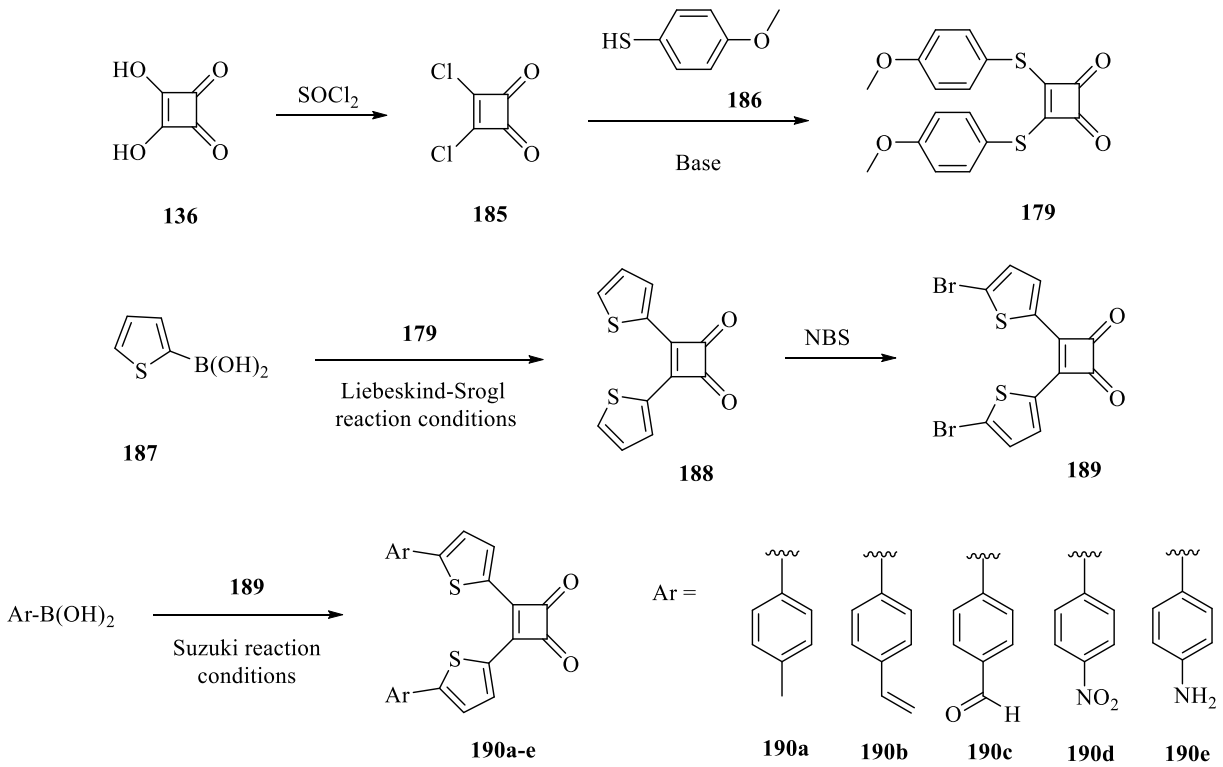


Scheme 25. Synthesis of unsymmetrically substituted cyclobutenedione derivatives **184a-h** via sequential Stille and Liebeskind-Srogl cross-coupling reactions.

2.2 Design and concept of the project.

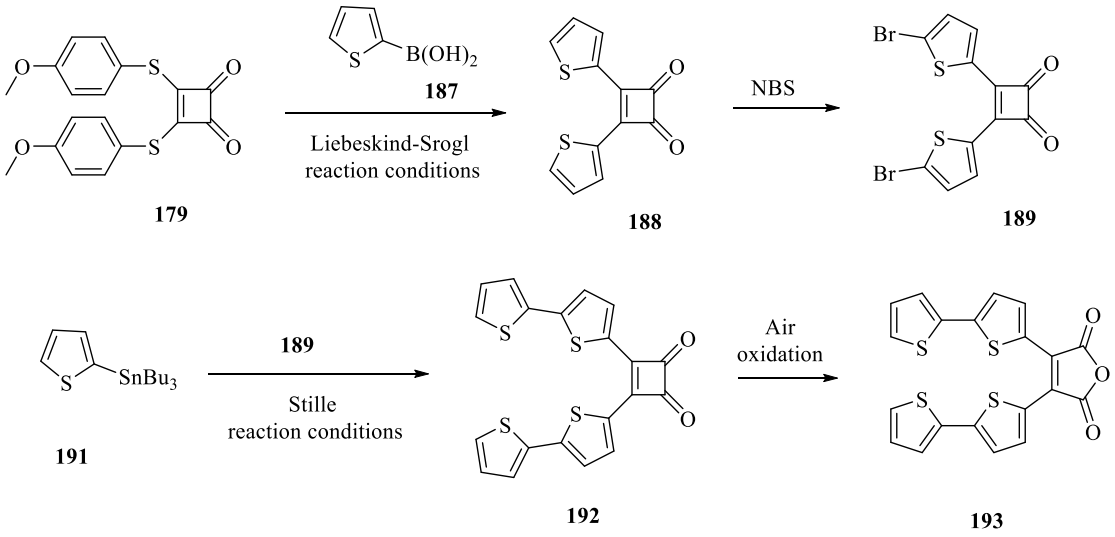
As mentioned earlier, our group successfully reported the synthesis of symmetrically and unsymmetrically substituted cyclobutenedione derivatives by means of transition-metal catalyzed cross-coupling reactions, like, Liebeskind-Srogl and Stille reactions.[201,211d] Even though, in those studies, we did not report the study of the optical properties of those cyclobutenedione derivatives, while synthesizing them, we observed that most of those derivatives showed fluorescence under UV lamp at 365 nm. So, we envisioned that, if, we extend the conjugation by attaching another aryl or heteroaryl ring to the already attached aryl or heteroaryl ring on the C-3 and/or C-4 position of the cyclobutenedione core, we can observe the bathochromic shift in the absorption and emission bands of those compounds. Thus, during this project, our objective was to functionalize the cyclobutenedione oligothiophenes and phenyl containing cyclobutenediones by means of cross-coupling reactions like, Liebeskind-Srogl, Suzuki, Stille, etc., and study the optical properties of the obtained derivatives. For that purpose, we proposed three different strategies, viz., strategy A, B and C.

Strategy-A is the functionalization of cyclobutenedione oligothiophenes by means by cross-coupling reactions. This strategy involves chlorination of squaric acid **136** to give 3,4-dichloro-3-cyclobutene-1,2-dione **185**, which can generate 3,4-bis(*p*-methoxythiophenoxy)-3-cyclobutene-1,2-dione **179** on its nucleophilic substitution reaction with *p*-methoxythiophenol **186**. The Liebeskind-Srogl cross-coupling reaction of **179** with 2-thienyl boronic acid **187** using Pd-catalyst and Cu co-catalyst can generate **188**, which on bromination can give **189**. The functionalization of 3,4-bis(5-bromothiophen-2-yl)cyclobut-3-ene-1,2-dione (cyclobutenedione oligothiophene) **189** can be achieved by its Suzuki cross-coupling reaction with several boronic acids using Pd-catalyst and base, to obtain substituted cyclobutenedione derivatives **190a-e** (Scheme 26).



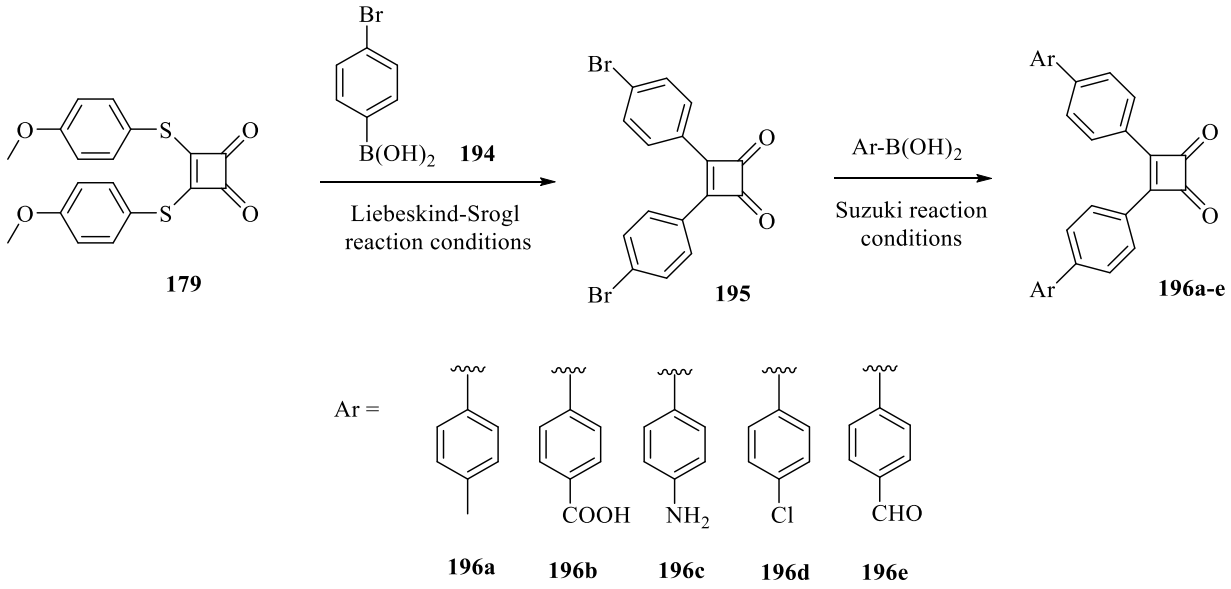
Scheme 26. The synthetic plan for strategy-A.

Strategy-B is the synthesis of bis-thienyl-substituted cyclobutenedione *via* the Liebeskind-Srogl and Stille cross-coupling reactions. This strategy also involves the Liebeskind-Srogl cross-coupling reaction of **179** with 2-thienyl boronic acid **187** using Pd-catalyst and Cu co-catalyst to generate **188**, which on bromination can give **189**. The Stille cross-coupling reaction between **189** and 2-(tributylstannyl)thiophene **191** using Pd-catalyst can generate the 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione (bis-thienyl-substituted cyclobutenedione) **192**, which on air oxidation can give the 2,3-bis(5-[2,2']-bithien-5-yl) maleic anhydride **193** (Scheme 27).



Scheme 27. Synthetic plan for strategy-B.

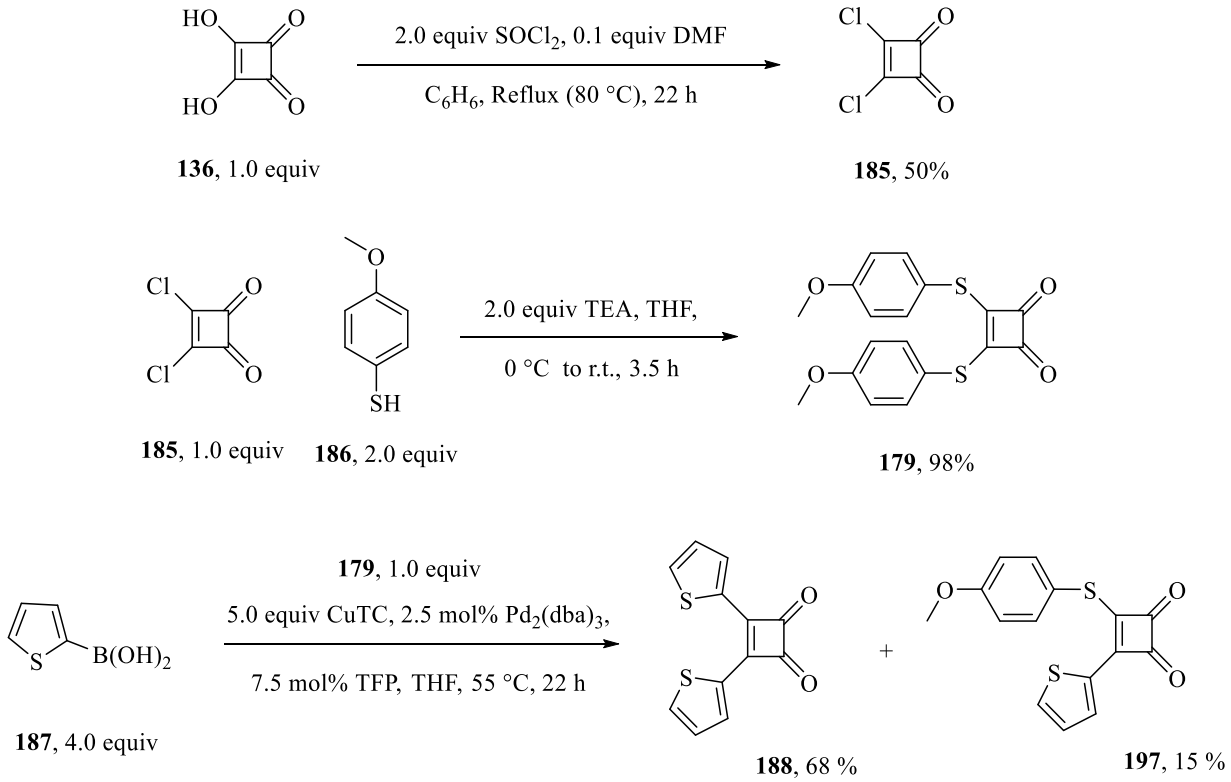
Strategy-C is the functionalization of phenyl containing cyclobutenediones by means of cross-coupling reactions. This strategy involves the Liebeskind-Srogl cross-coupling reaction of **179** with 4-bromophenylboronic acid **194** using Pd-catalyst and Cu co-catalyst to generate **195**. The functionalization of 3,4-bis(4-bromophenyl)cyclobut-3-ene-1,2-dione (phenyl containing cyclobutenedione) **195** can be achieved by its Suzuki cross-coupling reaction with several boronic acids using Pd-catalyst and base, to obtain substituted cyclobutenedione derivatives **196a-e** (Scheme 28).



Scheme 28. Synthetic plan for strategy-C.

2.3 Results and discussion.

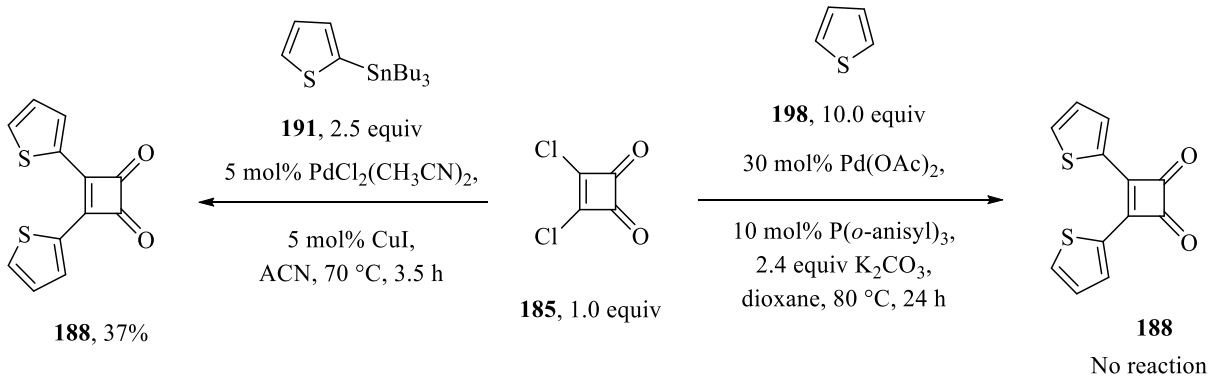
The project started with the synthesis of the starting material 3,4-bis(2-thienyl)-3-cyclobuten-1,2-dione **188**. For which, first, 3,4-bis(*p*-methoxythiophenoxy)-3-cyclobutene-1,2-dione **179** was synthesized in two steps using the reported method.[211d] The first step involved the chlorination of squaric acid **136** using thionyl chloride with DMF as a catalyst at reflux temperature (80 °C) afforded 3,4-dichloro-3-cyclobutene-1,2-dione **185** in 22 h with 50% yield.[221] We were able to perform that step at 5g scale. The second step involved the aromatic nucleophilic substitution reaction of **185** with *p*-methoxythiophenol **186** in the presence of triethyl amine (TEA) as a base at 0 °C to afford the desired 3,4-bis(*p*-methoxythiophenoxy)-3-cyclobutene-1,2-dione **179** in 3.5 h with 98% yield, shorter reaction time and higher yield than the reported literature.[211d] Then, the Liebeskind-Srogl cross-coupling reaction of **179** with 2-thienyl boronic acid **187** in THF using 2.5 mol% of $Pd_2(dba)_3$ catalyst, 7.5 mol% of TFP ligand and 5.0 equiv of CuTc co-catalyst under N_2 afforded the starting material 3,4-bis(2-thienyl)-3-cyclobuten-1,2-dione **188** in 22 h with 68% yield as a yellow solid (Scheme 29). In this step, the mono-substituted product **197** was also obtained in 15% yield, which was confirmed by ^{1}H NMR.



Scheme 29. Synthesis of the starting material 3,4-bis(2-thienyl)-3-cyclobuten-1,2-dione **188** right from squaric acid **136** in three different steps.

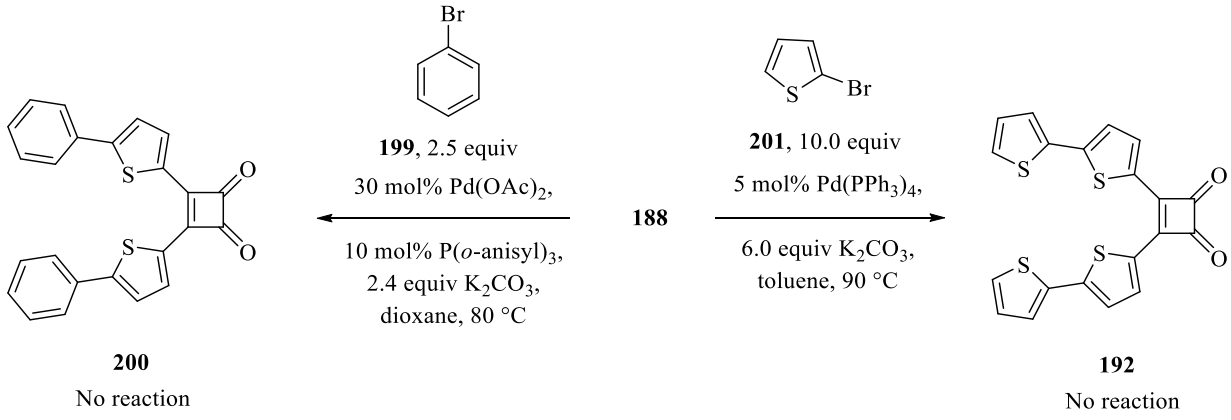
Additionally, two more routes were tried for the synthesis of starting material **188** right from the 3,4-dichloro-3-cyclobutene-1,2-dione **185**. The first route involved the direct C-H bond activation reaction between **185** and thiophene **198** using 30 mol% of $Pd(OAc)_2$ catalyst, 10 mol% of P(*o*-anisyl)$_3$ ligand and 2.4 equiv of K_2CO_3 as a base in dioxane at 80 °C under N_2 (Scheme 30).[222] However, it was seen that the reaction failed as there was no complete consumption of **185** and no formation of the desired product **188** even after 24 h. The second

route involved the Stille cross-coupling reaction between **185** and 2-(tributylstannyl)thiophene **191** using 5 mol% of $PdCl_2(CH_3CN)_2$ catalyst and 5 mol% of CuI co-catalyst in acetonitrile (ACN) at 70 °C under N_2, which afforded the desired product **188** in 3.5 h with 37% yield (Scheme 30).



Scheme 30. Two synthetic routes for the synthesis of **188**, first by direct C-H bond activation and second by Stille cross-coupling reaction.

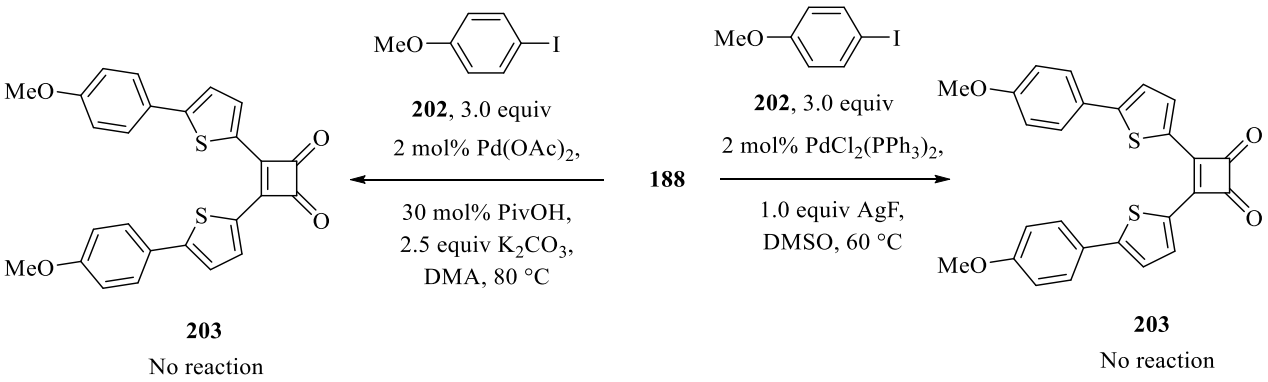
After successfully synthesizing **188**, firstly, we tried to carry out its direct C-H bond activation reaction with aryl(heteroaryl) halides to obtain the aryl(heteroaryl) substituted cyclobutenedione oligothiophenes. In the first attempt, we performed the C-H bond activation reaction of **188** with bromobenzene **199** using 30 mol% of $Pd(OAc)_2$ catalyst, 10 mol% of P(*o*-anisyl)$_3$ and 2.4 equiv of K_2CO_3 as a base in dioxane at 80 °C under N_2 (Scheme 31).[221] However, even after 48 hours of reaction time we did not see the total consumption of the starting material **188** and formation of the desired product **200**, while observing five different spots along with it on TLC plate. So, we concluded that the reaction did not work. In the second attempt, we carried out the C-H bond activation of **188** with bromothiophene **201** using 5 mol% of $Pd(PPh_3)_4$ catalyst and 6.0 equiv of K_2CO_3 as a base in toluene at 90 °C under N_2 (Scheme 31).[223] However, this reaction also failed as it did not show the formation of the desired product **192**.



Scheme 31. C-H bond activation reaction of **188** with bromobenzene **199** or bromothiophene **201**.

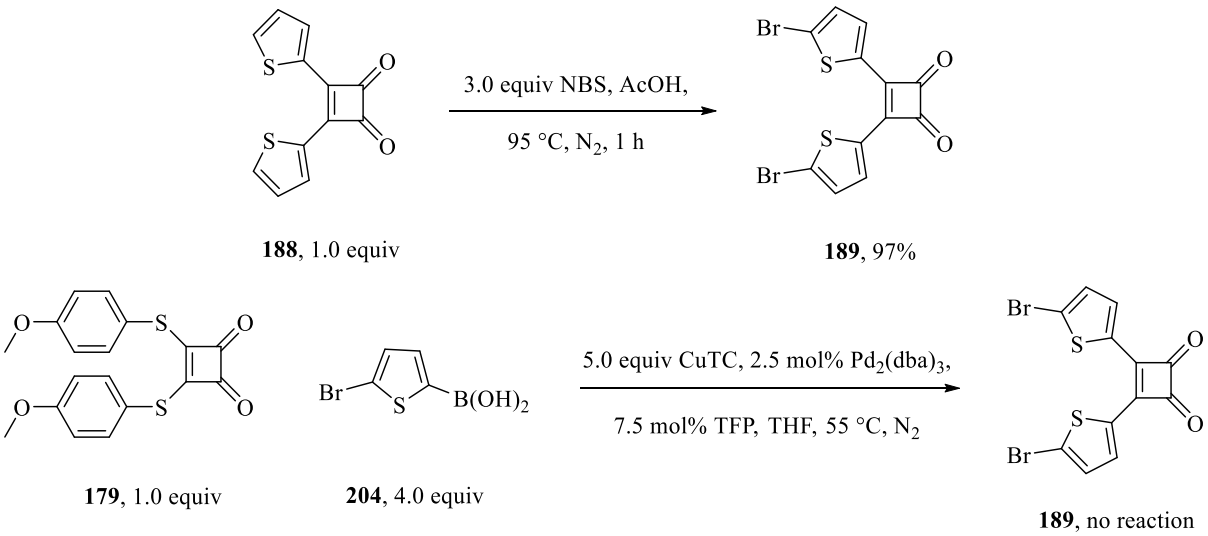
In the third attempt, we performed the C-H bond activation reaction of **188** with 4-methoxyiodobenzene **202** using 2 mol% of $Pd(OAc)_2$ catalyst, 30 mol% of pivalic acid

(PivOH) as a co-catalyst and 2.5 equiv of K_2CO_3 as a base in dimethylacetamide (DMA) at 80 °C under N_2 (Scheme 32).[222] However, this reaction also failed as there was no formation of the desired product **203**. After failure of this attempt, we perform C-H bond activation of same starting materials using different reaction conditions. We carried out the reaction using 2 mol% of $PdCl_2(PPh_3)_2$ catalyst and 1.0 equiv of AgF as a base in dimethyl sulfoxide (DMSO) at 60 °C under N_2 (Scheme 32).[222] However, this reaction also failed as there was no formation of the desired product **203**.



Scheme 32. C-H bond activation reaction of **188** with 4methoxyiodobenzene **202**.

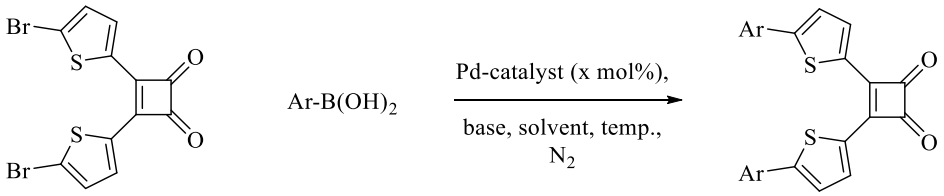
In order to incorporate aryl or heteroaryl rings to **188** via a transition metal-catalyzed cross-coupling reaction, bromination of **188** was carried out. The bromination of **188** was carried out with 3.0 equiv of NBS in AcOH at reflux temperature (95 °C). After one hour of reflux, the desired product 3,4-bis(5-bromothien-2-yl)cyclobut-3-ene-1,2-dione **189** was obtained in excellent yield (Scheme 33). Additionally, in order to synthesize **189** directly from **179**, we performed the Liebeskind-Srogl cross-coupling reaction of **179** with 5-bromo-2-thienyl boronic acid **204** (Scheme 33). However, it was observed that even after 63 hours of reaction time, the starting material was still present in the reaction along with four additional spots (in traces) on TLC plate. So, we concluded that this route failed to synthesize **189** directly from **179**.



Scheme 33. Synthesis of **189** via direct bromination using NBS or using Liebeskind-Srogl cross-coupling reaction.

With 3,4-bis(5-bromothien-2-yl)cyclobut-3-ene-1,2-dione **189** in hand, we proceeded to carried out its Suzuki cross-coupling reaction with aryl boronic acids to obtain the desired bis-thiophene containing cyclobutenediones with aryl functionalization. For the optimization purpose we used different kinds of Pd catalysts, bases, solvents, temperatures and boronic acids. The reaction conditions used for the optimization purpose are reported in Table **3**.

Table 3 Optimization of Pd-catalyzed Suzuki cross-coupling reaction of **189**.



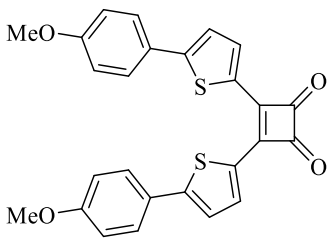
189 Aryl boronic acid **190**

Entry	Aryl boronic acid (equiv)	Pd-catalyst (x mol%)	Ligand or co-catalyst (x mol%)	Base (equiv)	T (°C)	Solvent[c]	Reaction Time (h)	Observations
1	4-methoxy phenylboronic acid (2.4 equiv)	$Pd(PPh_3)_4$ (5 mol%)	-	K_2CO_3[b] (6.0 equiv)	95	Toluene	1.5	Formation of desired product and its oxidized form
2	4-methoxy phenylboronic acid (2.4 equiv)	$Pd(PPh_3)_4$ (5 mol%)	-	Na_2CO_3[b] (6.0 equiv)	95	Toluene	1.0	Formation of desired product and its oxidized form
3	4-methoxy phenylboronic acid (4.0 equiv)	$Pd(PPh_3)_4$ (10 mol%)	-	Na_2CO_3 (5.0 equiv)	60	Dioxane: H_2O (2:1)	1.5	Formation of desired product and its oxidized form
4	4-nitro phenylboronic acid (4.0 equiv)	$Pd(PPh_3)_4$ (10 mol%)	-	Na_2CO_3 (5.0 equiv)	60	Dioxane: H_2O (2:1)	5.0	No formation of desired product
5	Phenylboronic acid (4.0 equiv)	$Pd(PPh_3)_4$ (10 mol%)	-	Na_2CO_3 (5.0 equiv)	60	Dioxane: H_2O (2:1)	1.0	Formation of desired product and its oxidized form
6	4-methoxy phenylboronic acid (4.0 equiv)	$Pd(PPh_3)_4$ (10 mol%)	-	Na_2CO_3 (5.0 equiv)	60	THF:H_2O (2:1)	24	No formation of desired product

7	4-methoxy phenylboronic acid (4.0 equiv)	$Pd(OAc)_2$ (5 mol%)	S-Phos (5 mol%)	K_3PO_4 (6.0 equiv)	r.t. to 55	THF	11	No formation of desired product
8	2-tributylstannyl-3,4-ethylenedioxythiophene (2.5 equiv)	$PdCl_2(PPh_3)_2$ (5 mol%)	CuI (5 mol%)	CsF (4.0 equiv)	50	DMF	24	No formation of desired product
9	Tributyl(4-methoxy phenyl)stannane (2.5 equiv)	$PdCl_2(PPh_3)_2$ (5 mol%)	CuI (5 mol%)	CsF (4.0 equiv)	50	DMF	24	Formation of desired product and its oxidized form

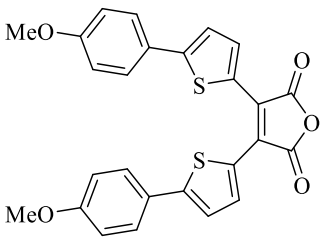
[a] All the reactions were carried out in 0.05 mmol scale of **189**. [b]1M of base was used. [c] Dry solvents were used for the reaction.

The optimization started with the cross-coupling reaction between **189** and 4-methoxy phenylboronic acid in the presence of 5 mol% of $Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium(0)) and 1M solution of K_2CO_3 as a base in toluene at 95 °C under nitrogen as shown in the first entry of Table 3. The TLC (30% EtOAc/hexane) of the reaction showed that the starting material got totally consumed after 1.5 h and showed the major new orange coloured spot, which was polar than the spot of starting material **189**. The orange-coloured spot was separated by using flash column chromatography with 2% EtOAc/hexane as a solvent system. During purification, it was observed that the desired product is getting oxidized as it was getting eluted from the column. However, the pure desired product was separated successfully, recrystallized using cold DCM/petroleum ether, dried under vacuum and sent for ^{1}H NMR analysis using $CDCl_3$. The ^{1}H NMR spectrum showed presence of desired product **203** and its oxidized form **205** as shown in figure 33. The TLC of the NMR sample also showed two spots, which are very close to each other. The ^{1}H NMR spectrum is showed in Figure 34, which showed the peaks of desired product **203** and its oxidized form **205**. Another obstacle during this reaction was its low yield. We only obtained 15% of the desired product.



203

Desired product



205

Oxidized form of the desired product

Figure 33. The structure of the desired product **203** and its oxidized form **205** obtained from entry 1, Table 3.

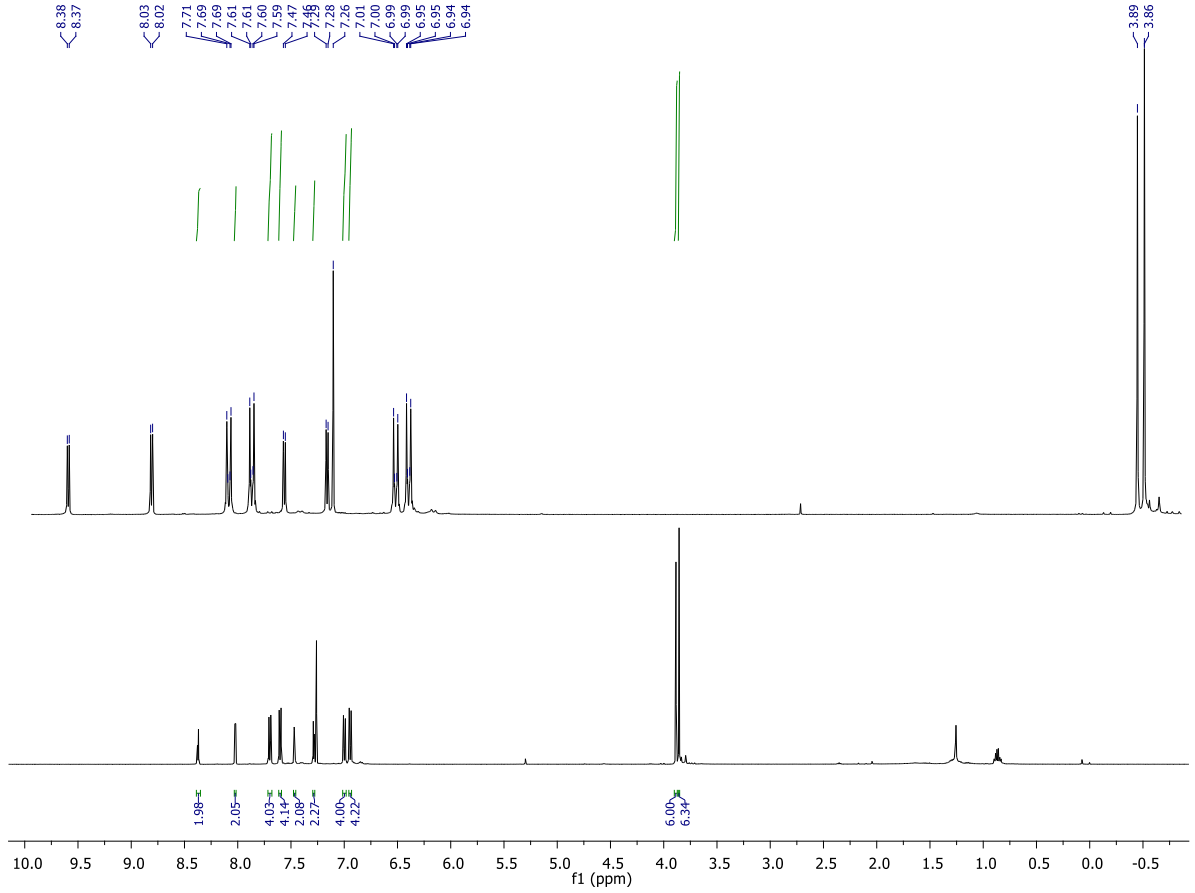
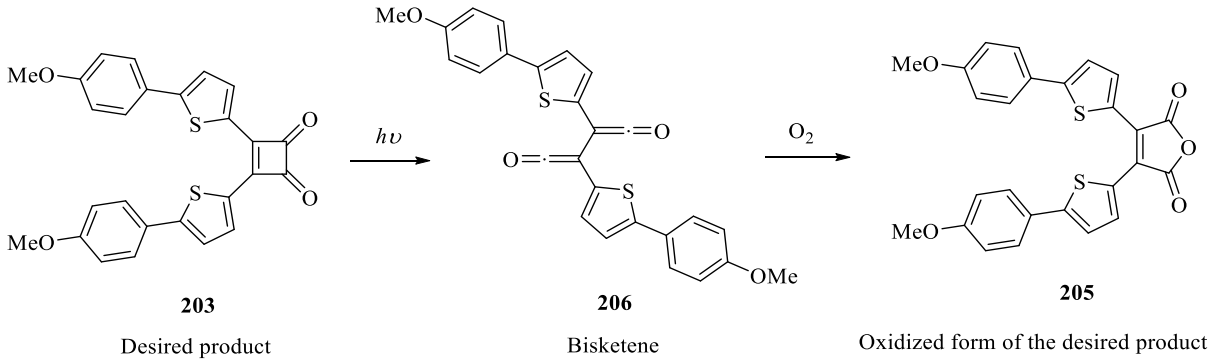


Figure 34. The ^{1}H NMR spectrum of the desired product **203** (top) and its oxidized form **205** (bottom).

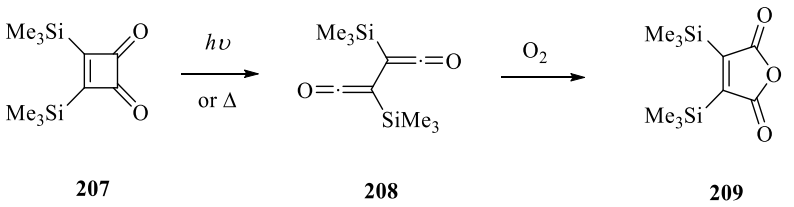
We believed that the insertion of the oxygen into the 4-membered cyclobutendione ring of **203** was happening through the formation of bisketene **206**, which was generated photochemically. Then, in presence of atmospheric oxygen, the bisketene **206** formed the oxidized product **205** (Scheme 34).



Scheme 34. The photochemical oxidation of **203** to give **205** through bisketene **206** generation.

Similar oxidation reaction was previously reported by Tidwell *et al.* They reported the formation of similar bisketene **208**, which was generated either photochemically or thermally

from its corresponding cyclobutenedione precursor **207**, which formed its corresponding substituted maleic anhydride **209** on exposure to oxygen (Scheme 35).[224]

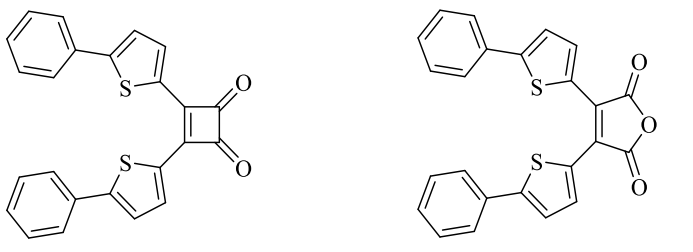


207 **208** **209**

Scheme 35. The insertion of oxygen into cyclobutenediones reported by Tidwell et al.

Further in optimization, we used milder base than K_2CO_3, Na_2CO_3, to see if we can avoid the unwanted oxidation of the desired product and increase the yield of the product (entry 2). Unfortunately, we observed the similar behaviour in entry 2 as well. The obtained product was getting oxidized during the purification (flash column chromatography), recrystallization and during ^{1}H NMR analysis as well. Here, we again obtained low yield of the desired product, 17% yield. Further in optimization, we decided to change the solvent and decrease the reaction temperature from 95 °C to 60 °C, to see effect of solvent polarity on the reaction time and yield of the reaction. For that purpose, we used dioxane:H_2O (2:1) (entry 3) and THF:H_2O (2:1) (entry 6) solvent system. Also, we increased the amount of boronic acid and Pd-catalyst from 2.4 equiv to 4.0 equiv and 5 mol% to 10 mol%, respectively. Instead of using 1M solution of Na_2CO_3, we just used solid Na_2CO_3 (5.0 equiv). Unfortunately, we saw similar behaviour in entry 3 as entry 1 and 2. The obtained product was seen to be getting oxidized during the flash column chromatography and the yield was also very less. In the reaction with THF:H_2O (2:1) (entry 6), the starting material **189** got consumed after 24 h, however, there was no formation of the desired product, and a lot of impurities were observed.

Further in the optimization, we used 4-nitro phenylboronic (entry 4) and phenylboronic acid (entry 5), to see if the effect of different boronic acid on the yield of the reaction and if it can avoid the formation of the undesired oxidized product. Other than that, we kept other reaction conditions similar to entry 3. Unfortunately, in entry 4 the starting material **189** got consumed after 5 h, however, there was no formation of the desired product, and a lot of impurities were observed. In the same way, in the entry 5 with phenylboronic acid, we saw similar behaviour as entry 1 and 2. The obtained desired product **210** was seen to be getting oxidised during the flash column chromatography to form its undesired oxidized form **211** (Figure 35) and the yield was also very less.



210 **211**

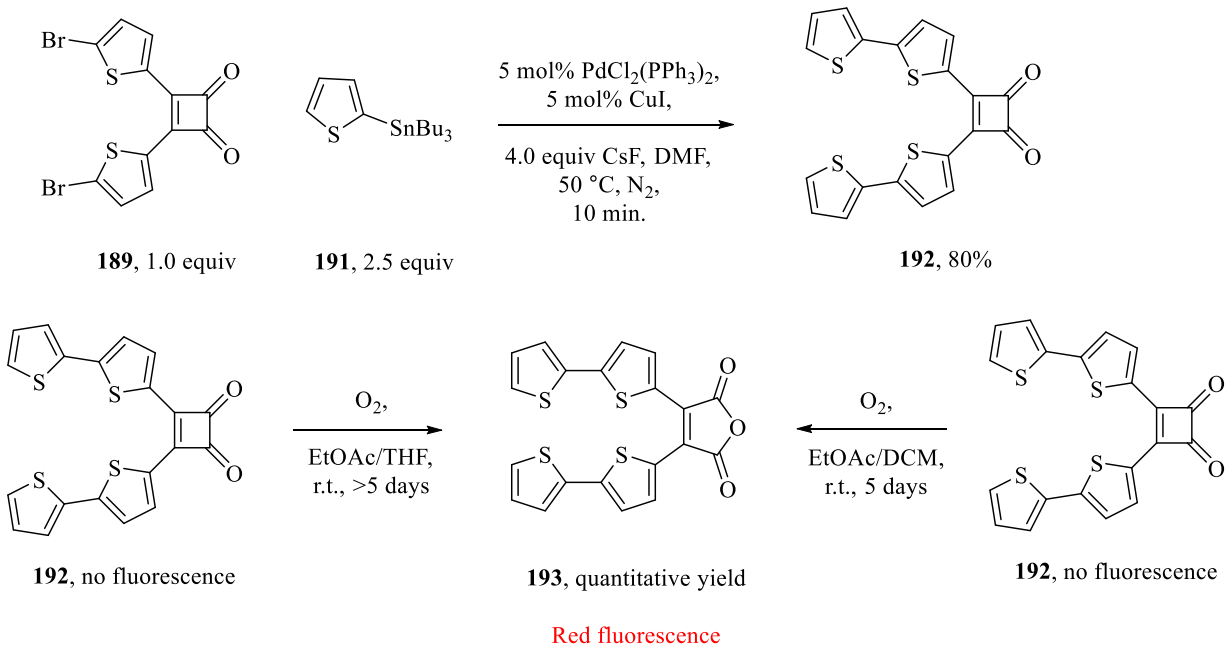
Desired product Oxidized form of the desired product

Figure 35. The structure of the desired product **210** and its oxidized form **211** obtained from entry 5, Table 3.

The reaction conditions used in entries 7, 8 and 9 are the reaction conditions used for similar kind of reactions which we used in the strategy-B. We were able to synthesize the tetrathienyl cyclobutenediones by using those reactions, so we decided to use the similar kind of approach here also. In the entry 7, instead of using $Pd(PPh_3)_4$ catalyst we used 5 mol% of $Pd(OAc)_2$ as a Pd source and 5 mol% S-Phos as a ligand in the catalytic system. Also, we used stronger base than K_2CO_3 and Na_2CO_3, K_3PO_4. Initially, the reaction was carried out at room temperature in THF, however, it was seen that the reaction was too sluggish as even after 5h there was no significant consumption of starting material or the formation of the desired product. So, we increase the temperature to 55 °C and kept monitoring the reaction through TLC. After 11 h, it was seen that the starting material **189** got consumed, however, it was seen that there was no formation of the desired product, and a lot of impurities were observed.

The entry 8 is the Stille cross-coupling reaction of **189** with 2-tributylstannyl-3,4-ethylenedioxythiophene. The reaction was carried out using 5 mol% of $PdCl_2(PPh_3)_2$ catalyst, 5 mol% of CuI as a co-catalyst and CsF as a base in DMF as a solvent at 50 °C under N_2. Similar reaction using tributyl(2-thiophene)stannane in strategy-B gave good yield of the product in just 10 min. (Scheme 36). However, here, the starting material was present in the reaction even until 24 h along with no formation of desired product. So, this reaction failed. The entry 9 is the Stille cross-coupling reaction of **189** with tributyl(4-methoxypheny)stannane. Here, similar reaction conditions were used as entry 8. In this reaction the starting material was present in the reaction even until 24 h along with formation of desired product **203**. It is important to mention that during the reaction the oxidized form of product **205** was not observed. After 24 h, the reaction was stopped and the product was purified using flash column chromatography, recrystallized, dried under vacuum and sent for ^{1}H NMR analysis. The ^{1}H NMR spectrum showed the presence of desired product **203** along with its oxidized form **205** as well. So, after carrying out a series of experiments we observed that this strategy was not working as we end up getting very low yield of desired product which kept getting oxidized during purification and ^{1}H NMR analysis. So, we decided to stop working on this strategy and move onto strategy-B.

Strategy-B is the synthesis of bis-thienyl-substituted cyclobutenedione *via* the Liebeskind-Srogl and Stille cross-coupling reactions. This strategy also involved the Liebeskind-Srogl cross-coupling reaction of **179** with 2-thienyl boronic acid **187** in THF using 2.5 mol% of $Pd_2(dba)_3$ catalyst, 7.5 mol% of TFP ligand and 5.0 equiv of CuTC co-catalyst under N_2 to give the starting material **188** in 22 h with 68% yield as a yellow solid, similar to strategy-A (Scheme 29). In order to incorporate another thiophene unit to **188** via a transition metal-catalyzed cross-coupling reaction, bromination of **188** was carried out. The bromination of **188** was carried out with 3.0 equiv of NBS in AcOH at reflux temperature (95 °C). After one hour of reflux, the desired product **189** was obtained in excellent yield, similar to strategy-A (Scheme 33). Then, the Stille cross-coupling reaction was carried out between **189** and 2-(tributylstannyl)thiophene **191** using 5 mol% of $PdCl_2(PPh_3)_2$ catalyst, 5 mol% of CuI as a co-catalyst and CsF (4.0 equiv) as a base in DMF as a solvent at 50 °C under N_2 to generate the 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione (bis-thienyl-substituted cyclobutenedione) **192** in 10 min. with 80% yield (Scheme 36). During reaction and purification traces of the oxidized product **193** was obtained which was removed by washing the obtained product several times with cold hexane under N_2. The obtained pure product **192** was characterized by using ^{1}H NMR, ^{13}C NMR, IR and HRMS analysis, which confirmed the formation of **192**.



Scheme 36. Synthesis of **192** via Stille cross-coupling reaction and synthesis of **193** via oxygen insertion.

During the purification and characterization of **192** it was observed that when the orange-coloured solution of **192** in solvents like EtOAc, DCM, hexane or $CDCl_3$ under N_2 was observed under UV light at 365 nm, it did not show any fluorescence. However, when that orange-coloured solution was exposed to air, it gradually turned into deep red (wine colour red) showing red coloured fluorescence under UV light at 365 nm (Figure 36). So, we performed two reactions with **192** as shown in Scheme 36. In one of these reactions, we kept stirring the compound **192** in THF: DCM (1:1) at room temperature in presence of air and in other reaction we used EtOAc: DCM (1:1) as solvent, solvents were added when necessary to avoid dryness. Reactions were monitored using TLC (30% EtOAc/hexane). TLC showed that **192** (*Rf* = 0.5) slowly transformed into a different compound (*Rf* = 0.54), which was slightly non-polar than **192**. We observed that the reaction with EtOAc: DCM was faster and it got completed in 5 days with forming a new compound with red fluorescence, whereas the reaction with EtOAc:THF took more than 5 days to finish.

Figure 36. Left: Compound **193** under normal light. Right: Compound **193** under UV light at 365 nm showing red fluorescence.

It was difficult to characterize the new compound by ^{1}H NMR analysis as its spectrum was not very informative, since it showed the almost similar signals as **192**, only slightly upfield. During the characterization of **192** it was observed that there is a carbonyl signal at 192.82 ppm in the ^{13}C NMR spectrum, which is typical of cyclobutenediones (190-200 ppm) but the new compound did not show carbonyl signal in that region. However, it showed a signal of a carbonyl group at 164.41 ppm, which is typically observed for carbonyl group of anhydrides (carbonyl signal of maleic anhydride appears at 164.5 ppm). Based upon this information, we believed that oxygen inserted between the carbonyl groups of **192** to form **193** (Figure 37). The characterization of **193** was also carried out using IR and HRMS analysis, which also confirmed the formation of **193**.

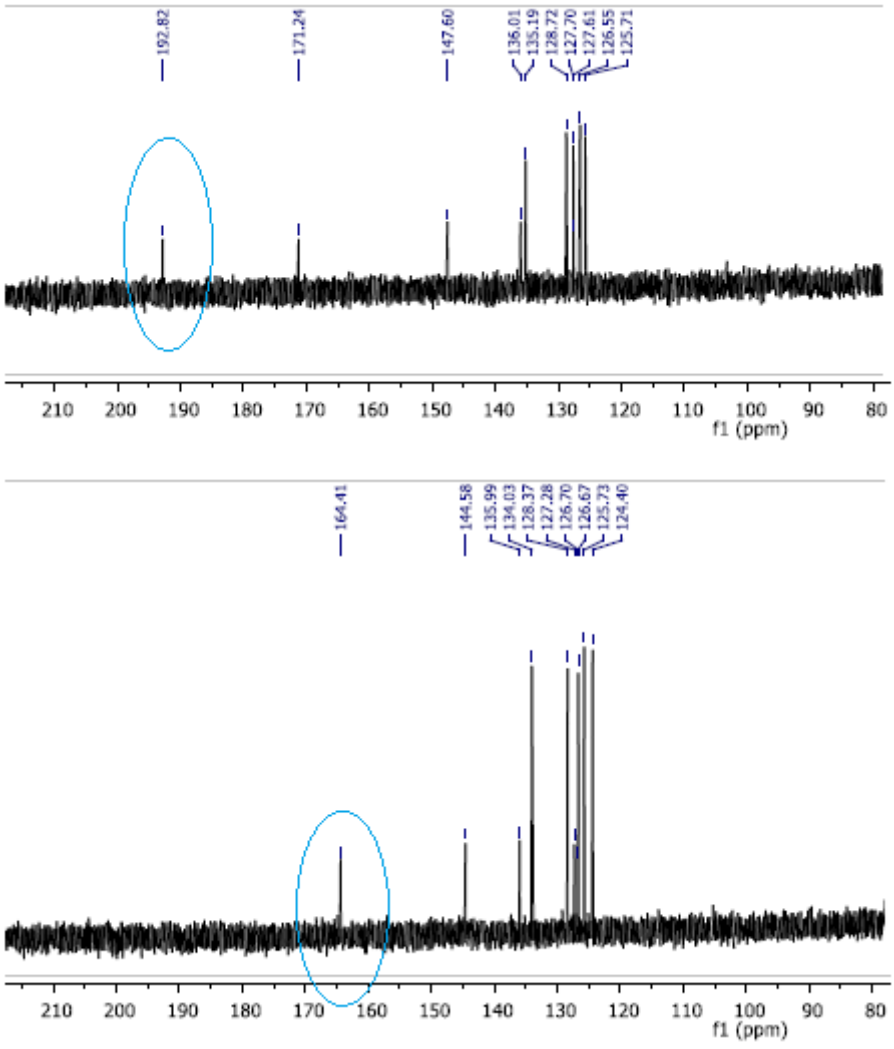
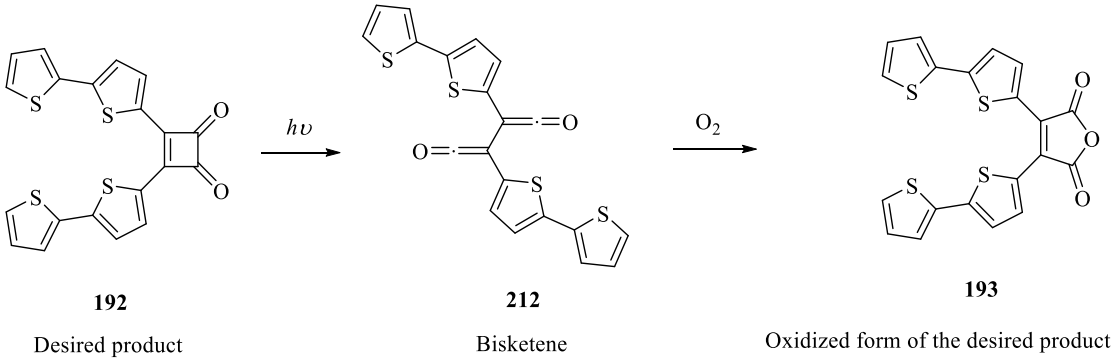


Figure 37. Comparison of ^{13}C NMR spectra of **192** (above) and **193** (below).

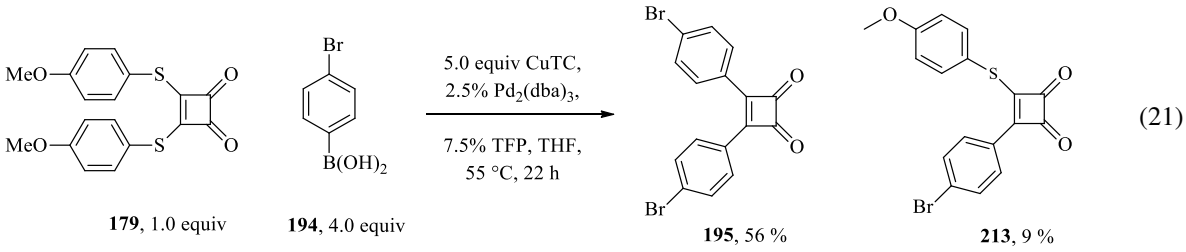
The oxygen insertion was believed to proceed through the formation of bisketene **212** from **192**, which was generated photochemically. Then, in presence of atmospheric oxygen, the bisketene **212** formed the oxidized product **193** (Scheme 37). The similar phenomenon was observed in strategy A, and it was previously reported by Tidwell et al. as earlier mentioned (Schemes 34 and 35). Here, it is important to notice that this photochemical oxygen insertion

took place only after incorporation of two thiophene units, which indicated that the extension of conjugation in cyclobutenediones triggered the oxygen insertion in their 4-membered ring.



Scheme 37. The photochemical oxidation of **192** to give **193** through bisketene **212** generation.

Strategy-C is the functionalization of phenyl containing cyclobutenediones by means of cross-coupling reactions. This strategy started with the Liebeskind-Srogl cross-coupling reaction of **179** with 4-bromophenylboronic acid **194** in THF using 2.5 mol% of $Pd_2(dba)_3$ catalyst, 7.5 mol% of TFP ligand and 5.0 equiv of CuTC under N_2 to afford the starting material 3,4-bis(4-bromophenyl)cyclobut-3-ene-1,2-dione **195** in 22 h with 56% yield as a yellow solid (eq 21). In this step, the mono-substituted product **213** was also obtained in 9% yield, which was confirmed by ^1H NMR. The yellow-coloured solution of compound **195** in $CDCl_3$ showed sky blue coloured fluorescence under UV light at 365 nm (Figure 38).



(21)

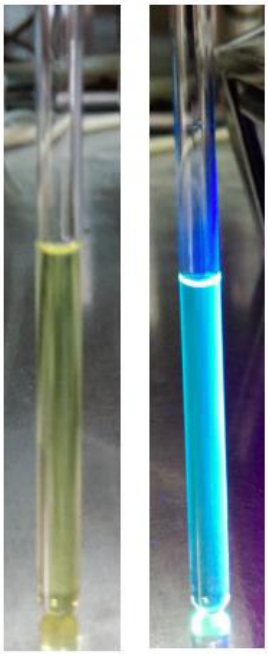
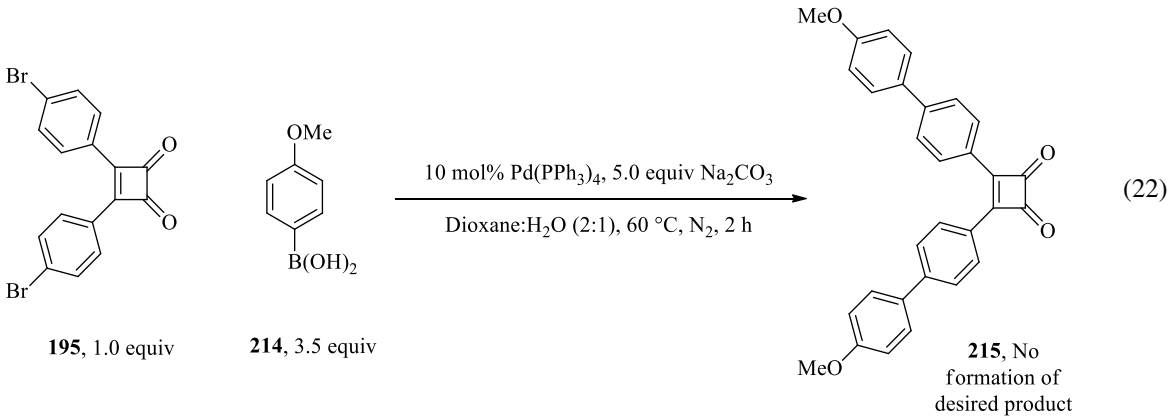


Figure 38. Left: solution of compound **195** in $CDCl_3$ under normal light. Right: solution of compound **195** in $CDCl_3$ under UV light at 365 nm.

For the functionalization of **195** by its Suzuki cross-coupling reaction with several boronic acids using Pd-catalyst and base, to obtain substituted cyclobutenedione derivatives **196a-e**, we started the synthesis with Suzuki reaction of **195** with 4-methoxyphenylboronic acid **214** using the reaction conditions as mentioned in eq 22. In this reaction the starting material did get consumed after 2 h, however, there was no formation of the desired product **215**.



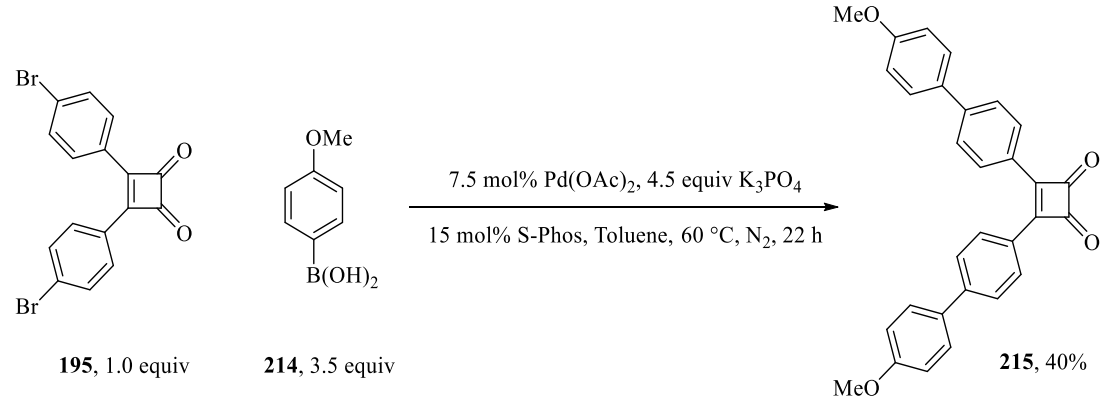
195, 1.0 equiv

214, 3.5 equiv

215, No formation of desired product

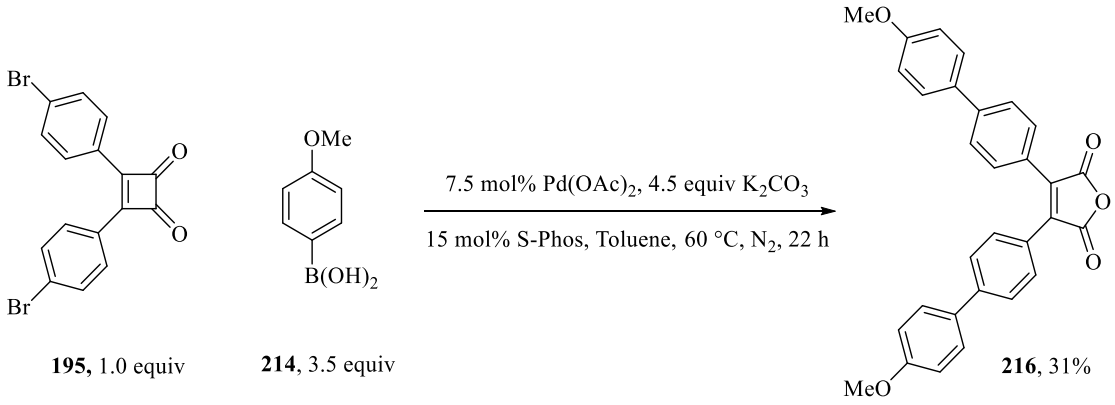
(22)

The above-mentioned reaction did not work, so, we decided to change the catalytic system and solvent. We used catalytic system and solvent as shown in eq (23). The reaction got completed after 22 h with 40% of yield. The obtained product **215** was characterized by ^{1}H NMR, ^{13}C NMR and HRMS analysis. We decided to use K_3PO_4 instead of Na_2CO_3 by referring the work done by Chan et al. [225] They successfully demonstrated the base and cation effects on the Suzuki Cross-Coupling of bulky arylboronic acids. In their work, they mentioned that the strong base and large size cation have been shown to accelerate the rate and the yield of Suzuki coupling of a sterically bulky boronic acid. As compared to Na_2CO_3, the cation size in K_3PO_4, is bigger. And also, K_3PO_4 is strong base than K_2CO_3. So, we choose K_3PO_4 for the reaction.



195, 1.0 equiv **214**, 3.5 equiv **215**, 40% (23)

We also tried the same reaction with K_2CO_3 (eq 24), keeping other reaction conditions similar as in eq 23. The only change was the use of K_2CO_3 instead of K_3PO_4. We changed the base to see its effect on the yield and time of reaction. This reaction also completed after 22 h. However, interestingly, instead of forming **215** we saw the formation of new compound.



195, 1.0 equiv **214**, 3.5 equiv **216**, 31% (24)

It was difficult to characterize the new compound by ^{1}H NMR analysis as its spectrum was not very informative, since it showed the almost similar signals as **215**, only slightly upfield. During the characterization of **215** by ^{13}C NMR analysis, it was observed that there is a carbonyl signal at 196.39 ppm in the spectrum, which is typical of cyclobutenediones (190-200 ppm) but the new compound did not show carbonyl signal in that region. However, it showed a signal of a carbonyl group at 165.20 ppm, which is typically observed for carbonyl group of anhydrides (carbonyl signal of maleic anhydride appears at 164.5 ppm). Based upon this information, we believed that oxygen inserted between the carbonyl groups of **215** to form **216** (Figure 39). The characterization of **216** was also carried out using HRMS analysis, which also confirmed the formation of **216**. However, we were not able to find out the reason behind such oxidation during the reaction as there was no source of oxygen for oxidation.

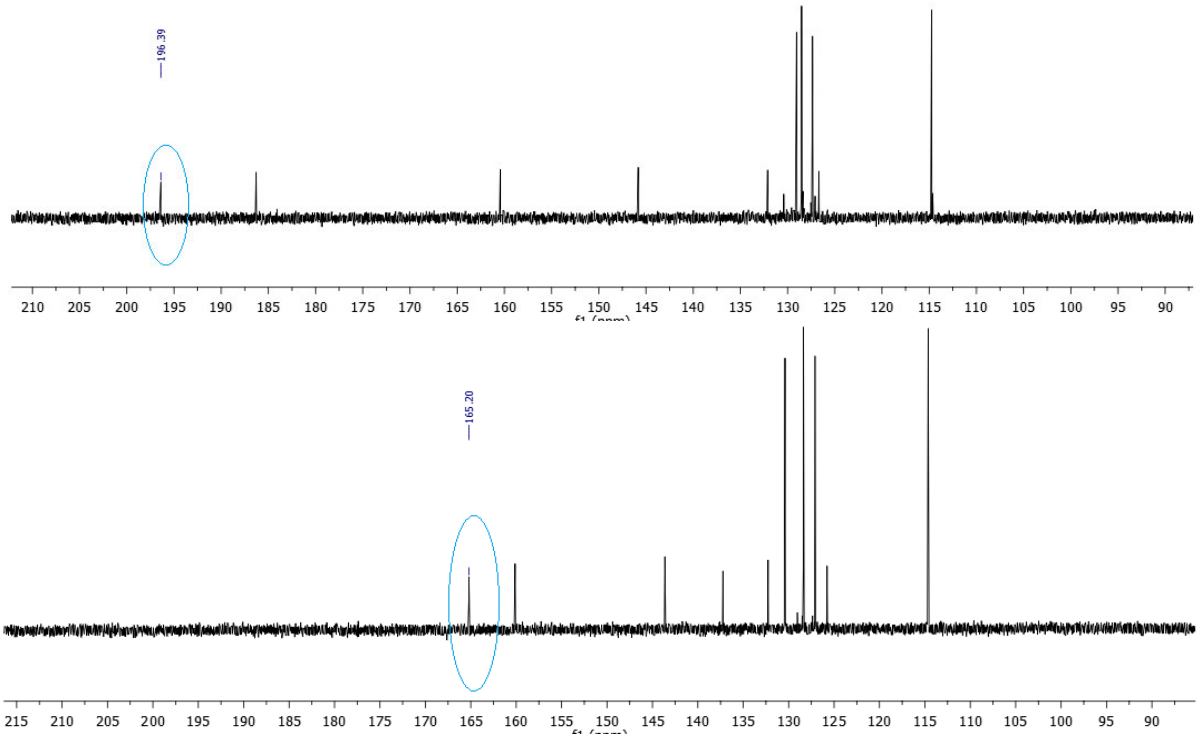
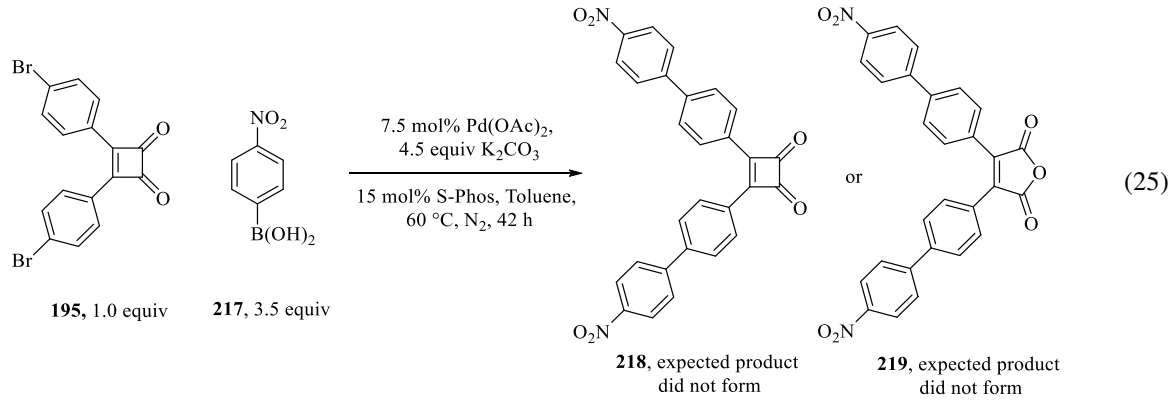


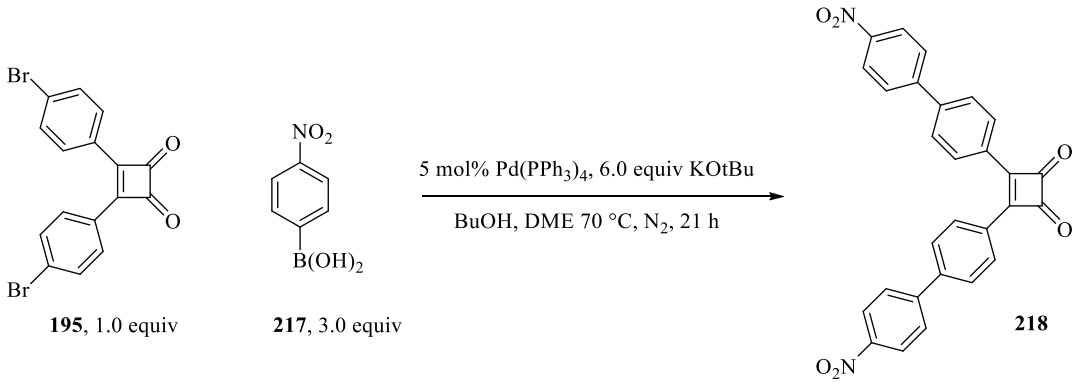
Figure 39. Comparison of ^{13}C NMR spectra of **215** (above) and **216** (below).

We performed the next reaction using the same reaction conditions as eq 24. Instead of 4-methoxyphenylboronic acid **214** we used 4-nitrophenylboronic acid **217** (eq 25). Surprisingly, this reaction was very sluggish as the starting material **195** got consumed only after 42 h with no formation of the desired product **218** or **219** but instead a lot of impurities were observed on the TLC plate.



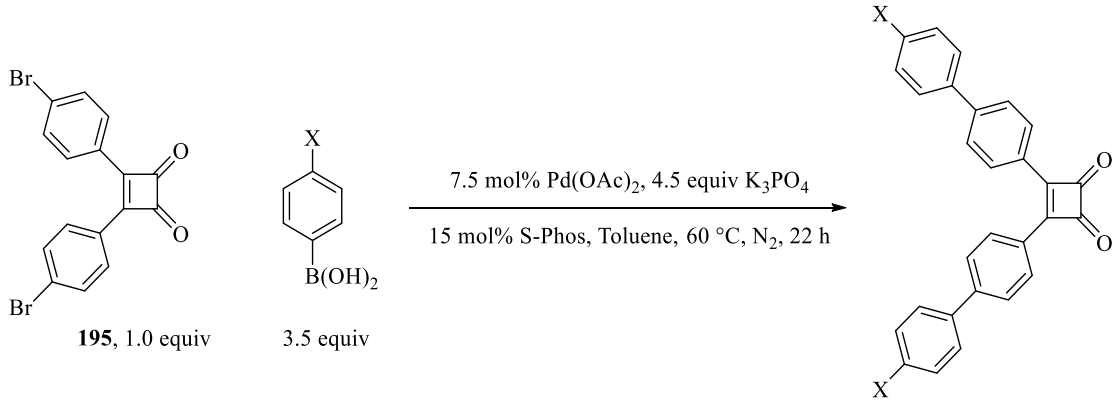
195, 1.0 equiv **217**, 3.5 equiv **218**, expected product did not form **219**, expected product did not form (25)

Further, we performed the next reaction using the same starting materials as used in eq 25 and used the reaction conditions reported by Chan et al.[224] Instead of K_3PO_4 we used even stronger base, KOtBu (eq 26). Here, we did see the total consumption of **195** in 21 h and formation of traces of **218** with a lot of impurities on the TLC plate.

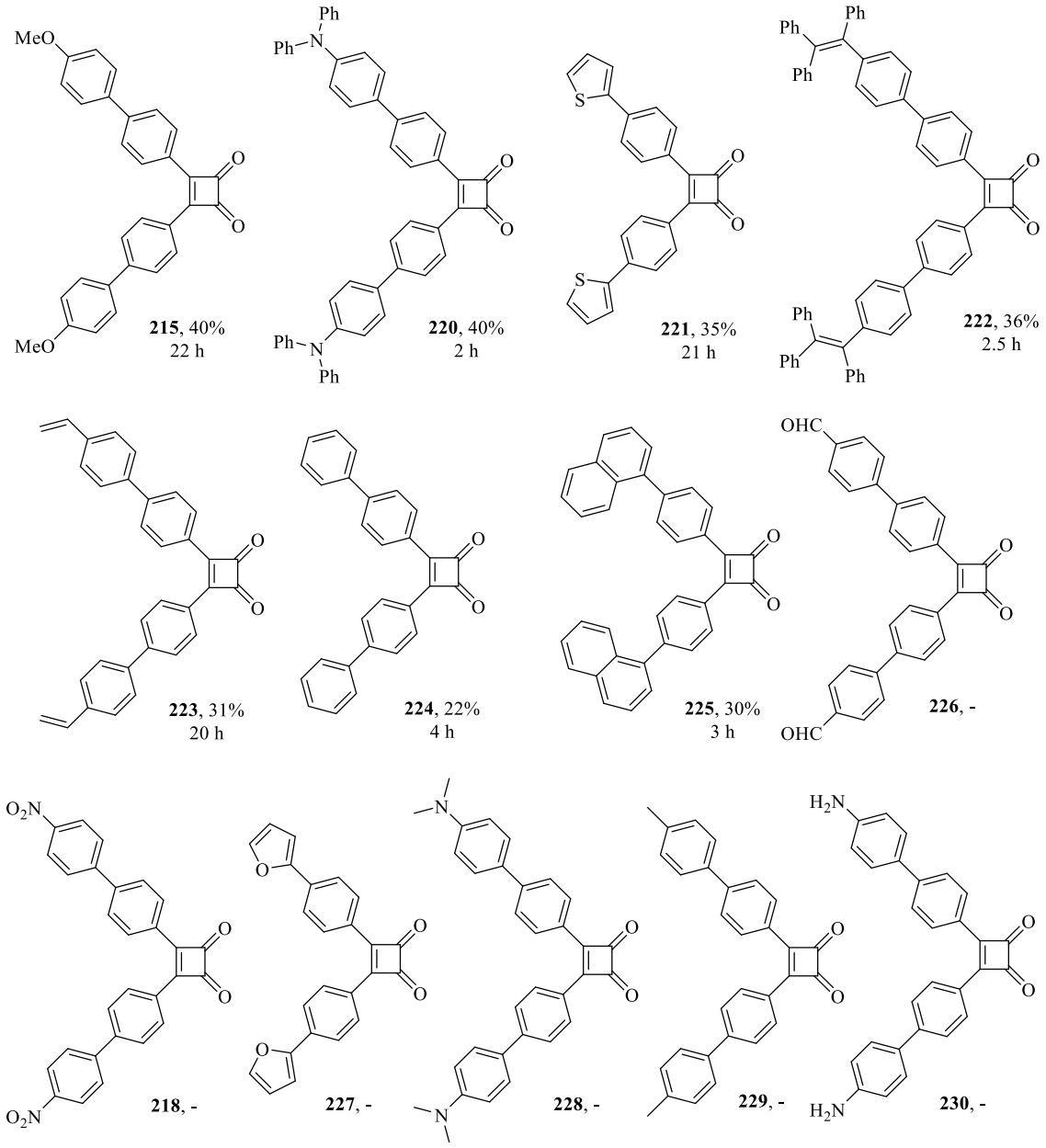


195, 1.0 equiv **217**, 3.0 equiv **218** (26)

After failure of the reaction conditions mentioned in eq 25 and eq 26, we decided to use the reaction conditions used in eq 23 for the synthesis of different derivatives of phenyl containing cyclobutenediones using different boronic acids and esters. The obtained results and observations are showed in Scheme 38.



195, 1.0 equiv 3.5 equiv



Scheme 38. Scope and limitation of Pd-catalyzed Suzuki cross-coupling reaction of **195** with different boronic acids and esters.

By using the reaction conditions mentioned in Scheme 38 we were able to synthesize compounds **220-222** in 2-21 h with 35-40% of yield. The stability of these compounds was better than **215** as only traces of those compounds got oxidized to their corresponding anhydride forms during their purification by flash chromatography and recrystallization, unlike what we observed in strategy A. All the obtained compounds, **215** and **220-222**, were characterized by ^{1}H NMR, ^{13}C NMR and HRMS analysis. The reaction for synthesis of **226** was sluggish as it took 47 h to finish the starting material and form very little amount of **226**. Even though we obtained some amount of **226** through the reaction, we observed that the product was getting oxidized into its anhydride form during purification and recrystallization (confirmed by ^{1}H NMR analysis), similar to what we observed in Strategy A. So, to avoid such unwanted oxidation, for derivatives **223-225**, we decided not to perform recrystallization after purification and sent the obtained compounds for ^{1}H NMR analysis directly without

recrystallization. The ^{1}H NMR spectra of those compounds, **223** and **224**, confirmed the formation of desired products. The ^{1}H NMR spectrum of **225** showed presence of desired product with its anhydride form in traces. However, the yields of those compounds, **223-225**, were poor (22-31%). The reactions of derivatives **227-229** were sluggish and did not form the desired products and showed presence of starting material **195** in the reaction even after 48 h. For the synthesis of **230**, we used 4-aminophenylbronic acid pinacol ester keeping other reaction conditions same. However, we did not observe the formation of the desired product from this route.

The derivatives **215** and **221-225** were obtained as yellow solids, whereas the derivatives **216** and **220** were obtained as orange-coloured solids. During the synthesis we observed that the derivatives showed good fluorescence colours under UV light at 365 nm. The derivatives **215** and its anhydride form **216** showed pale greenish-yellow and bright greenish-yellow colour fluorescence, **220** and **221** showed yellow colour fluorescence, **222** showed blue colour fluorescence, while **224** showed green colour fluorescence (Figure 40).

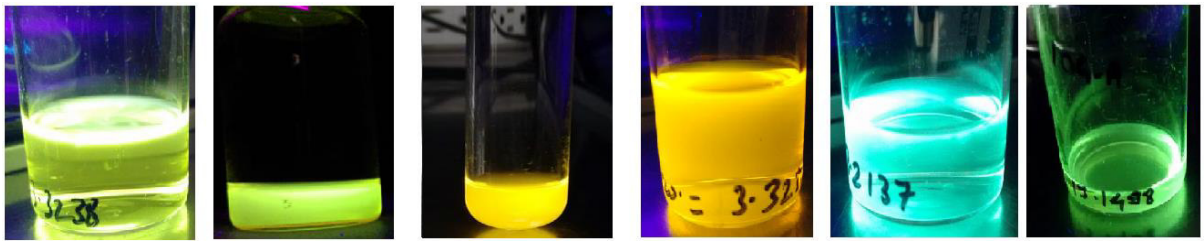


Figure 40. Observed fluorescence colours of derivatives **215-216** and **220-224** under UV light at 365 nm.

After exploring the scope of the reaction, we have seen that only a few numbers of derivatives were obtained in poor yields (22-40%). The oxidation of the derivatives to their anhydride forms during purification and recrystallization could be the reason behind their poor yields. So, we decided to stop working on strategy-C there only.

2.4 Conclusion.

In strategy A, after performing series of reactions using different cross-coupling reaction methods, like, Suzuki and Stille, different catalytic systems, bases and solvents, we reached to the conclusion that the products obtained after the reaction of bis-thienyl containing cyclobutendiones, were getting oxidized during purification and recrystallization to form the anhydride of the corresponding cyclobutenediones. Also, the yields were low.

In strategy B, an efficient methodology to prepare a donor-acceptor system consisting of two bis-thienyl groups attached to a cyclobutenedione has been developed. Both the Liebeskind-Srogl and Stille cross-coupling reactions were attempted to obtain the desired molecule. The best results were obtained from the Stille reaction. During the synthesis of **192** through Stille reaction, the use of CsF was crucial to obtain good yield in less time. On exposure to air, compound **192** was successfully transformed into its anhydride, **193**, through smooth photochemical insertion of oxygen between the carbonyl groups of 4-membered ring system. The compound **192** could show its application as an oxygen sensing probe, which in near future will be studied in our group.

In strategy C, we were able to synthesize bis-phenyl containing cyclobutenediones through Suzuki cross-coupling reaction of **195** with different boronic acids. The obtained derivatives **215** and **220-222** were more stable than derivatives **223-226**. Similar to strategy A in this strategy also, the derivatives were getting oxidized to their anhydride form during purification and recrystallization, however, in lesser amount than in strategy A. Due to which poor yields were observed.

Chapter 3. Synthesis of porphyrin-BODIPY hybrids.

3.1 Introduction

Undoubtedly, porphyrins are one of the most widely studied macrocyclic aromatic compounds which consists of nitrogen atoms. The interest in this naturally occurring tetrapyrrolic macrocycle is due to its multiple biological functions along with its capability to function as an exceptional metal-complexing ligand. Due to the chemical richness offered by of porphyrins, in recent times a wide range of porphyrin analogues has been studied. In nature, porphyrins are omnipresent. The widely known porphyrin analogue is heme (iron porphyrin, Figure 41). It is a cofactor of the protein haemoglobin, and present as the pigment in RBCs (red blood cells). The heme proteins take part in many crucial biological processes, such as oxygen activation and utilization (cytochrome P450 and cytochrome oxidase), electron transport (cytochromes b and c), and oxygen storage and transport (myoglobin and haemoglobin). Vitamin B-12 (cobalamin) is cobalt porphyrin, which can be found in animals and bacteria. It is a cofactor in DNA synthesis. However, undeniably, the most important porphyrin analogues are chlorophylls (magnesium porphyrin) and pheophytins (metal free), which can be observed in green plants and are very crucial for photosynthesis process, without which life as we know it, would be impossible.[226]

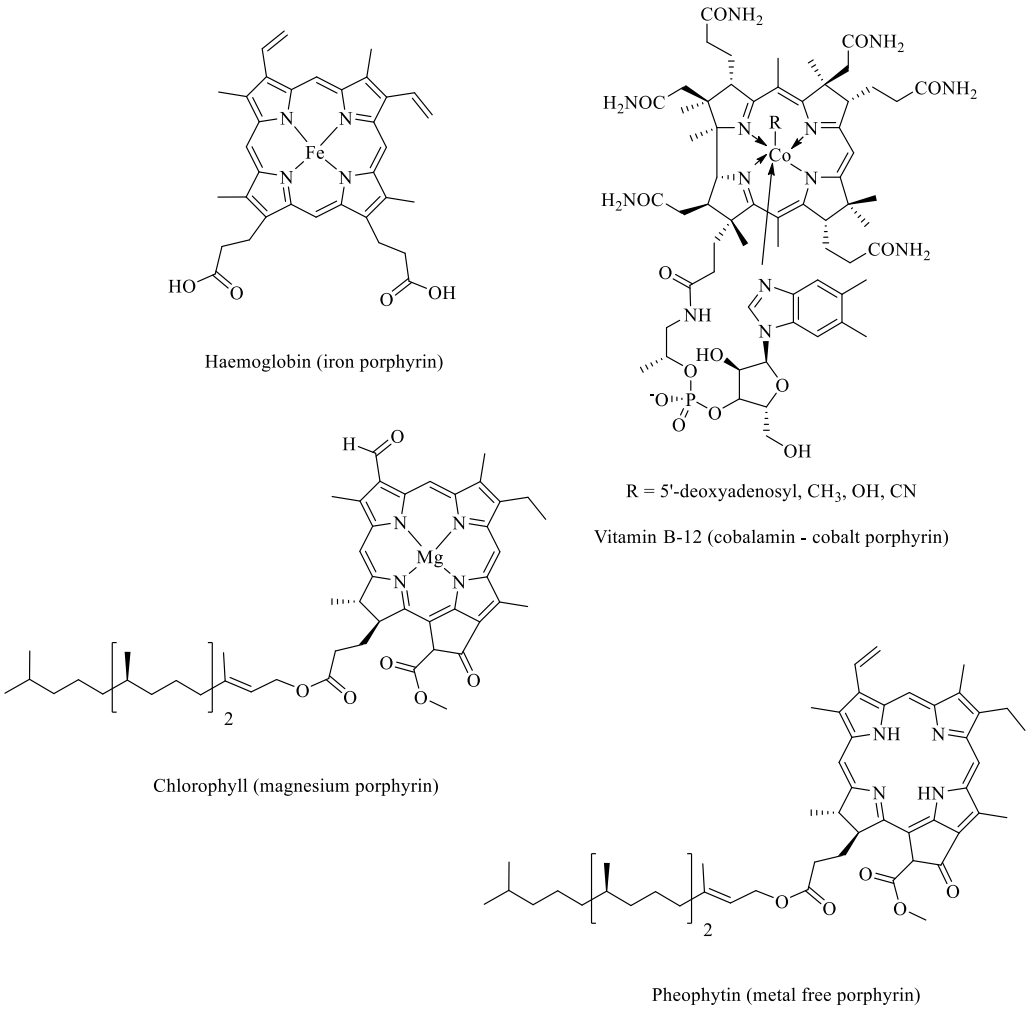


Figure 41. Structure of haemoglobin, vitamin B-12, chlorophyll and pheophytin.

3.2 Structure, properties and applications of porphyrins and its analogues.

The fascinating thing about porphyrins is that they show intense purple colour (Figure 42), which also explains their name, *porphyrin*. The word *porphyrin* is originated from ancient Greece word *porphura*, which was used to describe the colour purple in ancient Greece.

Figure 42. The intense purple colour of porphyrins.

Porphyrins are heterocyclic organic compounds, which consist of four modified pyrrole rings interlinked through methyne bridges (=CH-) at their α-carbon atoms forming larger macrocyclic rings. Porphine is the parent porphyrin (Figure 43) and porphyrins are the substituted porphines. Porphyrin consists of four *meso*-positions and eight α and β-positions. The porphyrin macrocycle has 26 π-electrons in total, out of which 18 π-electrons are delocalized over the macrocycle and forms a planar cyclic arrangement, making porphyrin macrocycle a highly conjugated system. Additionally, porphyrins obey Hückel's rule of aromaticity, possessing 4n+2 π electrons (n = 4).[225a]

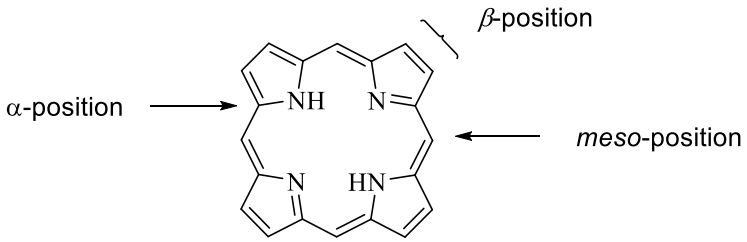


Figure 43. Structure of parent porphyrin, porphine.

Porphyrins and their metal complexes have exceptional optical and electronic properties, photochemical and thermal stability, due to which they have gained attention from the researchers all over the world. Porphyrins can form several types of complexes with metal ions[227] and some non-metals[228] due to the availability of large cavity and existence of four nitrogen atoms from pyrrole rings. The amenable coordination environment provided by porphyrins can be easily altered to desired oxidation by changing the peripheral substitution on the aromatic ring, either by EDGs or EWGs. This inner metal complexation and/or peripheral substitution at β-pyrrole or *meso*-positions in turn also benefits in systematic tailoring of the optical and electronic properties[229] (redox chemistry) of porphyrins, due to which porphyrins

have shown wide range of applications and present at the active site of many biological systems.[225b, 230]

The presence of porphyrins at the heart of many biological systems and possibility to alter their chemical and physical properties, like polarizability, catalytic properties, absorption spectrum, large dipole moments, non-linear optical response, energy transfer, etc. shows the potential of porphyrins and metalloporphyrins as a group of versatile chemical entities for the research in many areas of chemistry and physics like, artificial photosynthesis, non-linear optical materials, photodynamic therapy, chemical and gas sensors, catalysis, photocatalysis, electrochemistry, opto-electronics (LEDs), to name only a few. Porphyrins can bind and release gases and in catalytic reactions of biological systems they can act as active center. Thus, porphyrin-based films on semiconductor or metal surfaces showed great potential as gas and chemical sensors and also as nonporous catalysts (Figure 44).[231] Over the years porphyrins and metalloporphyrins showed great potential as photocatalysts.[232] For example, Manesh *et al.* reported the use of Pt porphyrins in the photooxidation of benzaldehyde derivatives to benzoic acid derivatives.[233]

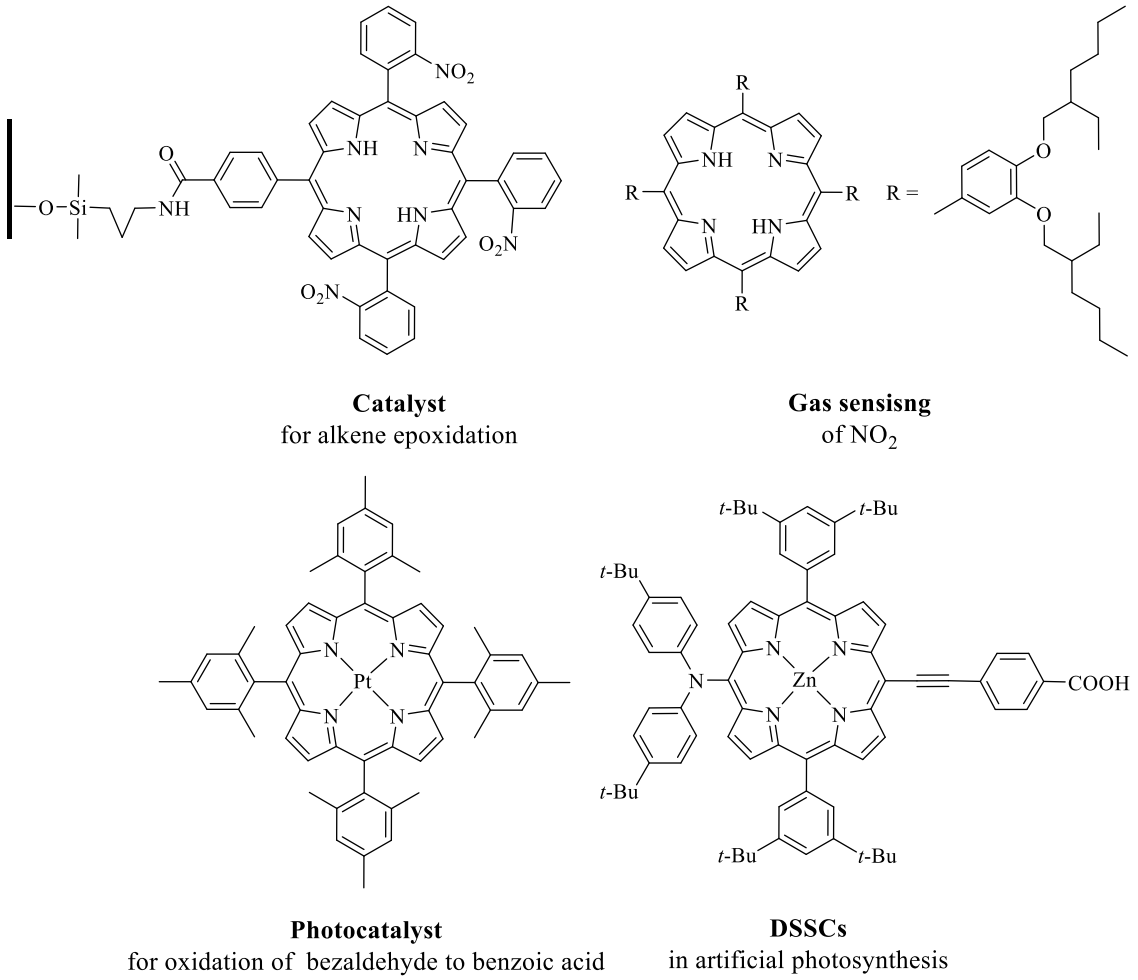


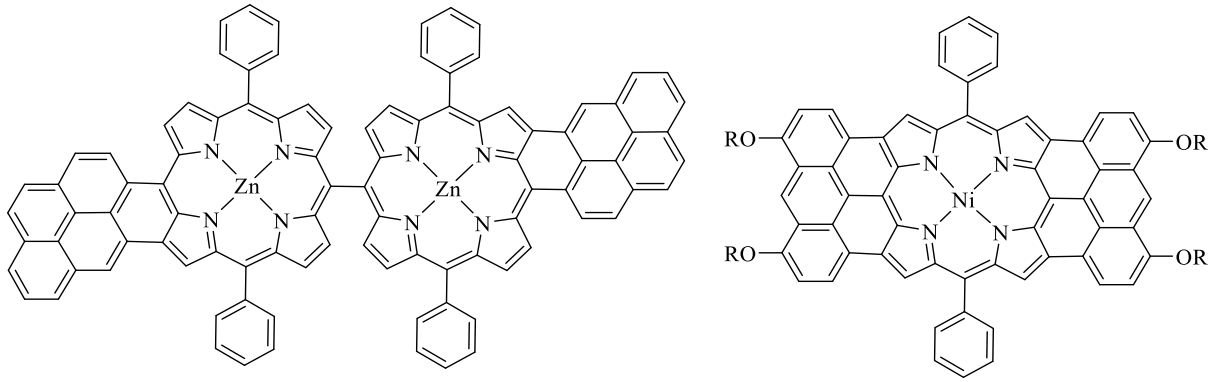
Figure 44. Applications of porphyrins and metalloporphyrins in various research areas.

However, undoubtedly, the most explored research area for the application of porphyrins and metalloporphyrins is their use as light harvesting antenna systems in biological systems and as photosensitizers in dye sensitized solar cells (DSSCs) in artificial photosynthesis.[234] Due to

their structural resemblance to natural chlorophylls, porphyrins derivatives greatly explored as model compounds to mimic biological processes like energy and electron transfer processes in photosynthesis.[235]

3.3 Porphyrin-BODIPY hybrids: need and concept.

Porphyrin derivatives are macrocyclic aromatic heterocycles. Porphyrin derivatives exhibit an intense absorption in 400-450 nm region, called Soret band, and relative weak absorptions as compared with the Soret band in the 500-700 nm region, called Q bands. Even though, porphyrins show many advantages as antenna chromophores, the absorption capability of porphyrin monomers in the visible, especially in blue-green region, and NIR region is very less. So, they are not ideal for broadband solar harvesting. This proved to be an important drawback of porphyrin monomers for their use in the organic solar cells as light harvesting antenna. 50% of the sunlight radiation energy is in the IR region, so, for the chemical entities best suited for use in organic solar cells they should have good absorption capabilities throughout the solar spectrum, in the UV/Vis region as well as in the NIR region (700-2000 nm). To better the light harvesting capability of porphyrins, attempts have been made to fuse the polyaromatic hydrocarbons (PAHs), like pyrene, azulene, perylene, and anthracene, to the core of the porphyrin derivatives (Figure 45).[236] However, it was observed that such compounds were unstable up-on the long exposure to light and air due to the high electron density obtained by π-extended conjugation.



231 **232**, R = *n*-C_8H_{17}

Figure 45. Structure of pyrene **231** and anthracene **232** fused porphyrins.

In order to overcome above mentioned problems, chromophores with complementary absorption i.e., green absorbing capabilities, such as phthalocynines,[237] carotenoids[238] and BODIPYs[239] have been attached to porphyrin derivatives to create complexes with donor-acceptor array. Among those, BODIPY chromophores exhibit strong absorption in the range 450-550 nm (blue-green) region and have been greatly coupled with porphyrins *via* either covalent bonds or non-covalent bonds improving their light harvesting capabilities throughout the solar spectrum. Along with that, BODIPYs are also preferred due to their excellent optical and chemical properties, like high quantum yields, large molar absorption coefficients, long excited state lifetimes, excellent photostability, high solubility in organic solvents, etc. Along with such excellent properties BODIPY derivatives also exhibited absorption in the visible and NIR region, due which they were widely used as light harvesting entities.[240] Based on this, a great number of porphyrin-BODIPY dyads have been reported to exploit their capability to act

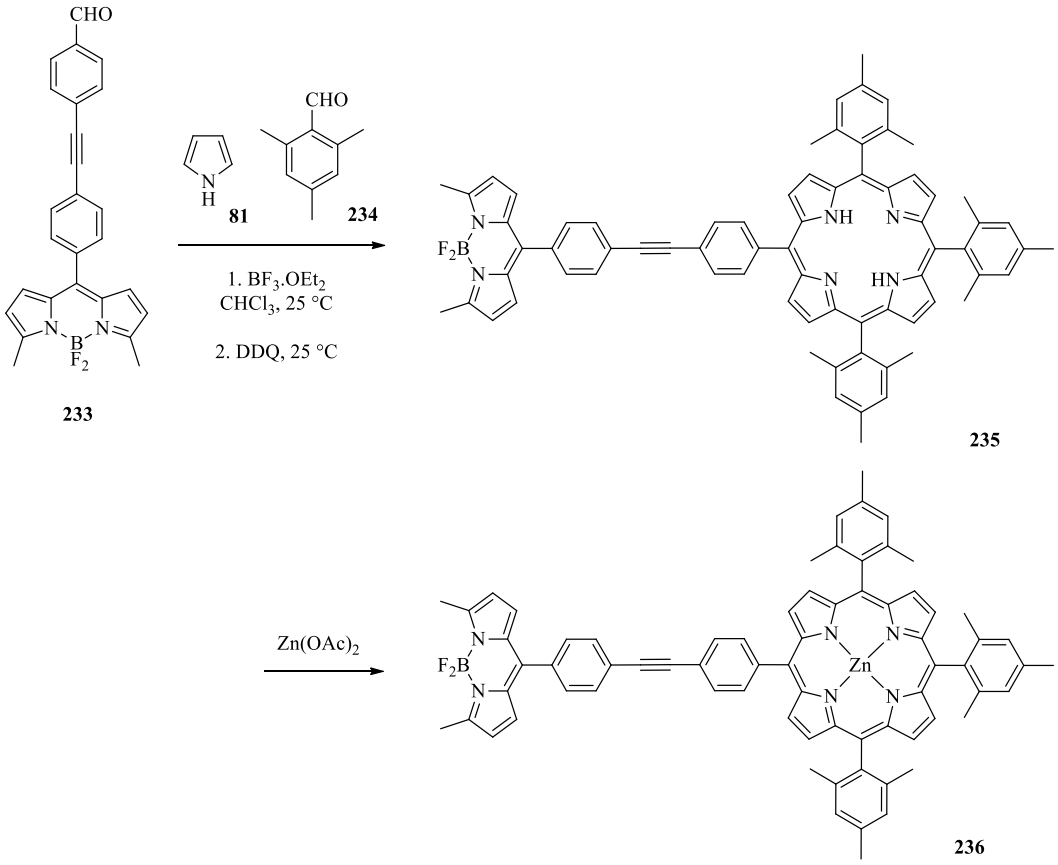
as antenna chromophore for light harvesting purposes.[241] Additionally, such dyads also showed applications in optoelectronic devices.[242]

3.4 Types of Porphyrin-BODIPY hybrids.

To have the better understanding about the different types of porphyrin-BODIPY hybrids, here they were categorized into four different types, which are as follows:

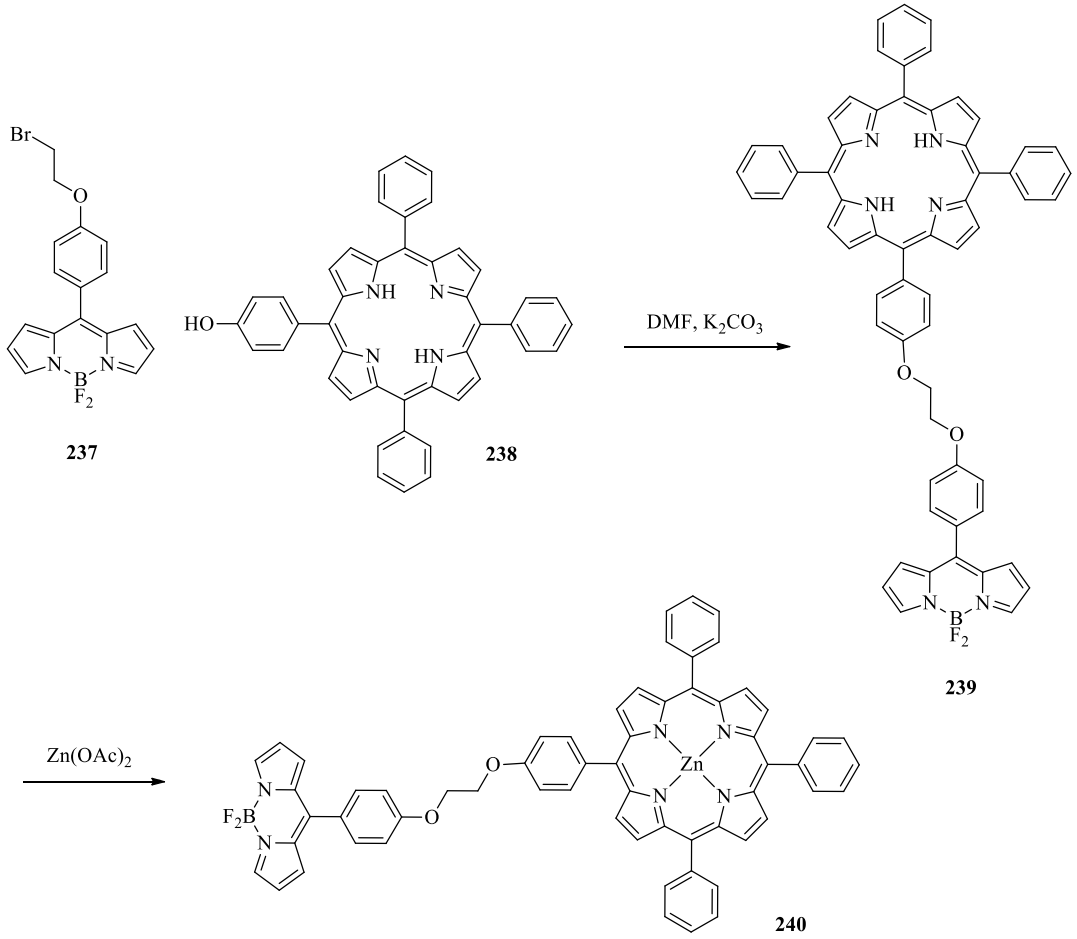
(a) Hybrids with one porphyrin and one BODIPY unit

Lindsay *et al.*, in 1998, were the earliest ones to report the first porphyrin-BODIPY hybrid **236** with one porphyrin and one BODIPY unit. They used a condensation method for that purpose. **235** was synthesized by condensation of benzaldehyde containing BODIPY substituent at *para*-position **233** with mesitaldehyde **234** and pyrrole **81** in chloroform in presence of catalytic amount of $BF_3.OEt_2$, followed by DDQ oxidation. **235** on zinc insertion using zinc acetate gave **236** (Scheme 39).[243]



Scheme 39. Synthesis of porphyrin-BODIPY hybrids **235** and **236**.

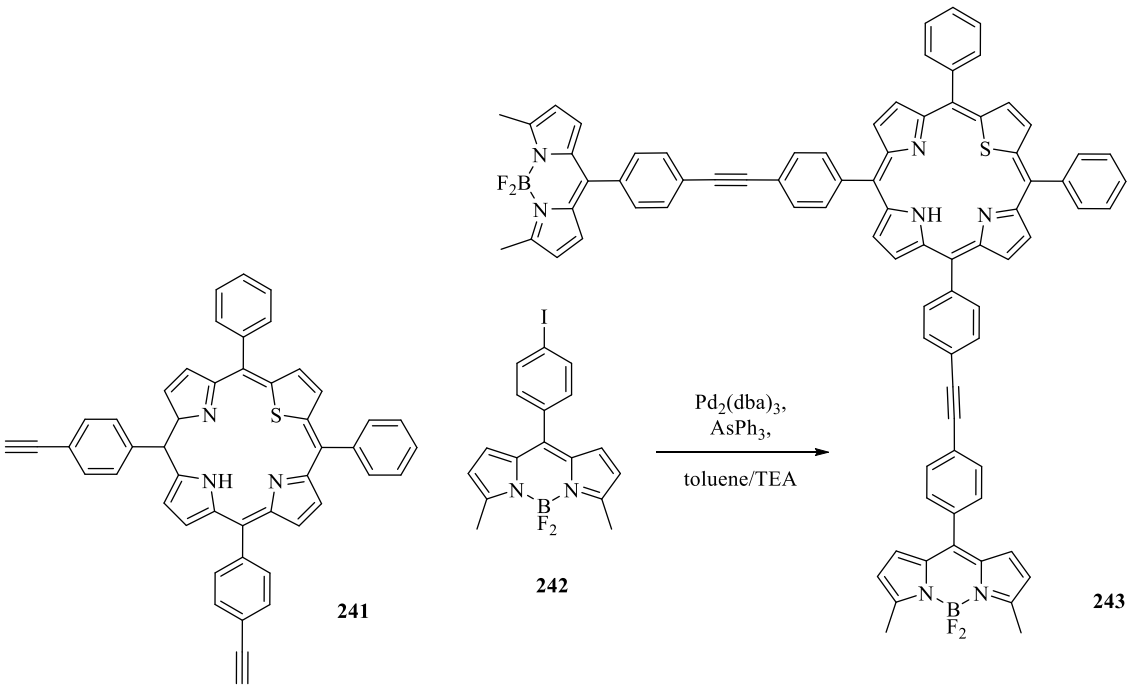
The covalently linked porphyrin-BODIPY hybrid with ether bridge **239** was reported by D'Souza *et al.* by reacting BODIPY **237** with porphyrin **238** in the presence of K_2CO_3. **239** on zinc insertion using zinc acetate gave **240** (Scheme 40).[244]



Scheme 40. Synthesis of ether bridged porphyrin-BODIPY hybrids **239** and **240**.

(b) Hybrids with one porphyrin and two BODIPY units

Ravikanth *et al.* reported the synthesis of thiaporphyrin-BODIPY hybrid **243** with one porphyrin and two BODIPY units. **243** was synthesized by the reaction between 21-thiaporphyrin **241** and iodo-BODIPY derivative **242** using the Sonogashira cross-coupling reaction conditions (Scheme 41).[245]

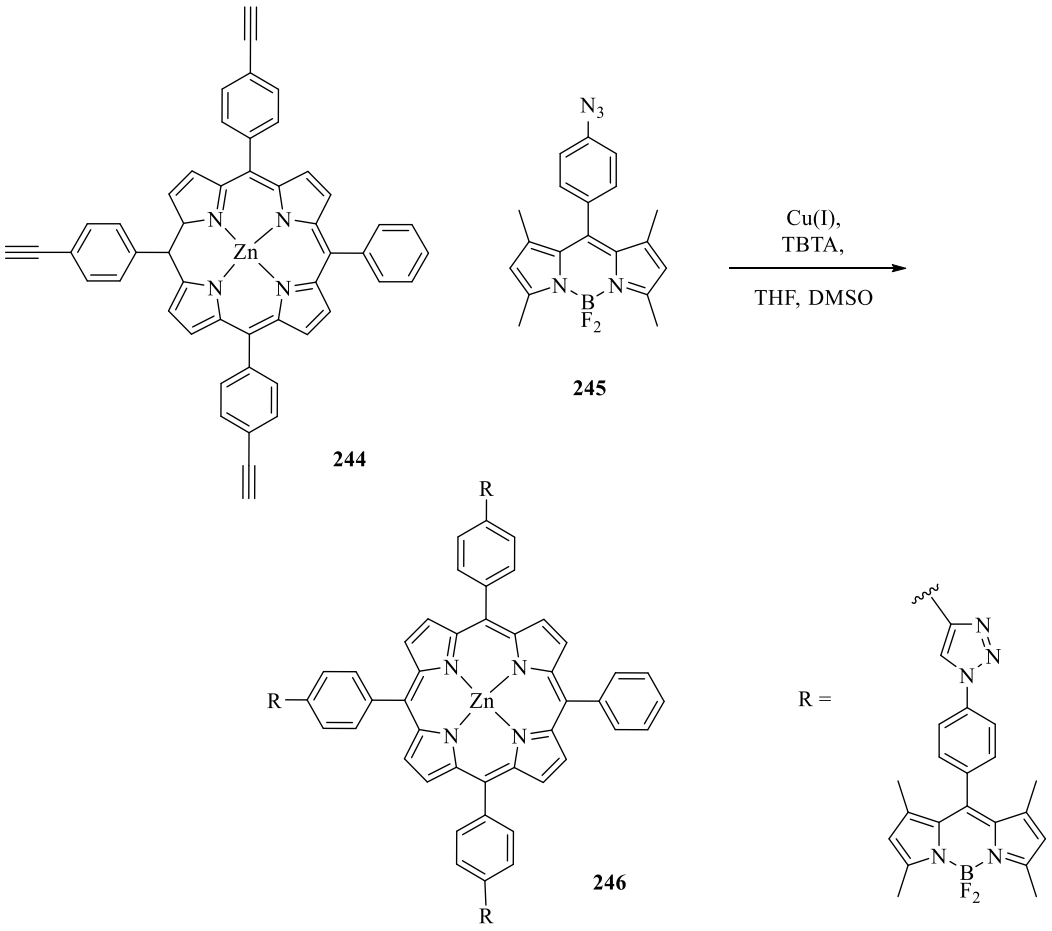


241 242 243

Scheme 41. Synthesis of thiaporphyrin-BODIPY hybrid **243** via Sonogashira coupling.

(c) Hybrids with one porphyrin and multiple BODIPY units

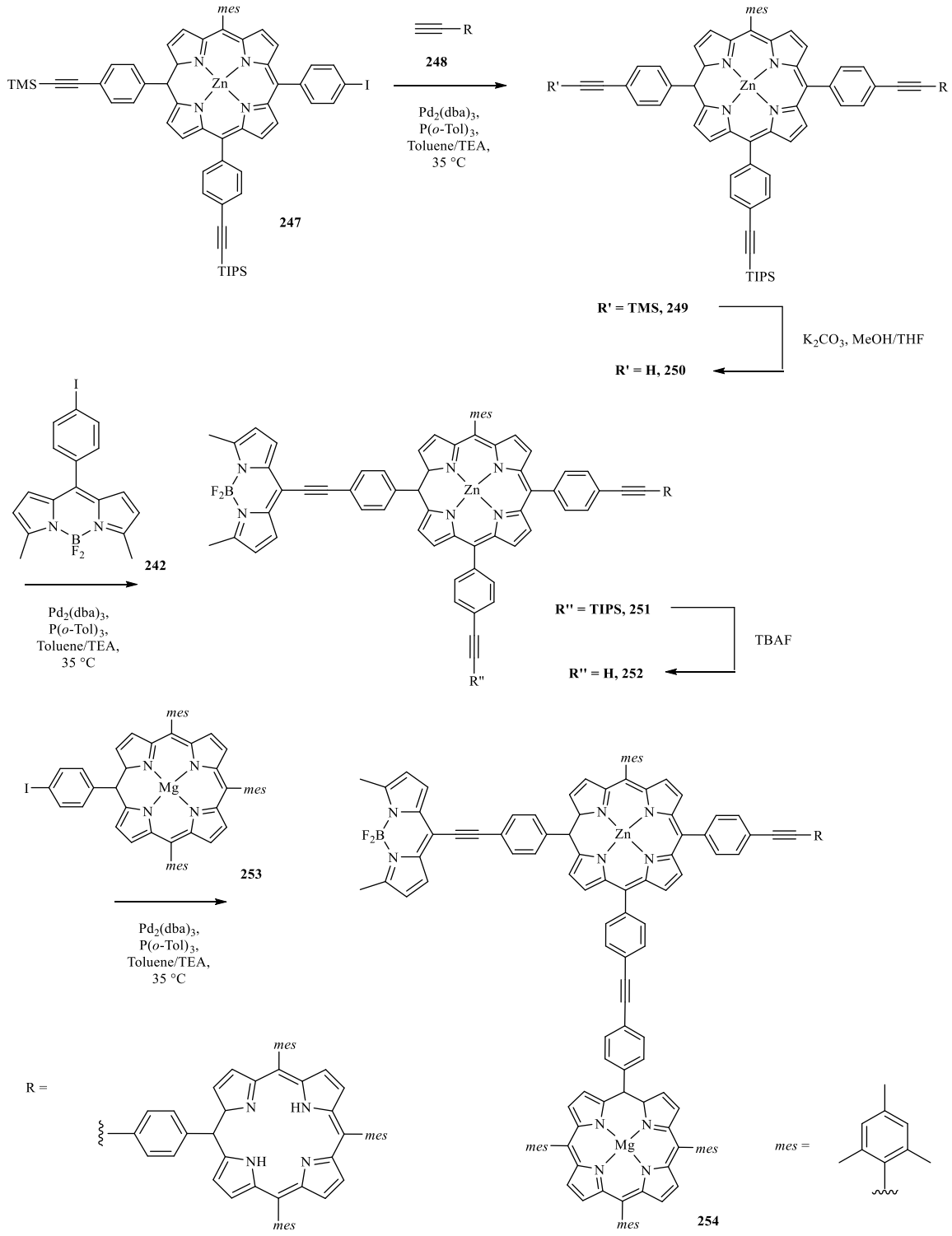
Dinolfo *et al.* reported the synthesis of hybrid of porphyrin-BODIPY **246** containing one porphyrin and multiple units. The synthesis of **246** was carried out by reacting one equivalent of porphyrin **244** and three equivalents of BODIPY **245** under standard conditions of Cu(I) catalyzed click reaction (Scheme 42).[246]



Scheme 42. Synthesis of porphyrin-BODIPY hybrid **246** under standard conditions of Cu(I) catalyzed click reaction.

(d) Hybrids with two or more porphyrins and one BODIPY unit

Rao *et al.* reported the synthesis of porphyrin-BODIPY hybrid **254** containing three porphyrin units and one BODIPY unit. They used **247** as a starting material containing three different functionalities, like, iodo, triisopropylethyne and trimtehylsilylethyne. The first Pd(0) coupling reaction of **247** at iodo functionality with ethynyl porphyrin **248** yielded **249**. The TMS deprotection of **249** gave compound **250** with free ethynyl group. The second Pd(0) coupling at that free ethynyl group with BODIPY derivative **242** yielded **251**. On triisopropyl group deprotection **251** gave **252** with free ethynyl group, which on third Pd(0) coupling reaction with Mg-porphyrin **253** yielded porphyrin-BODIPY hybrid **254** containing three porphyrin units and one BODIPY unit. [247]



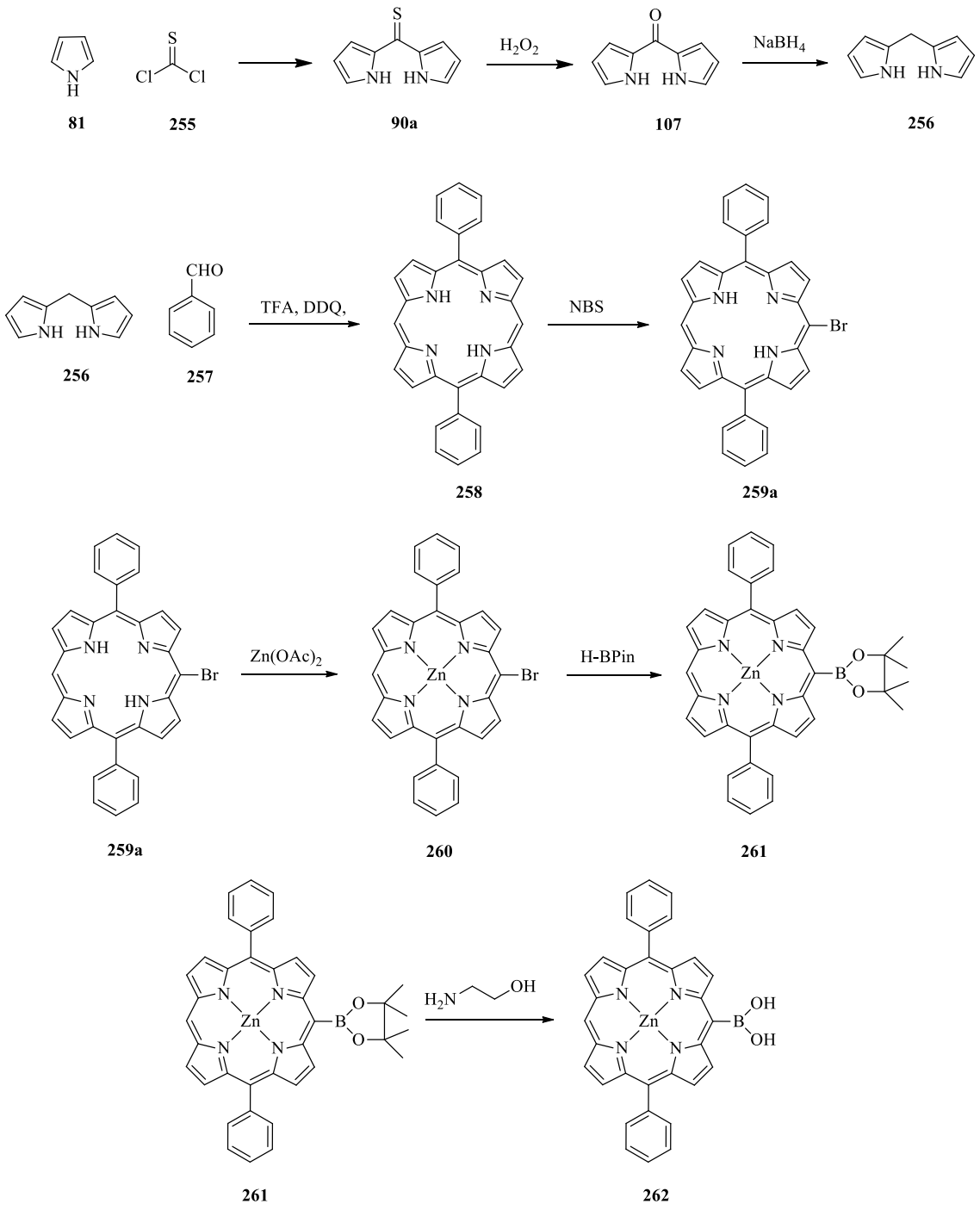
Scheme 43. Synthesis of porphyrin-BODIPY hybrid **254** containing three porphyrin units and one BODIPY unit.

3.5 Design and concept of the project.

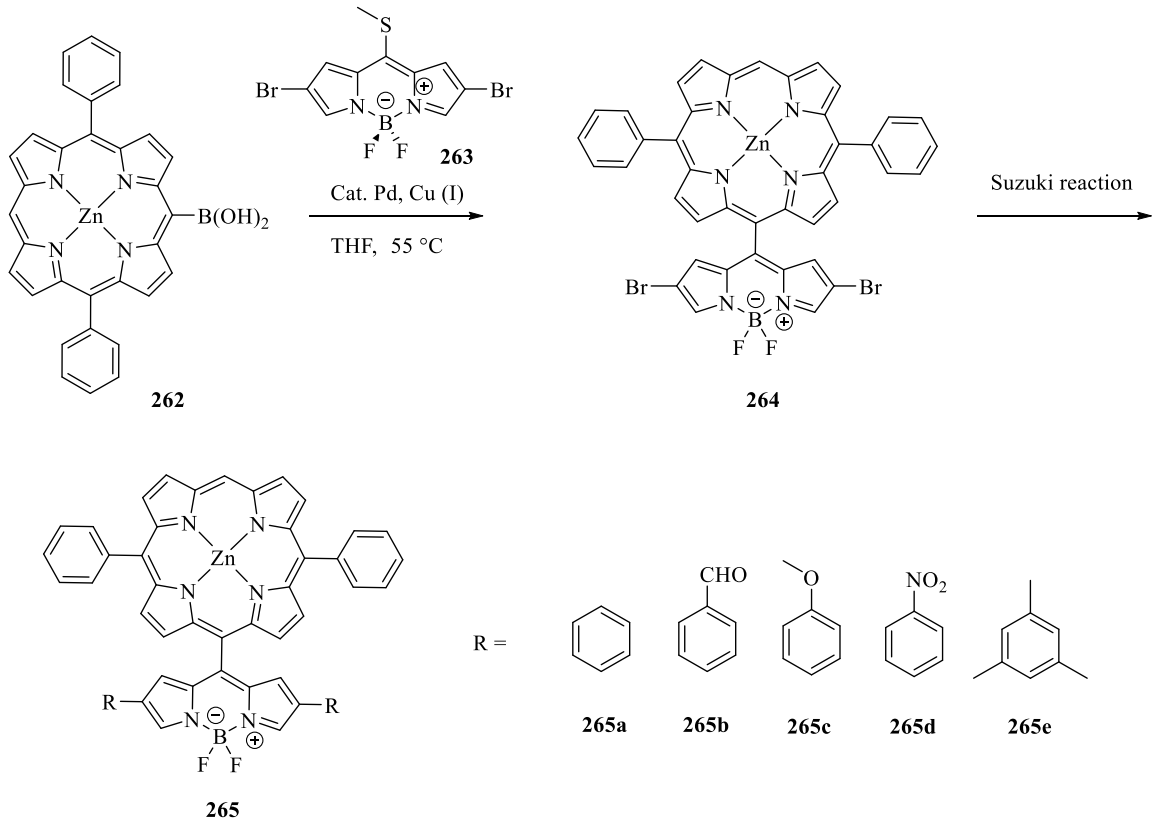
As mentioned earlier, porphyrins exhibit intense absorption in 400-450 nm region, called Soret band, and relative weak absorptions as compared with the Soret band in the 500-700 nm region, called Q bands. However, the absorption capability of porphyrins monomers is very weak in the visible (blue-green) and NIR region. Therefore, porphyrin monomers are not ideal for broadband solar harvesting. This can be improved by attaching porphyrins to chromophores such as BODIPYs which have complementary absorption i.e., green absorbing capabilities (450-550 nm). The hybrids of porphyrins with BODIPYs have shown great improvement in their light harvesting capabilities throughout the solar spectrum.

As mentioned earlier in chapter one, our group has done tremendous amount of work on the BODIPY chemistry and seen that BODIPY derivatives has green absorbing capabilities. However, this project "synthesis of porphyrin-BODIPY hybrids and study of their photophysical properties" is the new research area that we have started in our group. For this project we envisioned that, if, we extend the conjugation of porphyrin ring by attaching BODIPY chromophore at the *meso* position of the porphyrin ring, then we can observe the bathochromic shift in the absorption and emission bands of those porphyrin-BODIPY hybrids. Thus, during this project, our objective was to synthesize porphyrin-BODIPY hybrids by means of cross-coupling reactions like, Liebeskind-Srogl, Suzuki, Stille, etc., and study the photophysical properties of the obtained derivatives. For that purpose, we proposed three different strategies, viz., strategy A, B and C.

The first step of strategy A involves the synthesis of boronic acid of porphyrin **262** in eight steps through reported literature method (Scheme 44).[248] Then, the Liebeskind-Srogl cross-coupling reaction of the obtained boronic acid of porphyrin with brominated methylthio-BODIPY derivative **263** can give *meso-meso* linked porphyrin-BODIPY hybrid **264**. Which on Suzuki cross-coupling reaction with wide range of boronic acids can give *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** with different functionalities (Scheme 45).

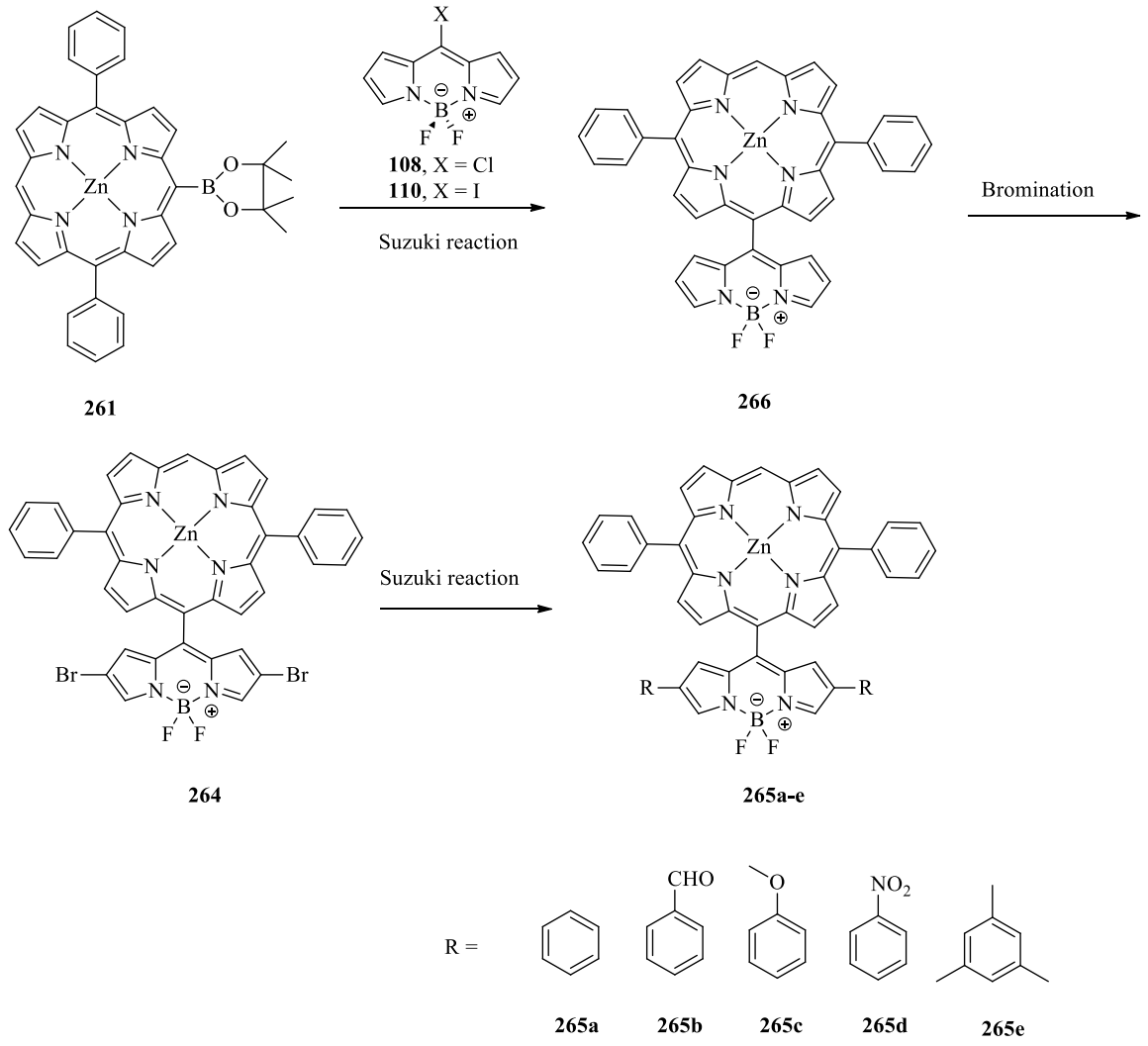


Scheme 44. Synthesis of boronic acid of porphyrin **262**.



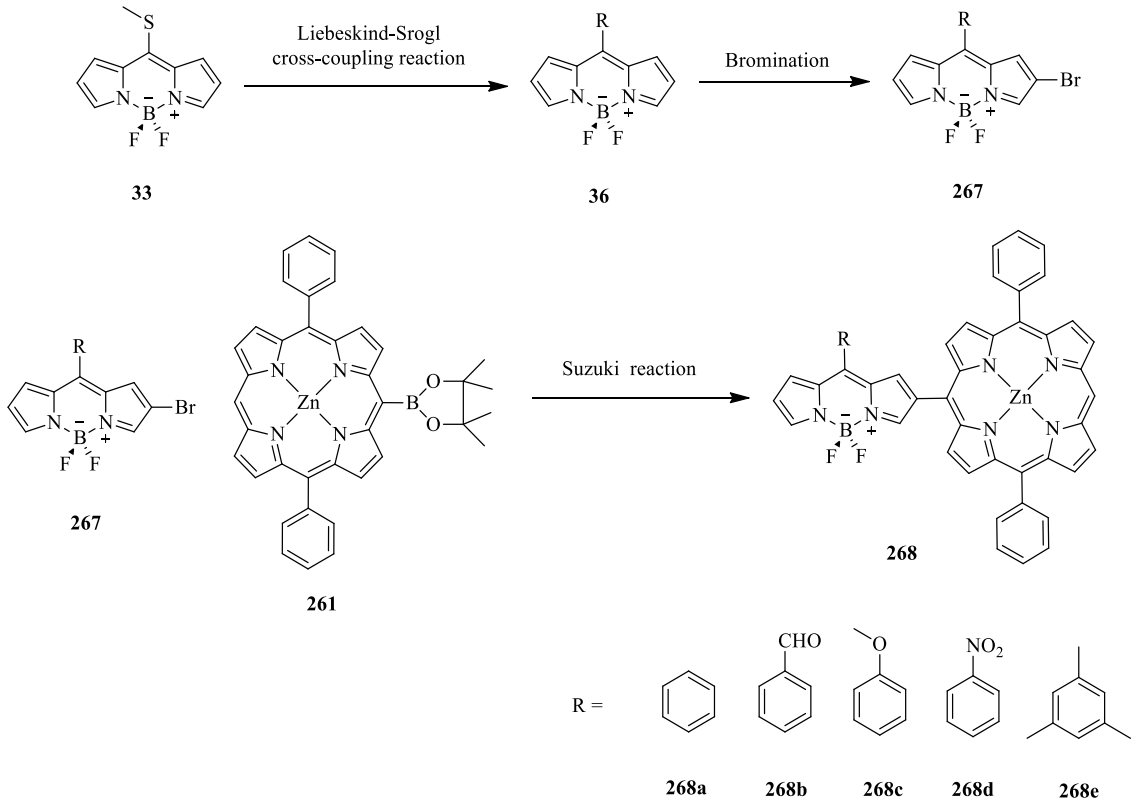
Scheme 45. Synthesis of *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** through strategy-A.

Strategy B involves synthesis of *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** through series of Suzuki, bromination and Suzuki reactions. First, the Suzuki coupling of 8-chloro BODIPY **108** or 8-iodo BODIPY **110** with boronic ester of porphyrin **261** can give *meso-meso* linked porphyrin-BODIPY hybrid **266**, which on bromination at the BODIPY core can give **264**. The Suzuki reaction of **264** with wide range of boronic acids can give *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** with different functionalities (Scheme 46).



Scheme 46. Synthesis of *meso-meso* linked porphyrin-BODIPY hybrids **265a-e** through strategy-B.

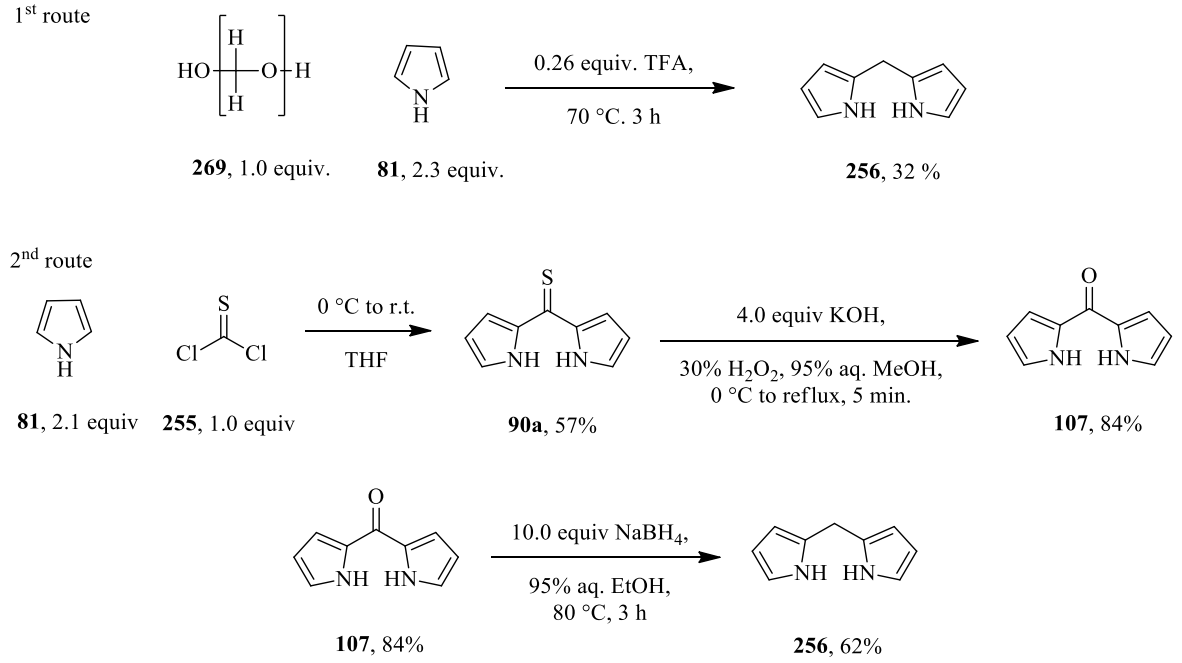
Strategy C involves the Suzuki coupling of 2-bromo *meso* substituted BODIPY derivatives **267** with the boronic ester of porphyrin **261** to give the *meso*-β linked porphyrin-BODIPY hybrids **268a-e** (Scheme 47). The *meso* substituted BODIPYs **36** can be synthesized via Liebeskind-Srogl coupling of 8-methylthioBODIPY **33** with wide range of boronic acids, which on bromination at C-2 position can give 2-bromo *meso* substituted BODIPY derivatives **267**.



Scheme 47. Synthesis of *meso-β* linked porphyrin-BODIPY hybrids **268a-e** through strategy-C.

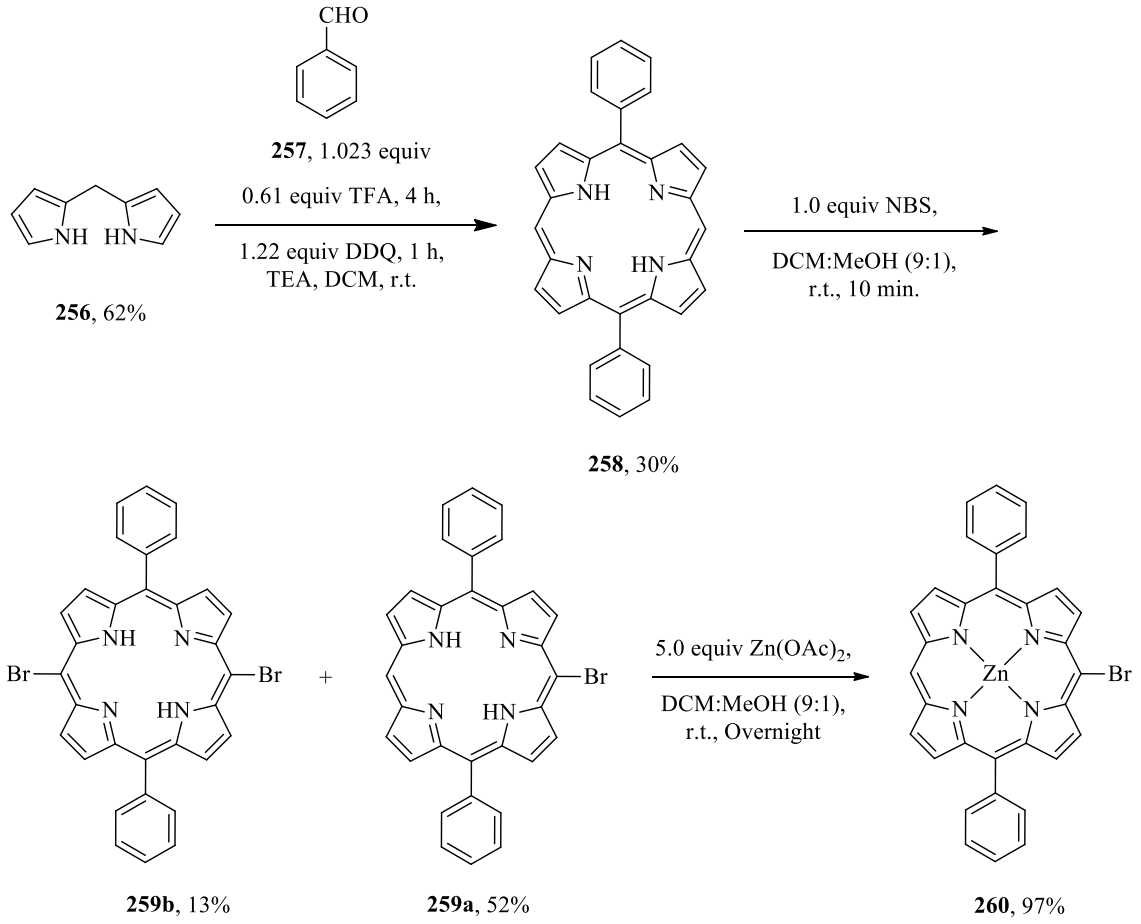
3.6 Results and discussion.

The first step of the project was to synthesize the boronic acid of porphyrin **262**. For that purpose, we synthesized dipyrromethane **256** by following two different reported routes. The first route involved the reaction of paraformaldehyde **269** in pyrrole **81** (here pyrrole was used as reactant as well as solvent) in the presence of catalytic amount of TFA in the dark to give dipyrromethane **256** in 32% yield. The second route involved three steps, starting from reaction of pyrrole **81** with thiophosgene **255** in THF to give thioketone **90a** (57% yield), which on oxidation using 30% hydrogen peroxide gave dipyrroketone **107** (84% yield). Then the reduction of **107** using $NaBH_4$ afforded **256** in 62% yield (Scheme 48).[249] We preferred the second route over the first one because it allowed us to prepare **256** in gram scale and also it involved minimum use of expensive pyrrole **81**.



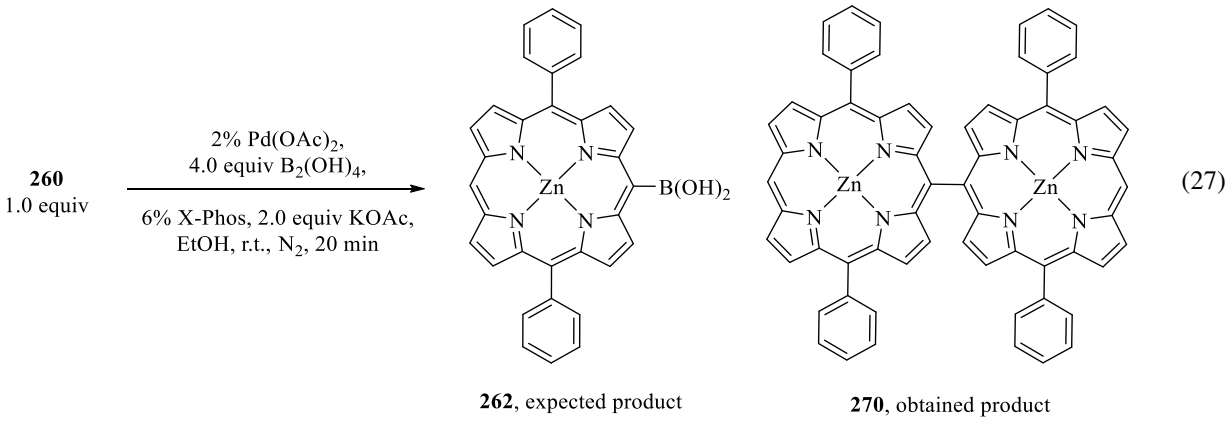
Scheme 48. Synthesis of dipyrromethane **256** using two different synthetic routes.

The next step was the synthesis of boronic acid of porphyrin **262**, which involved five steps starting from dipyrromethane **256**. The condensation reaction of dipyrromethane **256** with benzaldehyde **257** in presence of catalytic amount of TFA in the dark, followed by DDQ oxidation afforded 5,15-diphenylporphyrin **258** in 30% yield. The bromination reaction of **258** using NBS afforded 5-bromo-10,20-diphenylporphyrin **259a** and 5,15-dibromo-10,20-diphenylporphyrin **259b** in 52% and 13% yields, respectively. Overnight zinc insertion reaction at the core of **259a** using zinc acetate afforded 5-bromo-10,20-diphenylporphinato zinc (II) **260** in quantitative yield (Scheme 49).



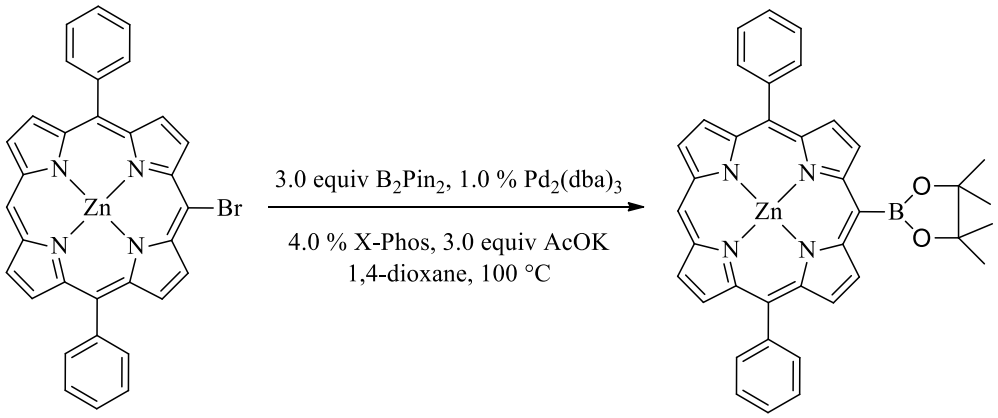
Scheme 49. Synthesis of 5-Bromo-10,20-diphenylporphinato zinc (II) **260**.

Further, we attempted direct synthesis of porphyrin boronic acid **262** from **260** using tetrahydroxydiboron and other catalytic systems as shown in eq 27.[250] However, to our surprise, instead getting the desired porphyrin boronic acid **262**, we observed the formation of porphyrin dimer **270** (confirmed by ^{1}H NMR spectroscopy). The same reaction conditions were used in our lab for the direct synthesis of BODIPY dimers, where the same behaviour was observed forming the BODIPY dimers. We performed the same reaction multiple times using less or more amount of catalytic system and tetrahydroxydiboron and also lesser reaction time (5 min.), however, we only saw the formation of dimer **270**.



(27)

Further, two different routes were attempted for the synthesis of pinacol ester of porphyrin boronic acid **261**. In the first route, bis(pinacolato)diboron was used as a boronic ester source along with the catalytic system as shown in eq 28. However, this route didn't work, as even after 24 hours there was no formation of the desired product and starting material was still there in large amount.



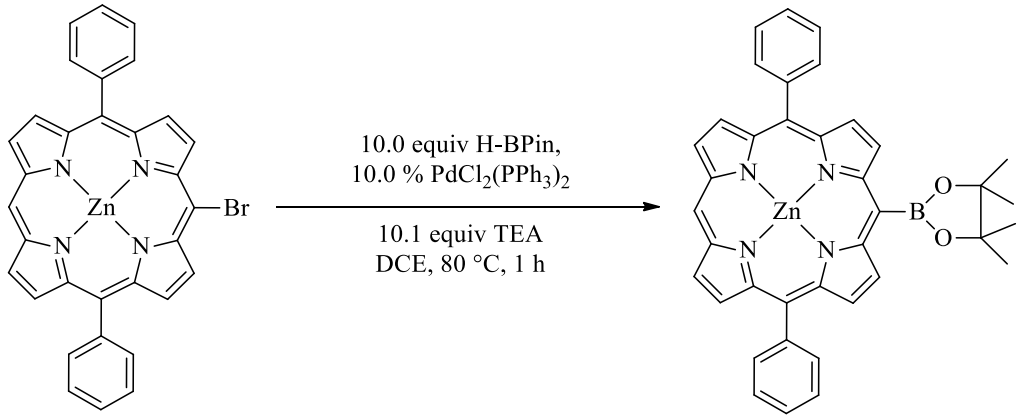
260, 1.0 equiv
20 mg

261, reaction didn't work

15.1 mg of **260** recovered

(28)

For the second route, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane was used as a boronic ester source along with the catalytic system as shown in eq 29.[251] One hour reflux reaction gave 65% of pinacol ester of porphyrin boronic acid **261**.

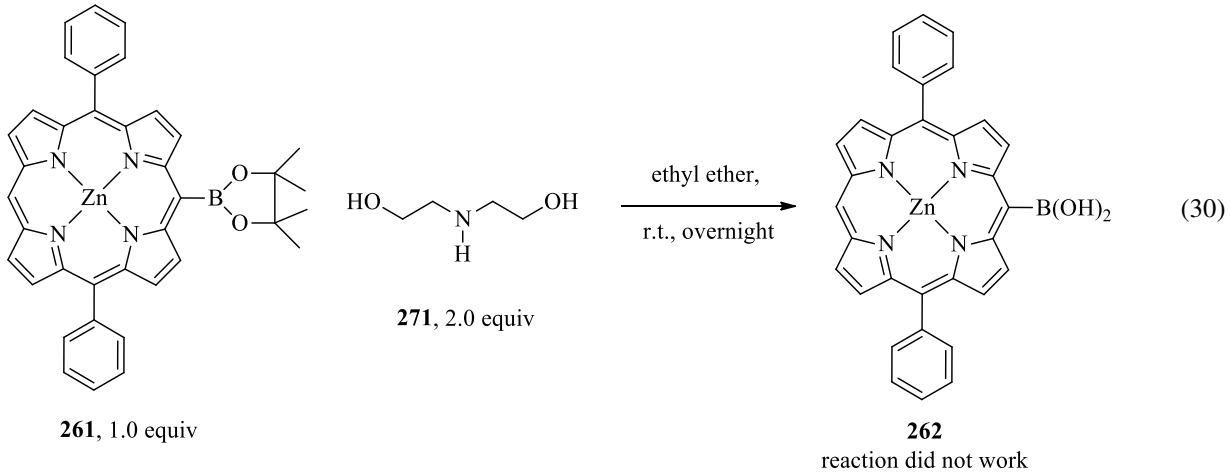


260, 1.0 equiv.

261, 65 %

(29)

The next step was the synthesis of boronic acid of porphyrin **262** by deprotecting the pinacol ester of porphyrin boronic acid **261**. For that purpose, we used the reported reaction conditions reported by our lab as shown in eq 30.[252] The reaction of **261** with diethanolamine **271** showed the total consumption of starting material **261**, however, there was no formation of the desired compound **262**, and only decomposition was observed at the base of TLC plate.

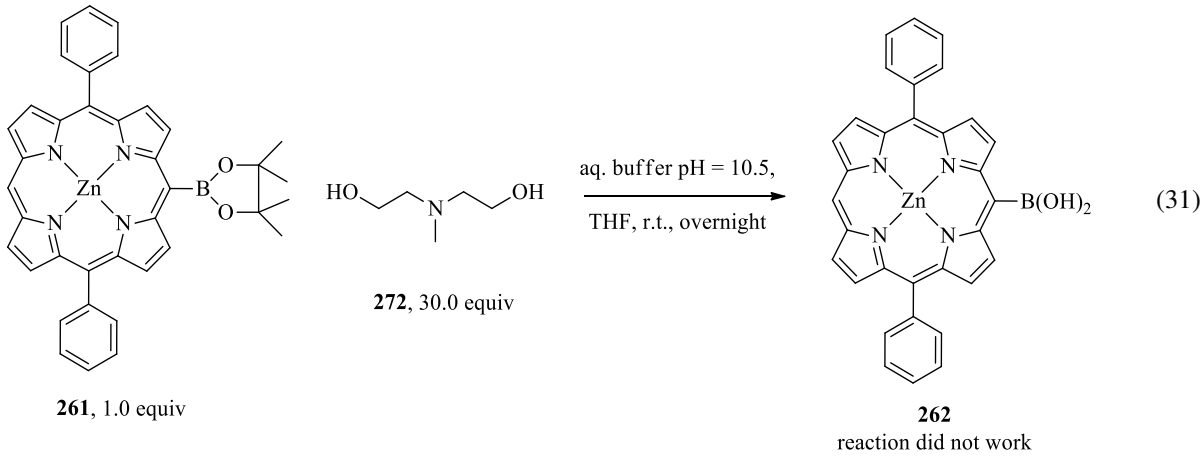


261, 1.0 equiv

271, 2.0 equiv

262
reaction did not work

Next, we tried to synthesize **262** by the reaction of **261** with *N*-methyldiethanolamine **272** as shown in eq 31. The overnight reaction showed the total consumption of starting material **261**, however, there was no formation of the desired compound **262**, and only decomposition was observed at the base of TLC plate.

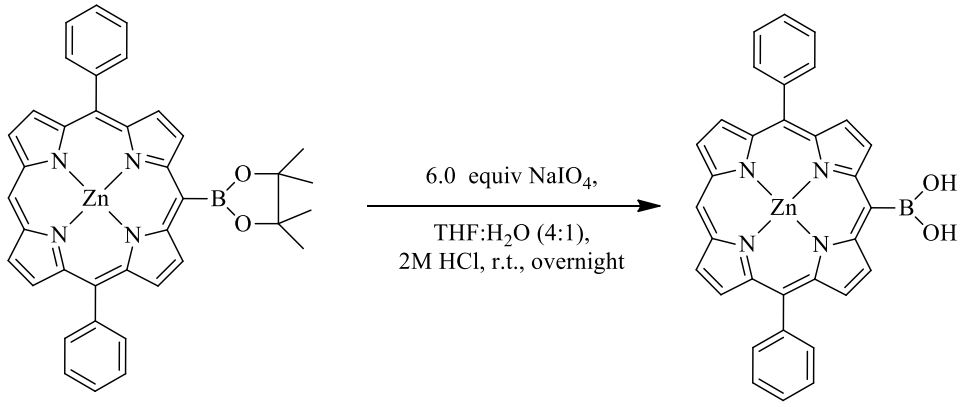


261, 1.0 equiv

272, 30.0 equiv

262
reaction did not work

We also tried the reaction of **261** with sodium periodate for the synthesis of **262** as shown in eq 32. The overnight reaction showed the total consumption of starting material **261**, however, there was no formation of the desired compound **262**, and only decomposition was observed at the base of TLC plate.

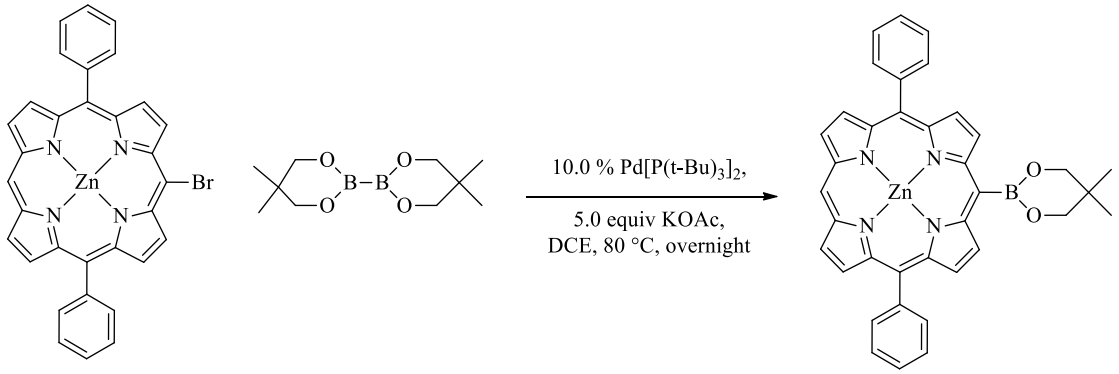


261, 1.0 equiv

262
reaction did not work

(32)

After the failure of above-mentioned strategies for the synthesis of porphyrin boronic acid **262**, we decided to synthesize neopentyl boronic ester of porphyrin **274**. It was synthesized in 30% yield by the reaction of **260** with bis(neopentylglycolato)diboron **273** as shown in eq 33.[253]



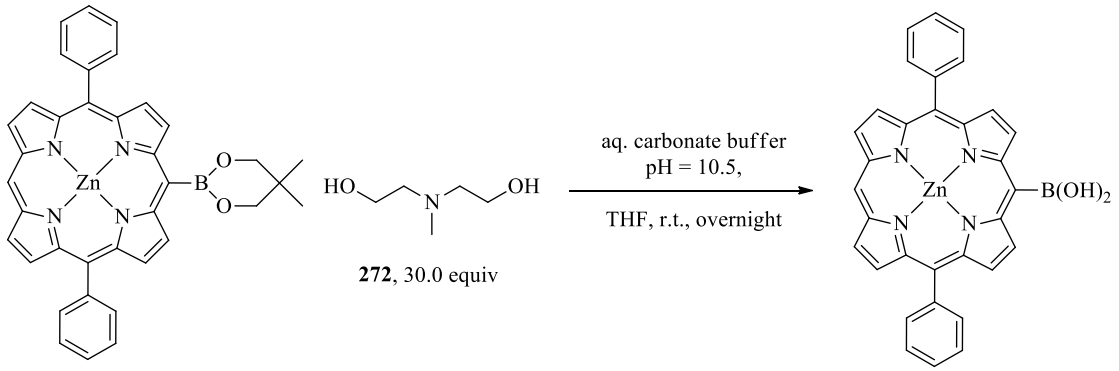
260, 1.0 equiv

273, 5.0 equiv

274, 30 %

(33)

Further, we tried to synthesize **262** by the reaction of **274** with N-methyldiethanolamine **272** as shown in eq 34. The overnight reaction showed the total consumption of starting material **274**, however, there was no formation of the desired compound **262**, and only decomposition was observed at the base of TLC plate.



274, 1.0 equiv

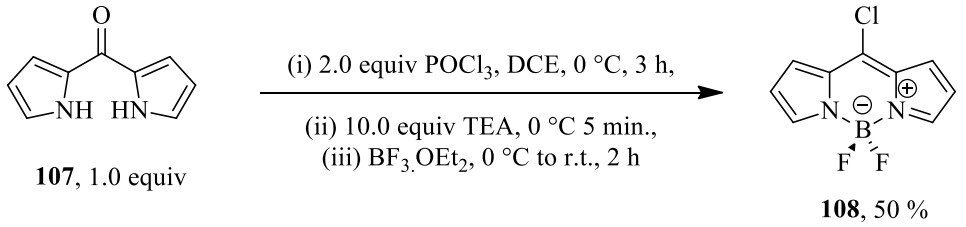
272, 30.0 equiv

262
reaction did not work

(34)

So, after carrying out series of experiments we observed that this strategy was not working as we end up observing decomposition at the base of the TLC plate. So, we decided to stop working on this strategy and move onto strategy-B.

Strategy-B involved the Suzuki cross-coupling reaction of 8-chloro BODIPY or 8-iodo BODIPY with pinacol ester of porphyrin boronic acid **261**. For that purpose, we first synthesized 8-chloro BODIPY **108** from dipyrroketone **107** using the reported method as shown in eq 35.[254]

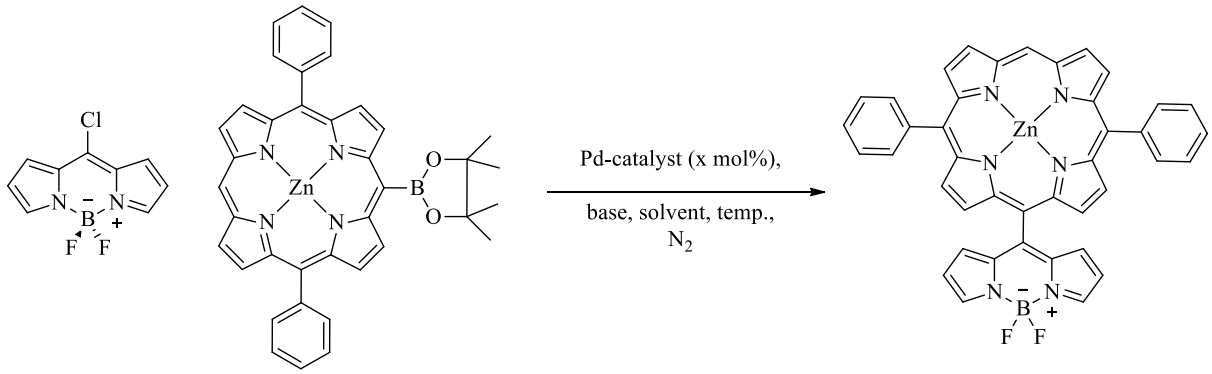


107, 1.0 equiv

108, 50 % (35)

Once **107** in hand we performed the optimization of the reaction conditions for the coupling of **107** with pinacol ester of porphyrin boronic acid **261**. For the optimization purpose we used different kinds of Pd catalysts, bases, solvents and temperatures. The reaction conditions used for the optimization purpose are reported in Table **4**.

Table 4 Optimization of Pd-catalyzed Suzuki cross-coupling reaction of **107** with pinacol ester of porphyrin boronic acid **261**.



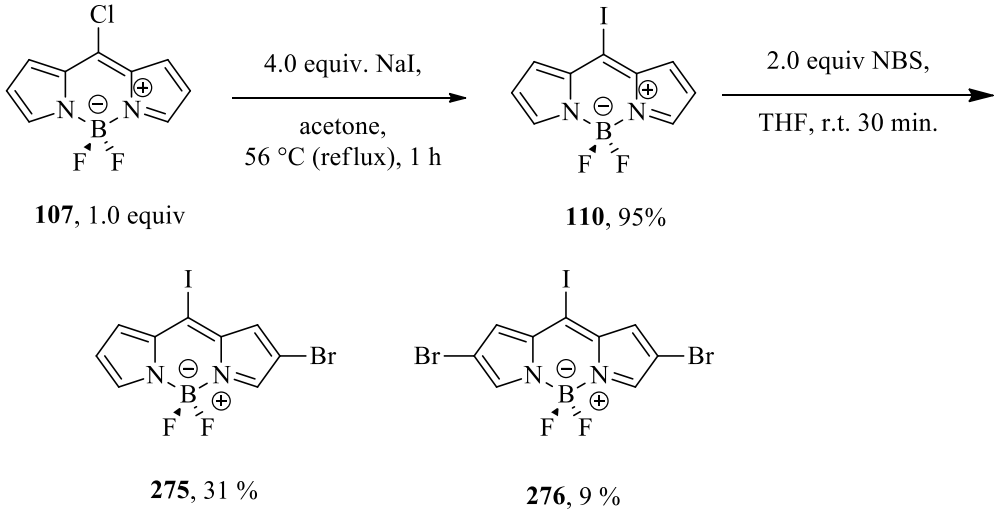
107, 1.0 equiv **261**, 1.3 equiv **266**

Entry	Pd-catalyst (x mol%)	Base (equiv)	T (°C)	Solvent[b]	Reaction Time (h)	Observations
1	$Pd(PPh_3)_4$ (5 mol%)	K_3PO_4 (3.0 equiv)	60	dioxane	2.0	Starting material decomposed
2	$Pd(PPh_3)_4$ (5 mol%)	K_3PO_4 (3.0 equiv)	60	dioxane: DMF (2:1)	1.0	Starting material decomposed
3	$Pd(PPh_3)_4$ (5 mol%)	K_3PO_4 (3.0 equiv)	90	DMF	1.0	Starting material decomposed

4	$Pd(PPh_3)_4$ (5 mol%)	K_3PO_4 (3.0 equiv)	90	Toluene: DMF (2:1)	18.0	Starting material decomposed
5	$Pd(PPh_3)_4$ (10 mol%)	Cs_2CO_3 (2.0 equiv)	90	Toluene: DMF (2:1)	16.0	Starting material decomposed
6	$Pd(PPh_3)_4$ (10 mol%)	Cs_2CO_3 (2.0 equiv)	77	THF	1.0	Starting material decomposed
7	$Pd(PPh_3)_4$ (5 mol%)	$Ba(OH)_2.8H_2O$ (3.0 equiv)	80	DME	11	-[c]

[a] All the reactions were carried out in 0.04 mmol scale of **107**. [b] Dry solvents were used for the reaction. [c] Even after 24 h there was no consumption of **107** and **261**, so added 2 drops of H_2O to the reaction mixture, TLC after 30 min. showed decomposition of starting material.

Since strategy with 8-chloro BODIPY did not work out, we decided to synthesize 8-iodo BODIPY **110** and 2-bromo-8-iodo BODIPY **275** and carry out their Suzuki cross-coupling reaction with **261**. The 8-iodo BODIPY was synthesized by the modified Finkelstein procedure (Scheme 50).[253] The 2-bromo-8-iodo BODIPY **275** was synthesized by the bromination of **110** using NBS in 31% yield along with 2,6-dibromo-8-iodo BODIPY **275** in 9% yield.



Scheme 50. Synthesis of 8-iodo BODIPY **110** and 2-bromo-8-iodo BODIPY **275**.

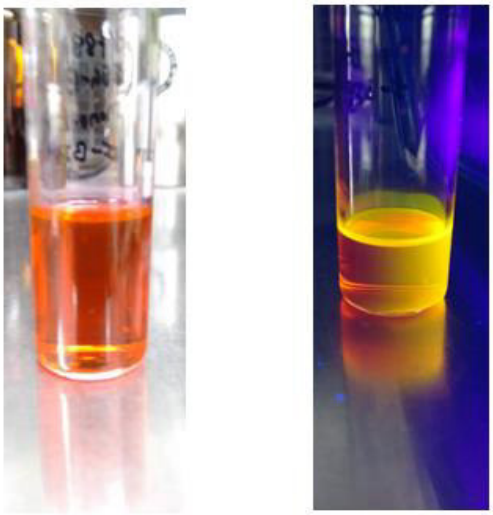
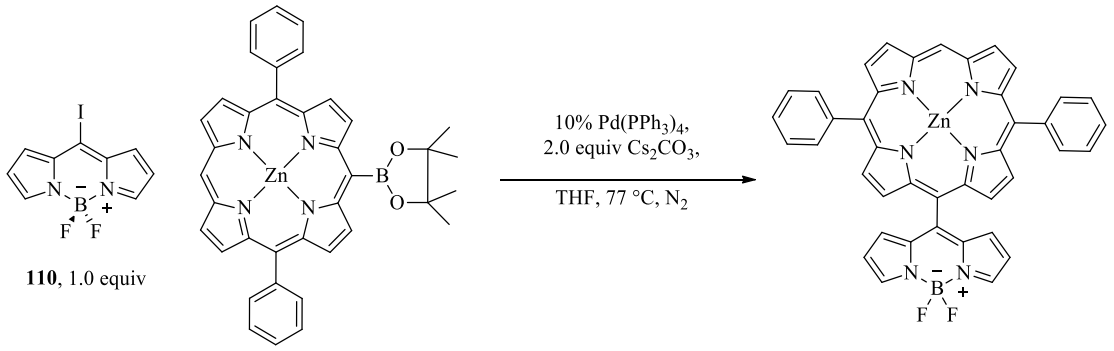


Figure 46. Left: solution of compound **275** in DCM under normal light. Right: solution of compound **275** in DCM under UV light at 365 nm.

Once **110** in hand, we performed the Suzuki coupling of **110** with **261** using reaction conditions as shown in eq 36. However, there was no formation of the desired product **266** and the starting material **110** got consumed in 2 hours.



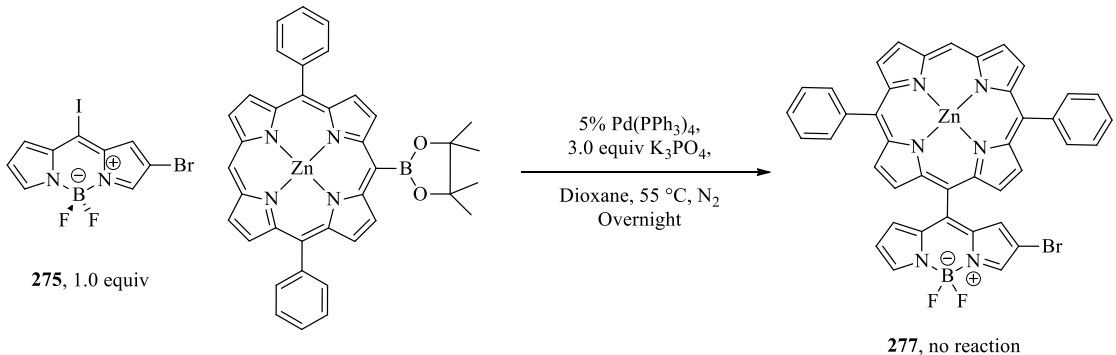
110, 1.0 equiv

261, 1.3 equiv

266, no formation of desired product.

(36)

Further, we performed the Suzuki cross-coupling reaction of **275** and **261** using the catalytic system as shown in eq 37. The reaction did not show formation of the desired product **277** and even after stirring the reaction mixture overnight both the starting materials were still present in the reaction.



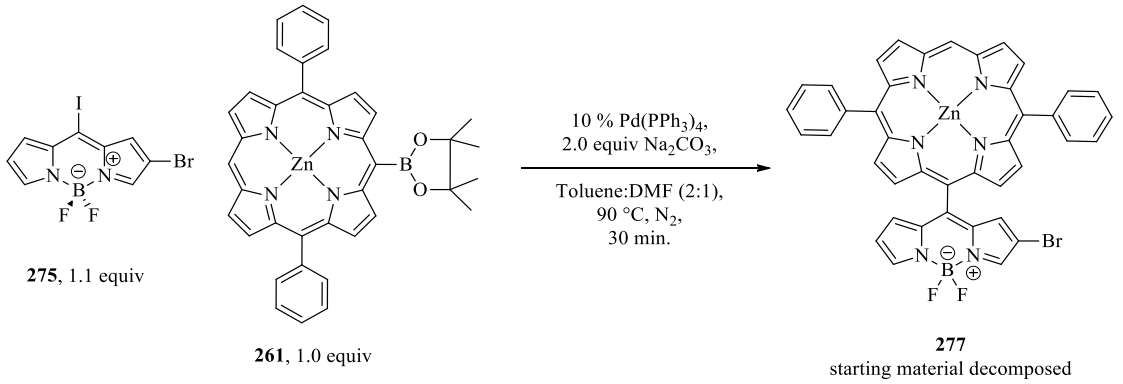
275, 1.0 equiv

261, 1.3 equiv

277, no reaction
both starting materials were still there

(37)

The Suzuki cross-coupling reaction of **275** and **261** using the catalytic system as shown in eq 38 did not show the formation of the desired product **277**. The compound **275** got decomposed in 30 minutes and there was no consumption of **261**. The reaction failed.



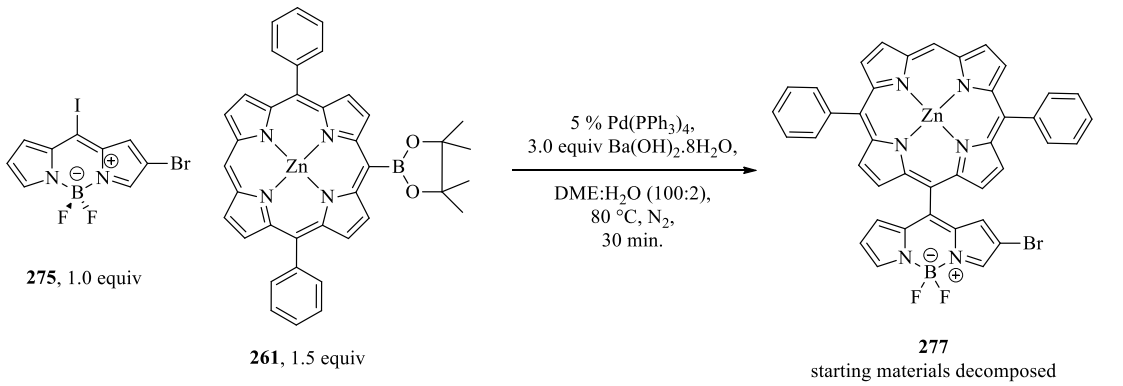
275, 1.1 equiv

261, 1.0 equiv

277
starting material decomposed

(38)

The Suzuki cross-coupling reaction of **275** and **261** using the catalytic system as shown in eq 39 did not show the formation of the desired product **277**. Both the starting materials got decomposed. The reaction failed.



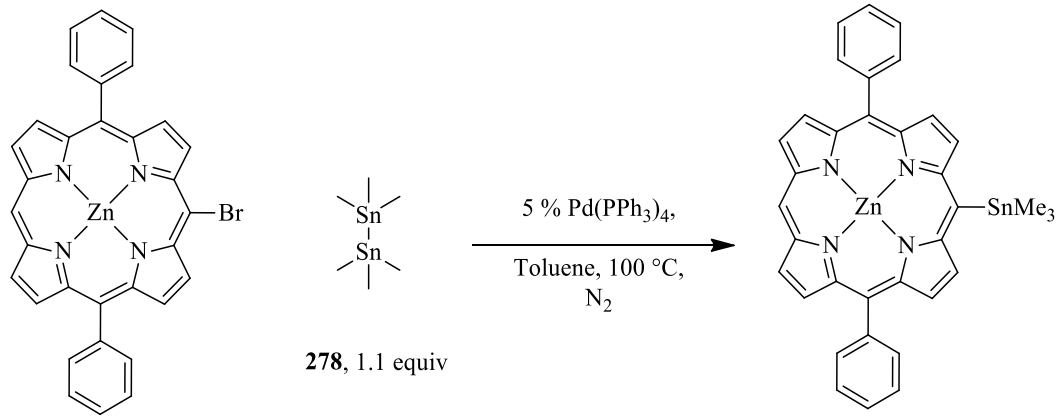
275, 1.0 equiv

261, 1.5 equiv

277
starting materials decomposed

(39)

We also tried to synthesize the tributylstannyl porphyrin **279** as shown in eq 40, from **260** by using 1,1,1,2,2,2-hexamethyldistannane **278**. However, even after 48 hours there was no consumption of starting material **260**, also no formation of the desired product **279**.



260, 1.0 equiv

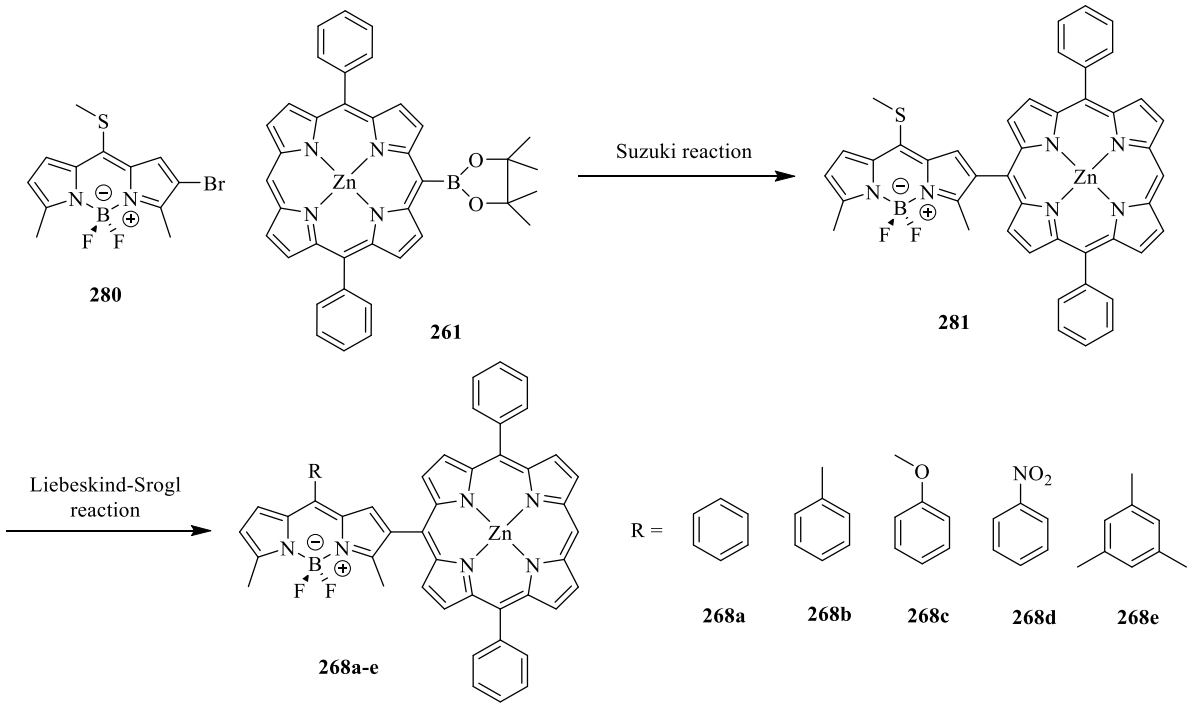
278, 1.1 equiv

279, no reaction

(40)

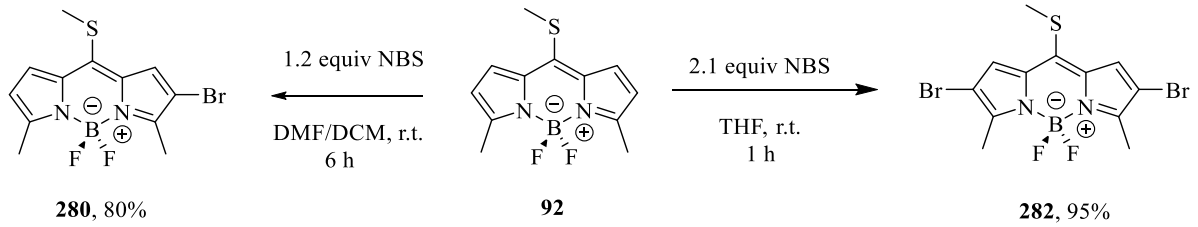
So, after carrying out series of experiments we observed that this strategy was not working as we ended up observing decomposition at the base of the TLC plate and no product formation in some cases. So, we decided to stop working on this strategy and move onto strategy-C.

The strategy C includes two parts. The first part involves the Suzuki coupling of 2-bromo-2,6-dimethyl-8-methylthioBODIPY **280** with the boronic ester of porphyrin **261** to give the *meso*-β linked porphyrin-BODIPY hybrid **281**, which on Liebeskind-Srogl coupling with various boronic acids can give *meso*-β linked porphyrin-BODIPY hybrids **268a-e** (Scheme 51).



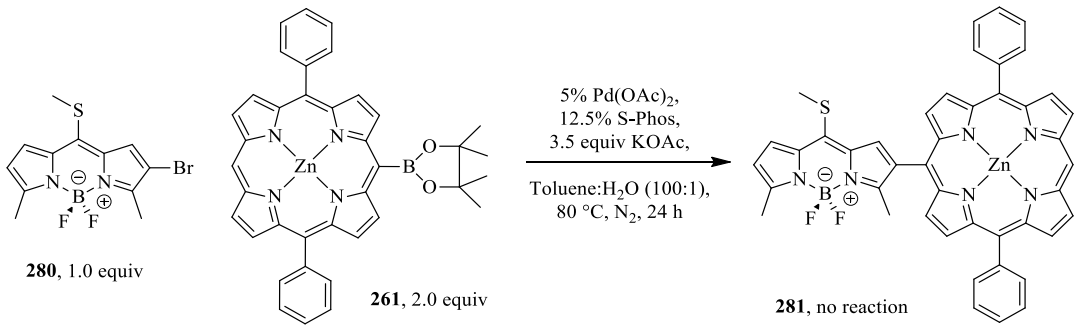
Scheme 51. Synthesis of **268a-e** via Suzuki followed by Liebeskind-Srogl coupling reactions.

For that purpose, we synthesized **280** and **282** from the NBS bromination of 2,6-dimethyl-8-methylthioBODIPY **92** in two different solvent systems in 80% and 95% yields, respectively (Scheme 52).



Scheme 52. Synthesis of **280** and **282** via NBS bromination of **92**.

Then, we carried out the Suzuki coupling reaction of **280** with **261** using the catalytic systems as shown in eq 41. However, even after 24 hours there was no consumption of starting material **280** and also there was no formation of the desired product **281**.



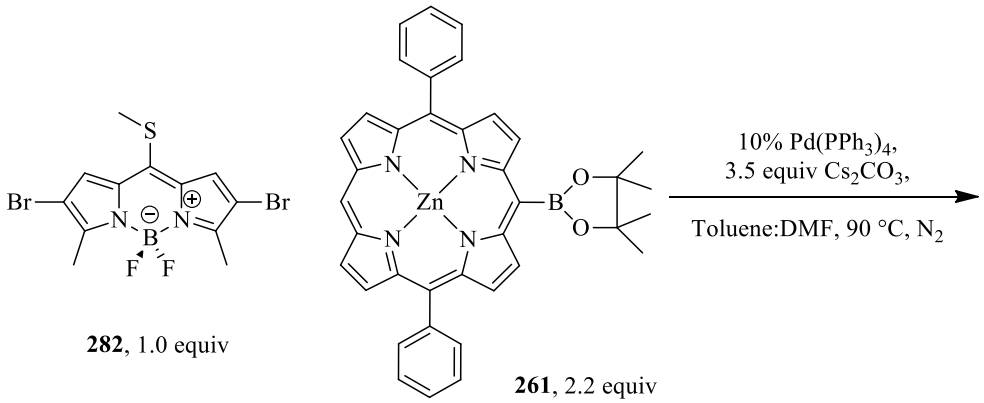
280, 1.0 equiv

261, 2.0 equiv

281, no reaction

(41)

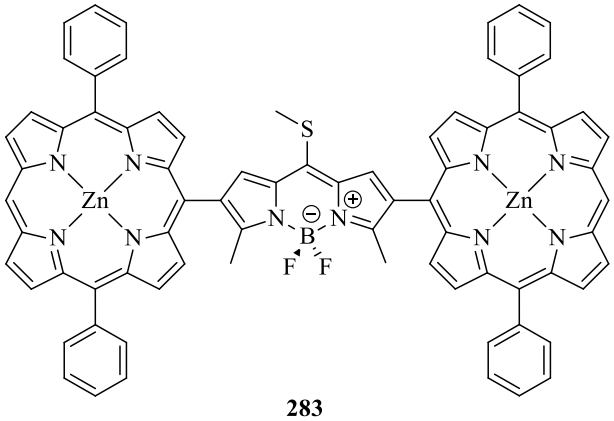
We also carried out the Suzuki coupling reaction between **282** and **261** using the catalytic systems as shown in eq 42. However, after one hour it was seen that the starting material **282** got decomposed and there was no formation of the desired product **283**.



282, 1.0 equiv

261, 2.2 equiv

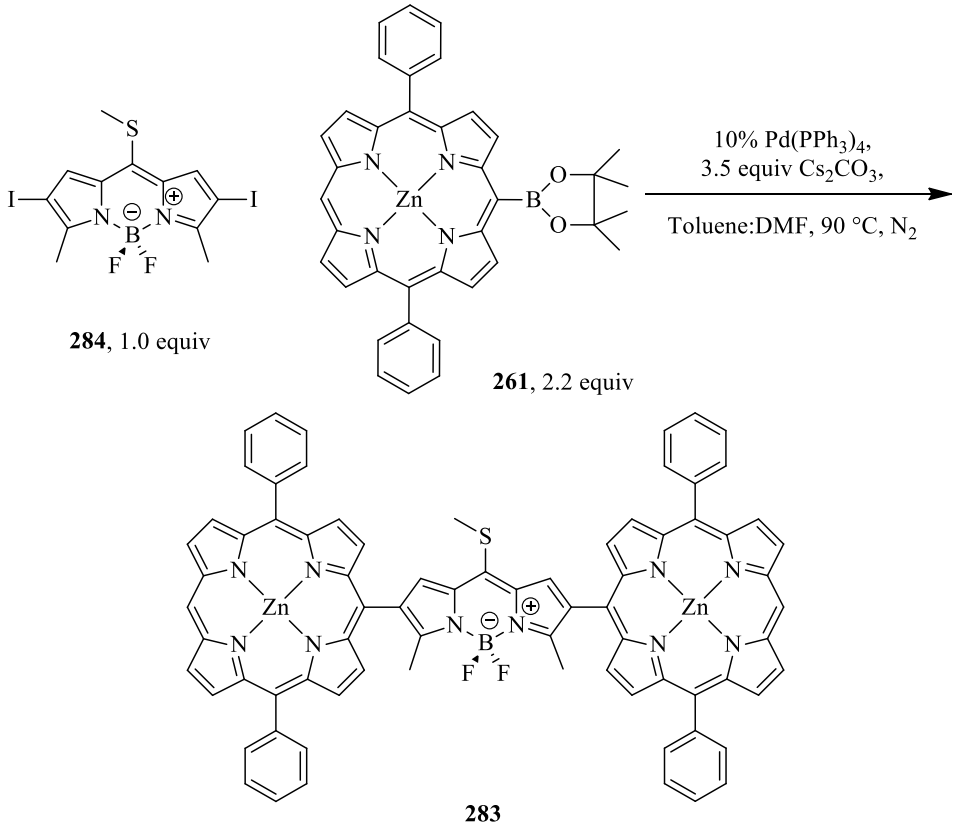
(42)



283

starting material **282** decomposed

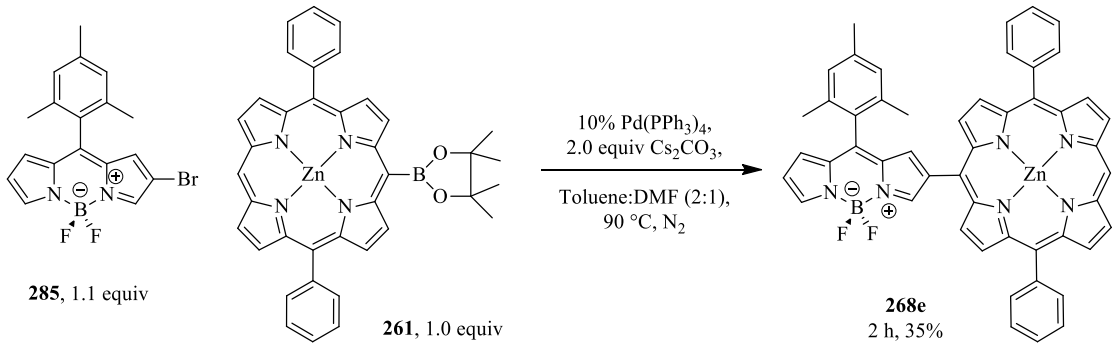
Further, we also performed the Suzuki coupling reaction between **284** and **261** using the catalytic systems as shown in eq 43. However, after 30 minutes it was seen that the starting material **284** got decomposed and there was no formation of the desired product **283**.



(43)

The second part of the strategy C involves the Suzuki coupling of 2-bromo *meso* substituted BODIPY derivatives **267** with the boronic ester of porphyrin **261** to give the *meso*-β linked porphyrin-BODIPY hybrids **268a-e**. The *meso* substituted BODIPYs **36** can be synthesized via Liebeskind-Srogl coupling of 8-methylthioBODIPY **33** with wide range of boronic acids, which on bromination at C-2 position can give 2-bromo *meso* substituted BODIPY derivatives **267**.

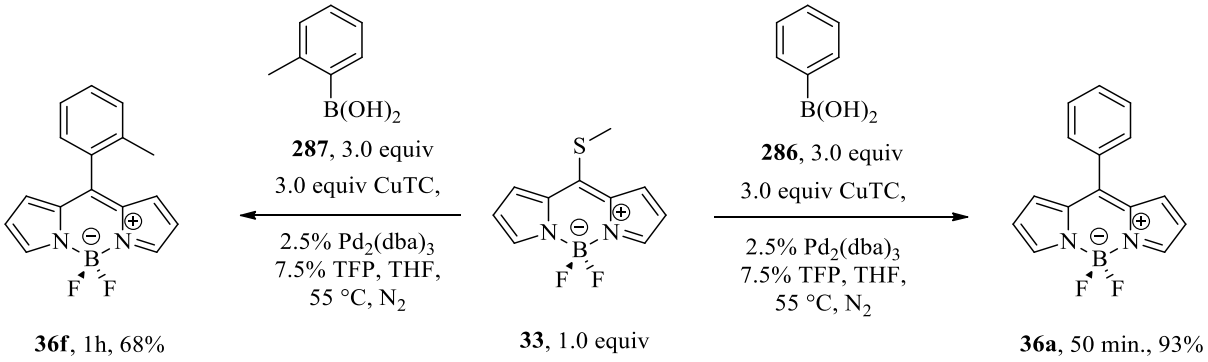
For that purpose, we choose 2-bromo-8-mesityl BODIPY **285**. The Suzuki coupling reaction of **285** with **261** in the presence of catalytic system as shown in eq 44 afforded *meso*-β linked porphyrin-BODIPY hybrid **268e** in 35% yield in two hours.



(44)

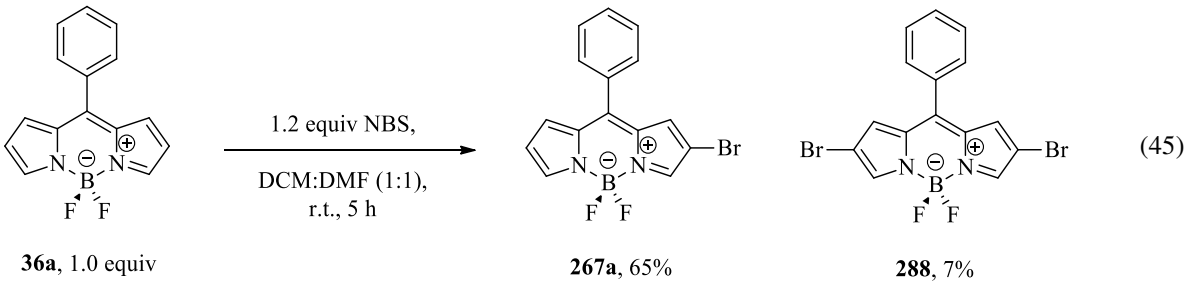
To synthesize more derivatives of **268**, we first synthesized more *meso* substituted BODIPY derivatives such as **36a** and **36f** by carrying out Liebeskind-Srogl coupling reaction of 8-

methylthioBODIPY **33** with phenyl boronic acid **286** and *o*-tolyl boronic acid **287** (Scheme 53).



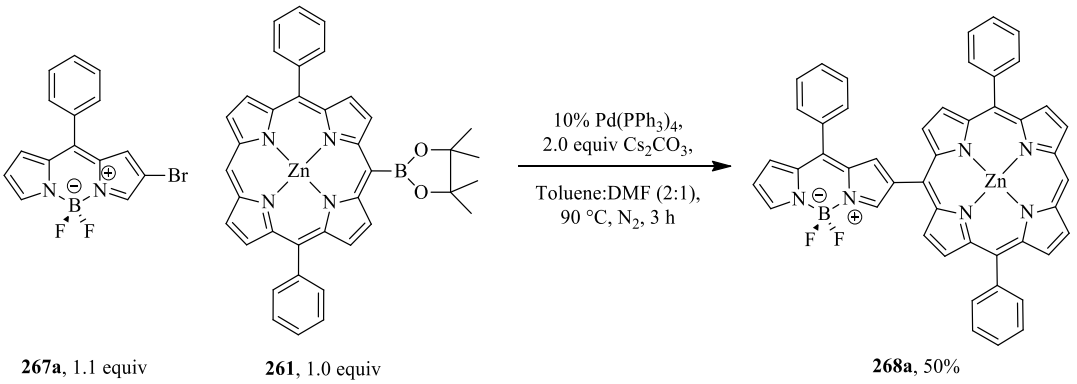
Scheme 53. Synthesis of **36a** and **36f** via Liebeskind-Srogl coupling of **33.**

Further, **36a** on NBS bromination afforded mono brominated product **267a** and dibrominated product **288** in 65% and 7% yields as shown in eq 45.



(45)

Then, the Suzuki coupling reaction of **267a** with **261** in the presence of catalytic system as shown in eq 46 afforded *meso*-β linked porphyrin-BODIPY hybrid **268a** in 50% yield in three hours.



(46)

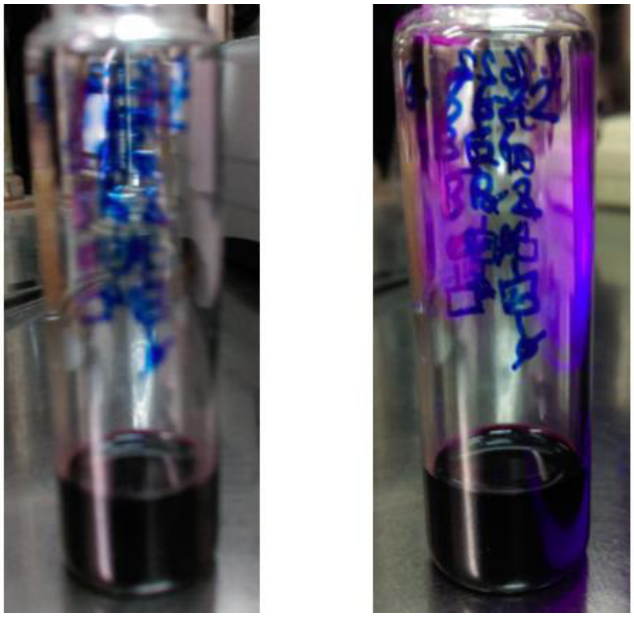


Figure 47. Left: solution of compound **268a** in DCM under normal light. Right: solution of compound **268a** in DCM under UV light at 365 nm.

To synthesize more *meso*-β linked porphyrin-BODIPY hybrids **268**, in future, we will synthesize more *meso* substituted BODIPYs **36** and also 2-bromo *meso* substituted BODIPY derivatives **267**.

3.7 Conclusion.

In strategy A, after a series of failed reactions for the synthesis of porphyrin boronic acid **262**, we concluded that the strategy A is not working for the synthesis of porphyrin-BODIPY hybrids.

In strategy B, a series of optimization reactions were carried out using different reaction conditions, such as, base, solvent system and temperature, in that we observed that during the reaction either starting materials are getting decomposed or there is no reaction at all. Reactions with 8-chloro BODIPY and 8-iodo BODIPY showed the same observations. So, we came to conclusion that the strategy B is not working for the synthesis of porphyrin-BODIPY hybrids.

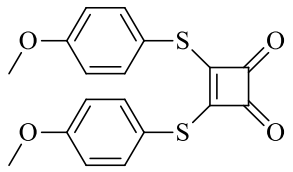
In strategy C, the first part involving Suzuki reaction of **280** and **261** also showed similar observations like, either decomposition of starting materials or no reaction at all. However, second part of strategy-C showed promising results. By using this route of synthesis, we were able to synthesize two different derivatives of *meso*-β linked porphyrin-BODIPY hybrids **268a** and **268e**. In future, we will be focusing on synthesizing such derivatives and study their photophysical properties.

Chapter 4. Experimental section

General: Unless otherwise indicated, all reactions were carried out under a nitrogen atmosphere. The glassware was previously dried with a heating gun and /or oven at 100 °C for 12 hours. The solvents used as reaction medium (THF, dioxane, CH_3CN, DME, BuOH, DMF, toluene, dichloromethane) were dried over a 4 Å molecular mesh under nitrogen atmosphere and deoxygenated before use. The rest of the analytical reagent grade solvents were used as purchased. All reagents were purchased from Sigma Aldrich reagent grade.

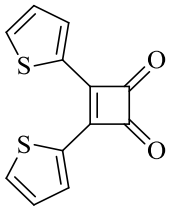
Chromatography: Thin layer chromatography (TLC) was performed on silica gel plates on aluminium support (0.25 mm). Chromatographic columns were run on silica gel (pore 60-200), standard grade (pore 150, 58 Å). Detection was done by UV light (254 or 365 nm).

NMR data: The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on Bruker Advance III HD 400 (^1H, 400 MHz; ^{13}C 100 MHz) or Bruker Ultrashield 500 (^1H, 500 MHz; ^{13}C 125 MHz) spectrometers in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS (0.00 ^1H, 0.00 ^{13}C) or chloroform (7.26 ^1H, 77.16 ^{13}C). The data are reported in the following order: chemical shift in ppm (δ), multiplicity, coupling constant (*J*) and integration. Multiplicities are reported as bs (broad signal), s (singlet), d (doublet), dd (double of doublets), ddd (double of double of doubles), dt (doublet of triplets), or m (multiplet). Coupling constants are reported in Hz. Melting points were determined on an EZ-Melt fusiometer. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR spectrometer (on potassium bromide pellet). The peaks are reported (cm^{-1}) according to their relative intensities as follows: s (strong, 67–100 %), m (medium, 40–67%), and w (weak, 20–40%). High resolution mass spectra (HRMS) were obtained on a MaXis Impact ESI-QTOF-MS equipment (Bruker Daltonics) by electrospray ionization (ESI +) with time of flight (TOF) method.



179

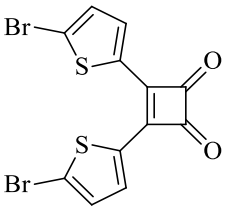
4.1 Synthesis of 3,4-Bis(*p*-methoxythiophenoxy)-3-cyclobutene-1,2-dione 179. To a cool (0 °C) THF (10 mL) solution of dichlorodione **185** (250 mg, 1.6 mmol) was added *p*-methoxythiophenol (0.4 mL, 3.3 mmol) dropwise via syringe under N_2, followed by the addition of triethylamine (0.43 mL, 3.3 mmol). The reaction mixture gradually reached 25 °C and after 3.5 h was quenched with an equivalent volume of aq. NH_4Cl. Then, it was extracted with CH_2Cl_2 (5 × 30 mL), dried (anhyd. $MgSO_4$) and filtered. The solvent was removed in vacuo to give a yellow solid. The remaining solid was triturated in hexanes (5 times) and then dried under vacuum (580.4 mg, 98% yield). For characterization purposes, the product was crystallized from hexanes/EtOAc: TLC (R*f* = 0.3, Silica gel, 30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.94 Hz, 2H), 6.91 (d, *J* = 8.89 Hz, 2H), 3.84 (s, *J* = 1.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 188.2, 186.6, 161.7, 136.3, 115.8, 114.9, 55.6.



188

4.2 Synthesis of 3,4-Bis(thien-2-yl)-3-cyclobuten-1,2-dione 188 using the Liebeskind-Srogl cross-coupling. A 50 mL Schlenk tube under N_2 was charged with **179** (100 mg, 0.28 mmol, 1.0 equiv), 2-thienylboronic acid **187** (142.8 mg, 1.1 mmol, 4.0 equiv), and anhyd THF (10 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. Then, CuTC (266 mg, 1.4 mmol, 5.0 equiv), $Pd_2(dba)_3$ (6.4 mg, 2.5×10^{-3} mmol), and trifurylphosphine (4.9 mg, 7.5×10^{-3} mmol) were added. The reaction mixture was heated at 55 °C for 22 h, the heating bath was removed, and the volatiles were removed in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, 5% ethyl acetate/hexanes gradient) to give the product as a yellow solid (46.7 mg, 68% yield). Recrystallization was carried out by using DCM/cold petroleum ether. Mp = 200-201 °C; TLC (SiO_2, 20% EtOAc/hexanes, *Rf* = 0.4); IR (KBr, cm^{-1}): 3108.4 (w), 3085 (d), 1764 (s), 1567 (s), 1417 (m), 1405 (m); ^1H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, *J* = 3.7 Hz, 2H), 7.96 (d, *J* = 4.9 Hz, 2H), 7.39 (t, *J* = 4.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 173.4, 135.3, 134.1, 129.5, 129.4; HRMS ($C_{12}H_7O_2S_2$, M+1H) calcd. 246.9882, found 246.9883. Along with **188**, the mono-coupled product **197** was isolated (13.0 mg, 15%) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 3.4 Hz, 1H), 7.91 (d, *J* = 5.0 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.35 – 7.33 (t, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H).

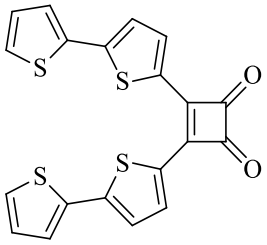
4.3 Synthesis of 3,4-Bis(thien-2-yl)-3-cyclobuten-1,2-dione 188 using the Stille cross-coupling. A 25 mL Schlenk tube was charged with thien-2-yl stannane **191** (309 mg, 0.828 mmol, 2.5 equiv), CH_3CN (3.2 mL), and a stir bar under N_2. The reaction mixture was purged with N_2 during 5 min after which dichlorocyclobutenedione **185** (50 mg, 0.331 mmol, 1 equiv), $PdCl_2[CH_3CN]_2$ (4.3 mg, 0.017 mmol, 5 mol%) and CuI (3.15 mg, 0.017 mmol, 5 mol%) were added. The reaction mixture was heated at 70 °C for 3.5 h then it was allowed to reach rt. Once the reaction mixture reached rt, an abundant yellow precipitate formed. The acetonitrile volume was doubled, and the solid dissolved completely. The acetonitrile layer was extracted with hexanes (3 x 15 mL) to eliminate the tin by-products, then the solvent was evaporated under reduced pressure. The final product was purified by flash chromatography (SiO_2-gel) using an AcOEt/hexanes gradient. The resulting solid was washed with hexanes (3 x 15 mL) and dried under vacuum. The product (30 mg, 37% yield) was obtained as yellow crystalline solid. Mp 200-201 °C.



189

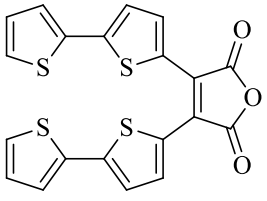
4.4 Synthesis of 3,4-Bis(5-bromothien-2-yl)cyclobut-3-ene-1,2-dione 189. A 50 mL two-neck round bottom flask was charged with **188** (20 mg, 0.0812 mmol, 1.0 equiv.), *N*-

bromosuccinimide (43.36 mg, 0.2436 mmol, 3.0 equiv.), glacial acetic acid (3.0 mL) under N_2. The reaction mixture was stirred at rt for 5 min, then heated at reflux at 95 °C for 1 h, after which it was allowed to reach rt. An abundant yellow solid was observed. A saturated aq NH_4Cl solution was added (4 mL) followed by 0.25M NaOH (4 mL) and stirring continued for 10 min. The yellow solid was filtered using a Whatmann filter paper and washed with 0.1M NaOH (4 x 5 mL) and then with H_2O (2 x 5 mL). The yellow solid was dried under vacuum (31.6 mg, 97% yield). Recrystallization was carried out using DCM/cold petroleum ether. Mp = 192-193 °C; TLC (30% EtOAc/Hexanes, *Rf* = 0.7); IR (KBr, cm^{-1}): 3095 (w), 1786 (s), 1761 (s), 1584 (m), 1411 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 3.8, 2H), 7.35 (d, *J* = 3.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 171.3, 134.5, 132.6, 130.8, 125.0; HRMS ($C_{12}H_5Br_2O_2S_2$, M+1H) calcd. 404.8100, found 404.8071.



192

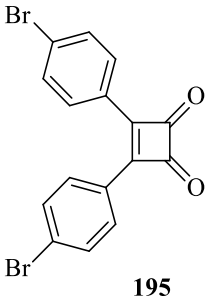
4.5 Synthesis of 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione 192. A 25 mL Schlenk tube under N_2 was charged with **189** (20 mg, 0.0498 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (1.74 mg, 0.0025 mmol, 5 mol%), CuI (0.47 mg, 0.0025 mmol, 5 mol%), CsF (30.24 mg, 0.1991 mmol, 4.0 equiv), DMF (4 mL). The reaction was stirred at rt for 1 min after which 2-(tributylstannyl)thiophene **191** was added (47 mg, 0.1244 mmol, 2.5 equiv). The reaction mixture was stirred at 50 °C for 10 min. After 10 min., the reaction was allowed to reach rt and quenched by adding Et_2O (15 mL) and equal volume of H_2O. The aqueous layer was extracted with Et_2O (5 x 15 mL) and the organic layers were combined and dried over $MgSO_4$. The mixture was filtered through a cotton plug and concentrated under reduced pressure to get a red coloured oily material. After trituration with hexanes, a red solid formed, which was washed further with hexanes (10 x 5 mL) to remove tin impurities. Finally, the material was washed with 2.5% EtOAc/hexanes (5 mL) to give the final product (16.4 mg, 80%). Mp > 196 °C (dec); TLC (30% EtOAc/Hexane, *Rf* = 0.5); IR (KBr, cm^{-1}): 3098 (w), 1756 (s), 1572 (m), 1438 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.1 Hz, 2H), 7.46 (dd, *J* = 3.6, 0.9 Hz, 2H), 7.44 – 7.41 (m, 4H), 7.13 (dd, *J* = 5.1, 3.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 171.2, 147.6, 136.0, 135.1, 128.7, 127.7, 127.6, 126.5, 125.7; HRMS ($C_{20}H_{11}O_2S_4$, M+1H) calcd 410.9636, found 410.9639.



193

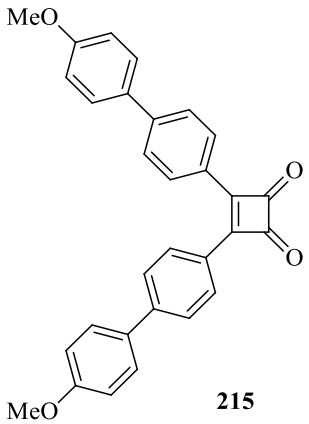
4.6 Synthesis of 2,3-bis(5-[2,2']-bithien-5-yl) maleic anhydride 193. Compound **192** (49 mg, 0.1192 mmol) was dissolved in a 1 :1 AcOEt:DCM mixture (20 mL) in a beaker. The reaction mixture was stirred at rt under air for 5 days, solvent was replenished when necessary, to avoid

dryness. After evaporation of the solvent the dark red coloured compound **193** was obtained (50.9 mg, 100%). Mp = 186-187 °C. TLC (30% EtOAc/Hexane, *Rf* = 0.54); IR (KBr, cm^{-1}): 3108 (d), 1745 (s), 1439 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 4.1 Hz, 2H), 7.34 (dd, *J* = 6.7, 4.4 Hz, 4H), 7.25 (d, *J* = 4.1 Hz, 2H), 7.08 (dd, *J* = 5.0, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 144.7, 136.1, 134.1, 128.5, 127.4, 126.7, 126.8, 125.8, 124.5; HRMS ($C_{20}H_{11}O_3S_4$, M+1H) calcd 426.9600, found 426.9586.



195

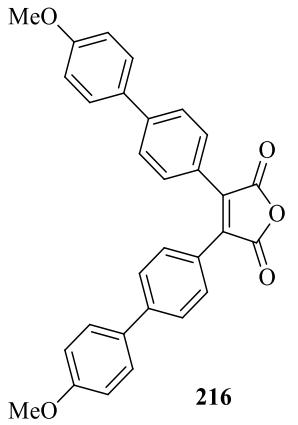
4.7 Synthesis of 3,4-Bis(4-bromo phenyl)-3-cyclobuten-1,2-dione 195. A 50 mL Schlenk tube under N_2 was charged with **179** (100 mg, 0.28 mmol, 1.0 equiv), 4-bromo phenylboronic acid **194** (224.1 mg, 1.1 mmol, 4.0 equiv), and anhyd THF (10 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. Then, CuTC (266 mg, 1.4 mmol, 5.0 equiv), $Pd_2(dba)_3$ (6.4 mg, 2.5×10^{-3} mmol), and trifurylphosphine (4.9 mg, 7.5×10^{-3} mmol) were added. The reaction mixture was heated to 55 °C for 22 h, the heating bath was removed, and the volatiles were eliminated in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, ethyl acetate/hexanes gradient) to give the product as a yellow solid (61.2 mg, 56%). Recrystallization done by using DCM/cold petroleum ether. TLC (30% EtOAc/hexanes, *Rf* = 0.7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.5, 186.3, 133.1, 129.7, 128.6, 126.9. Along with **195**, the mono-coupled product **213** was isolated (9.5 mg, 9%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 2H).



215

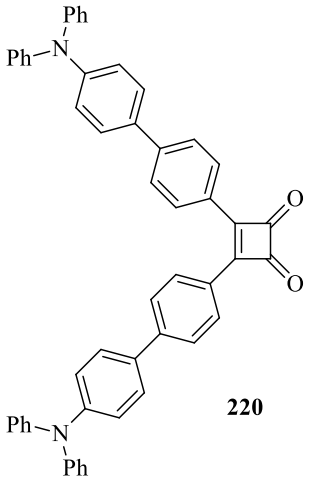
4.8 Synthesis of 3,4-bis(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclobut-3-ene-1,2-dione 215 using Suzuki cross-coupling. A 25 mL Schlenk tube under N_2 was charged with **195** (10 mg, 0.025 mmol, 1.0 equiv), 4-methoxyphenylboronic acid **214** (13.6 mg, 0.089 mmol, 3.5 equiv), K_3PO_4 (24.37 mg, 0.115 mmol, 4.5 equiv), $Pd(OAc)_2$ (0.43 mg, 7.5×10^{-3} mmol), and S-Phos (1.57 mg, 15×10^{-3} mmol) and anhyd toluene (2 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. The reaction mixture was heated at 60 °C for 22 h, the

heating bath was removed, and the volatiles were removed in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, 20% ethyl acetate/hexanes gradient) to give the product as a yellow solid (4.6 mg, 40% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 30% EtOAc/hexanes, *Rf* = 0.36); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4, 4H), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.8 Hz, 4H), 7.03 (d, *J* = 8.8 Hz, 4H), 3.88 (s, 6H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4, 186.3, 160.4, 145.8, 132.1, 129.0, 128.5, 127.4, 126.7, 114.7, 55.6; HRMS ($C_{30}H_{22}O_4$, M+1H) calcd. 446.1522, found 446.1530.



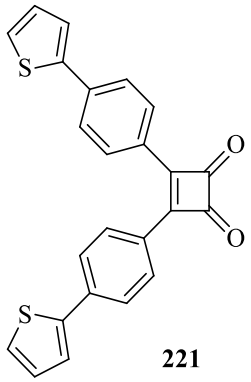
216

4.9 Synthesis of 3,4-bis(4'-methoxy-[1,1'-biphenyl]-4-yl)furan-2,5-dione 216 using Suzuki cross-coupling. A 25 mL Schlenk tube under N_2 was charged with **195** (10 mg, 0.025 mmol, 1.0 equiv), 4-methoxyphenylboronic acid **214** (13.6 mg, 0.089 mmol, 3.5 equiv), K_2CO_3 (15.86 mg, 0.115 mmol, 4.5 equiv), $Pd(OAc)_2$ (0.43 mg, 7.5×10^{-3} mmol), and S-Phos (1.57 mg, 15×10^{-3} mmol) and anhyd toluene (2 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. The reaction mixture was heated at 60 °C for 22 h, the heating bath was removed, and the volatiles were removed in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, 20% ethyl acetate/hexanes gradient) to give the product as a yellow solid (3.6 mg, 31% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 30% EtOAc/hexanes, *Rf* = 0.4); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.1 Hz, 4H), 7.61 (d, *J* = 8.1 Hz, 4H), 7.57 (d, *J* = 8.3 Hz, 4H), 7.00 (d, *J* = 8.3 Hz, 4H), 3.86 (s, 6H). 8.43 (dd, *J* = 3.8, 0.9 Hz, 2H), 7.96 (dd, *J* = 5.0, 0.9 Hz, 2H), 7.39 (dd, *J* = 4.9, 3.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 160.1, 143.6, 137.2, 132.2, 130.4, 128.3, 127.0, 125.7, 114.6, 55.5; HRMS ($C_{30}H_{22}O_4$, M+1H) calcd. 462.1471, found 462.1483.



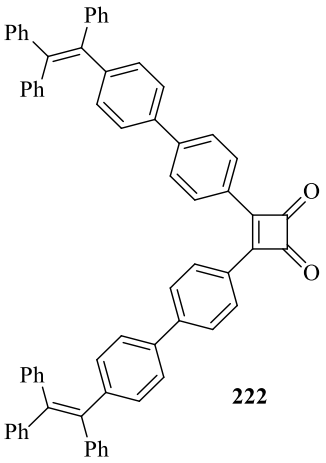
220

Synthesis of 220. Synthetic procedure similar to synthetic procedure of derivative **215**. **195** (10 mg, 0.025 mmol, 1.0 equiv), (4-(diphenylamino)phenyl)boronic acid (25.81 mg, 0.089 mmol, 3.5 equiv), K_3PO_4 (24.37 mg, 0.115 mmol, 4.5 equiv), $Pd(OAc)_2$ (0.43 mg, 7.5×10^{-3} mmol), and S-Phos (1.57 mg, 15×10^{-3} mmol) in anhyd toluene (2 mL). After 2 h the product was purified using 2% ethyl acetate/hexanes gradient, giving **220** as an orange solid (7.3 mg, 40% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 30% EtOAc/hexanes, *Rf* = 0.7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.2 Hz, 4H), 7.76 (d, *J* = 8.2 Hz, 4H), 7.55 (d, *J* = 8.5 Hz, 4H), 7.30 (t, *J* = 7.7 Hz, 8H), 7.16 (d, *J* = 8.0 Hz, 12H), 7.08 (t, *J* = 7.3 Hz, 4H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 185.9, 148.5, 147.3, 145.4, 132.5, 129.4, 128.9, 127.8, 127.0, 126.5, 124.9, 123.5, 123.0; HRMS ($C_{52}H_{36}N_2O_2$, M+1H) calcd. 720.2786, found 720.2779.



221

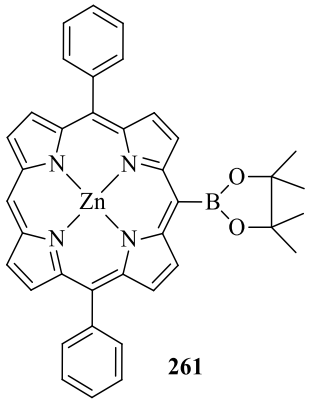
Synthesis of 221. Synthetic procedure similar to synthetic procedure of derivative **215**. **195** (10 mg, 0.025 mmol, 1.0 equiv), 2-thienylboronic acid (11.42 mg, 0.089 mmol, 3.5 equiv), K_3PO_4 (24.37 mg, 0.115 mmol, 4.5 equiv), $Pd(OAc)_2$ (0.43 mg, 7.5×10^{-3} mmol), and S-Phos (1.57 mg, 15×10^{-3} mmol) in anhyd toluene (2 mL). After 2 h the product was purified using 5% ethyl acetate/hexanes gradient, giving **221** as a yellow solid (3.6 mg, 35% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 30% EtOAc/hexanes, *Rf* = 0.6); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 4H), 7.80 (d, *J* = 8.5 Hz, 4H), 7.50 (dd, *J* = 3.6, 0.9 Hz, 2H), 7.42 (dd, *J* = 5.0, 0.9 Hz, 2H), 7.16 (dd, *J* = 5.0, 3.7 Hz, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 185.6, 142.7, 139.1, 129.0, 128.5, 127.0, 126.9, 126.2, 125.0; HRMS ($C_{24}H_{14}O_2S_2$, M+1H) calcd. 398.0442, found 398.0460.



222

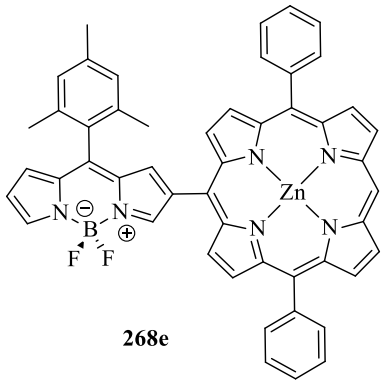
Synthesis of 222. Synthetic procedure similar to synthetic procedure of derivative **215**. **195** (10 mg, 0.025 mmol, 1.0 equiv), (4-(1,2,2-triphenylvinyl)phenyl)boronic acid (33.59 mg, 0.089

mmol, 3.5 equiv), K_3PO_4 (24.37 mg, 0.115 mmol, 4.5 equiv), $Pd(OAc)_2$ (0.43 mg, 7.5×10^{-3} mmol), and S-Phos (1.57 mg, 15×10^{-3} mmol) in anhyd toluene (2 mL). After 2.5 h the product was purified using 5% ethyl acetate/hexanes gradient, giving **222** as a yellow solid (8.2 mg, 36% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 30% EtOAc/hexanes, *Rf* = 0.72); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.3 Hz, 4H), 7.74 (d, *J* = 8.3 Hz, 4H), 7.43 (d, *J* = 8.2 Hz, 4H), 7.15 – 7.03 (m, 34H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 186.3, 145.6, 144.5, 143.7, 143.6, 143.6, 141.9, 140.3, 137.2, 132.2, 131.5, 131.5, 131.4, 128.9, 127.9, 127.9, 127.8, 127.6, 127.0, 126.8, 126.7, 126.7, 126.4; HRMS ($C_{68}H_{46}O_2$, M+1H) calcd. 894.3504, found 894.3524.



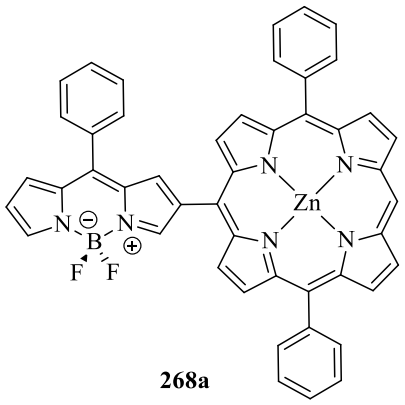
261

4.10 Synthesis of 10,20-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)porphyrinato(2-)zinc 261. 5- Bromo-10,20-diphenylporphyrinato-(2-)zinc (**260**, 20.0 mg, 0.0331 mmol) and $PdCl_2(PPh_3)_2$ (2.32 mg, 0.0031 mmol, 10 mol%) were flushed with nitrogen in a Schlenk tube. Freshly distilled 1,2-dichloroethane (6 mL), triethylamine (33.5 mg, 46.6 µL, 0.3340 mmol) and pinacolborane (42.32 mg, 48 µL, 0.3307 mmol) were added and the mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature, diluted with chloroform (40 mL) and quenched with saturated aqueous sodium chloride solution (20 mL). The organic layer was separated, dried with sodium sulphate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with DCM/hexane (gradient elution, 10-20, *v*/*v*%) as an eluent. **261** was isolated as a violet solid (14.1 mg, 65% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 50% DCM/hexanes, *Rf* = 0.15); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.31 (s, 1H), 9.95 (d, *J* = 4.5 Hz, 2H), 9.42 (d, *J* = 4.2 Hz, 2H), 9.14 (d, *J* = 4.5 Hz, 2H), 9.09 (d, *J* = 4.2 Hz, 2H), 8.25 (d, *J* = 6.9 Hz, 4H), 7.83 – 7.75 (m, 6H), 1.86 (s, 12H); HRMS ($C_{38}H_{31}BN_4O_2Zn$, M+1H) calcd. 650.1835, found 650.1842.



268e

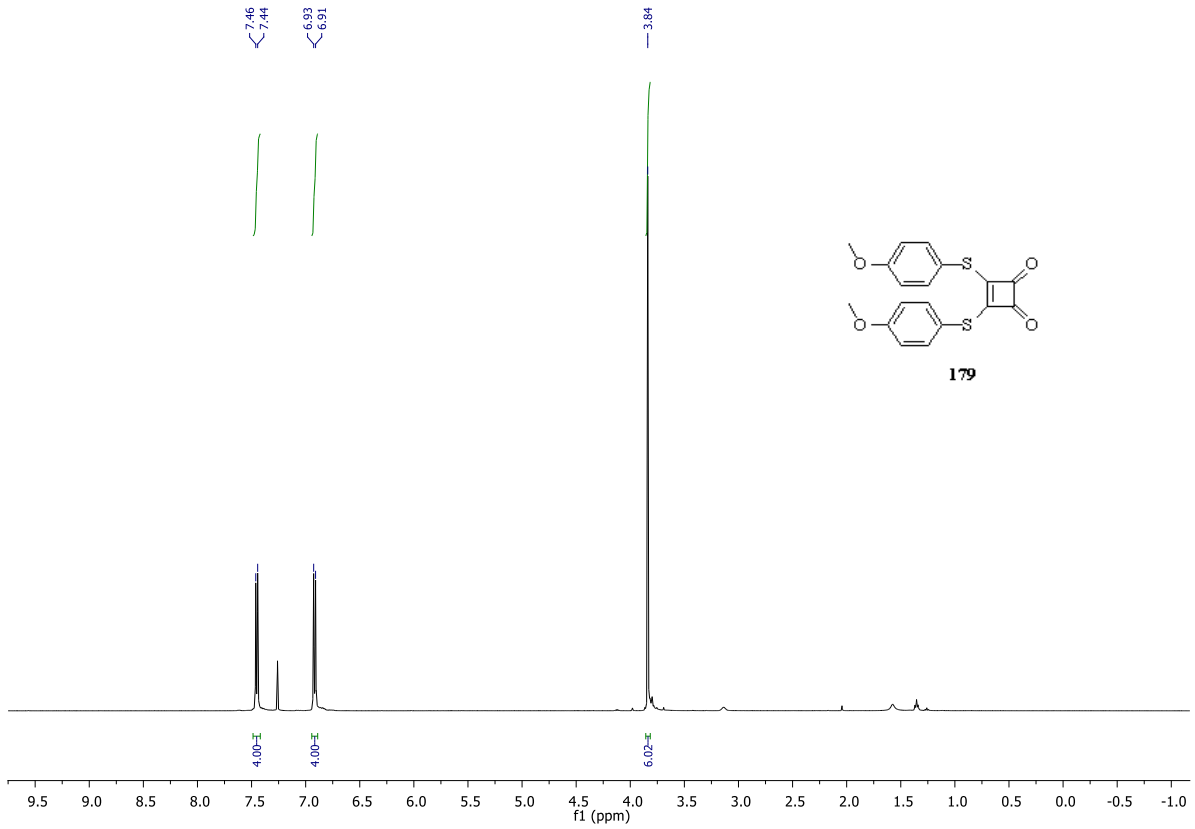
4.11 Synthesis of *meso*-β linked porphyrin-BODIPY hybrid 268e. 2-bromo-8-mesityl BODIPY (**285**, 13.13 mg, 0.0337 mmol), 10,20-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)porphyrinato(2-)zinc (**261**, 20.0 mg, 0.0307 mmol), $Pd(PPh_3)_4$ (3.55 mg, 0.0031 mmol, 10 mol%) and Cs_2CO_3 (20.0 mg, 0.0614 mmol) were flushed with nitrogen in Schlenk tube. Freshly distilled dry toluene (2mL) and dry DMF (1 mL) were added, and the mixture was heated at 90 °C for 2 h. The reaction mixture was allowed to cool to room temperature and quenched with water (10 mL) and extracted with diethyl ether (10 mL). The organic layer was separated, dried with sodium sulphate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with DCM/hexane (gradient elution, 40-50, *v*/*v*%) as an eluent. **266e** was isolated as a dark violet solid (8.9 mg, 35% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 50% DCM/hexanes, *Rf* = 0.2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 1H), 9.32 (d, *J* = 4.3 Hz, 2H), 9.24 (d, *J* = 4.5 Hz, 2H), 9.03 (t, *J* = 4.7 Hz, 4H), 8.71 (s, 1H), 8.21 (d, *J* = 6.5 Hz, 4H), 8.11 (s, 1H), 7.84 – 7.74 (m, 6H), 7.43 (s, 1H), 6.99 (s, 2H), 6.88 (d, *J* = 3.6 Hz, 1H), 6.63 (s, 1H), 2.41 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 150.2, 149.9, 149.5, 148.8, 147.2, 144.7, 142.5, 139.0, 136.4, 136.2, 135.2, 134.5, 132.7, 132.3, 131.8, 131.1, 130.4, 129.8, 128.3, 127.6, 126.6, 126.5, 120.8, 118.9, 118.6, 112.2, 106.1, 21.0, 20.3; HRMS ($C_{50}H_{35}BF_2N_6Zn$, M+1H) calcd. 832.2280, found 832.2275.



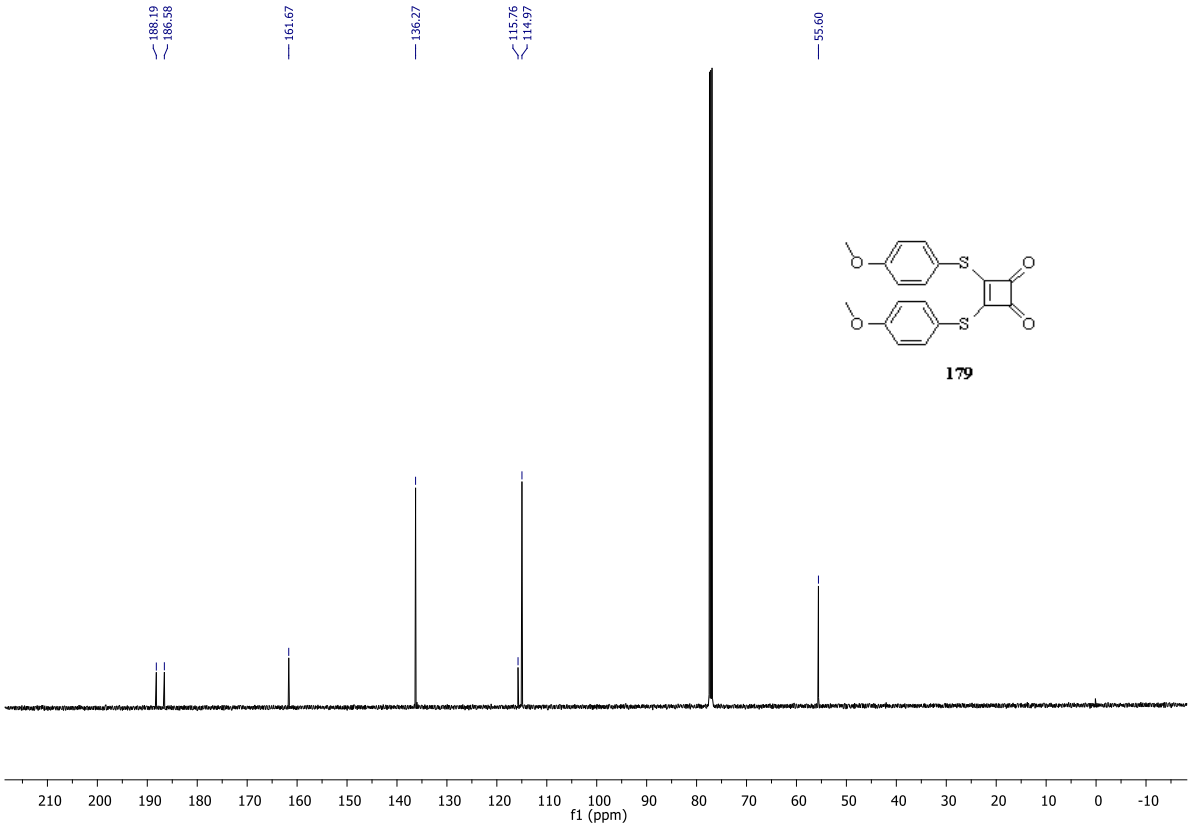
268a

Synthesis of 268a. Synthetic procedure similar to synthetic procedure of derivative **268e**. 2-bromo-8-phenyl BODIPY (**267a**, 11.71 mg, 0.0337 mmol, 1.1 equiv), 10,20-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)porphyrinato(2-)zinc (**261**, 20.0 mg, 0.0307 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (3.55 mg, 0.0031 mmol, 10 mol%) and Cs_2CO_3 (20.0 mg, 0.0614 mmol, 2.0 equiv) in dry toluene (2mL) and dry DMF (1 mL). After 3 h the product was purified by using 5% ethyl acetate/hexanes gradient, giving **268a** as a dark violet solid (12.2 mg, 50% yield). Recrystallization was carried out by using DCM/cold petroleum ether. TLC (SiO_2, 10% EtOAc/hexanes, *Rf* = 0.23); ^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.19 (s, 1H), 9.35 (d, *J* = 4.4 Hz, 2H), 9.27 (d, *J* = 4.6 Hz, 2H), 9.04 (dd, *J* = 14.4, 4.5 Hz, 4H), 8.73 (s, 1H), 8.22 (d, *J* = 6.3 Hz, 4H), 8.14 (s, 1H), 7.85 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.82 – 7.74 (m, 6H), 7.70 (s, 1H), 7.55 (d, *J* = 6.8 Hz, 3H), 7.13 (d, *J* = 3.9 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.28, 150.25, 149.94, 149.59, 148.55, 147.05, 144.55, 142.54, 135.82, 135.35, 135.33, 134.80, 134.55, 134.00, 133.93, 132.73 132.33, 131.89, 131.21, 130.92, 130.72, 128.64, 127.59, 126.65, 120.90, 118.94, 112.11, 106.23.

Annex-A: ^{1}H and ^{13}C NMR spectra of compounds from chapter-2 and 3.



179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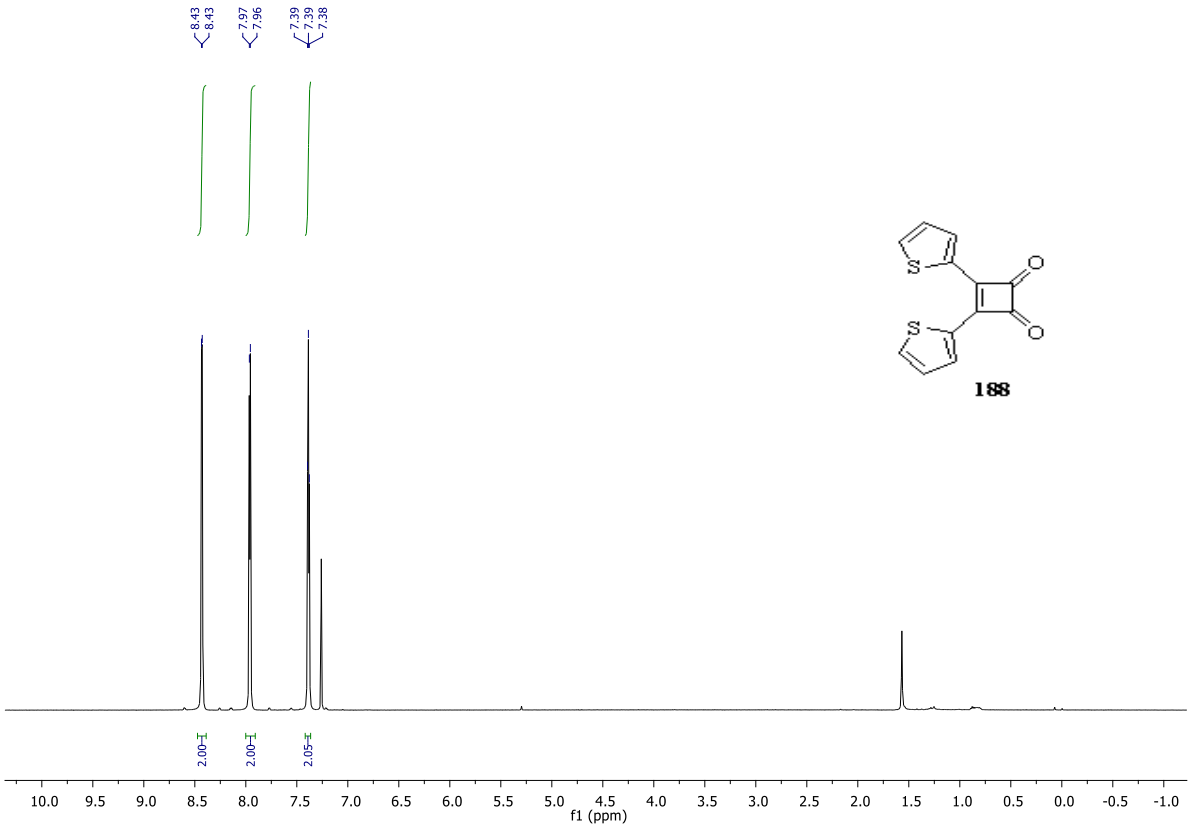
161.67
136.27
115.76
114.97
55.60
f1 (ppm)

179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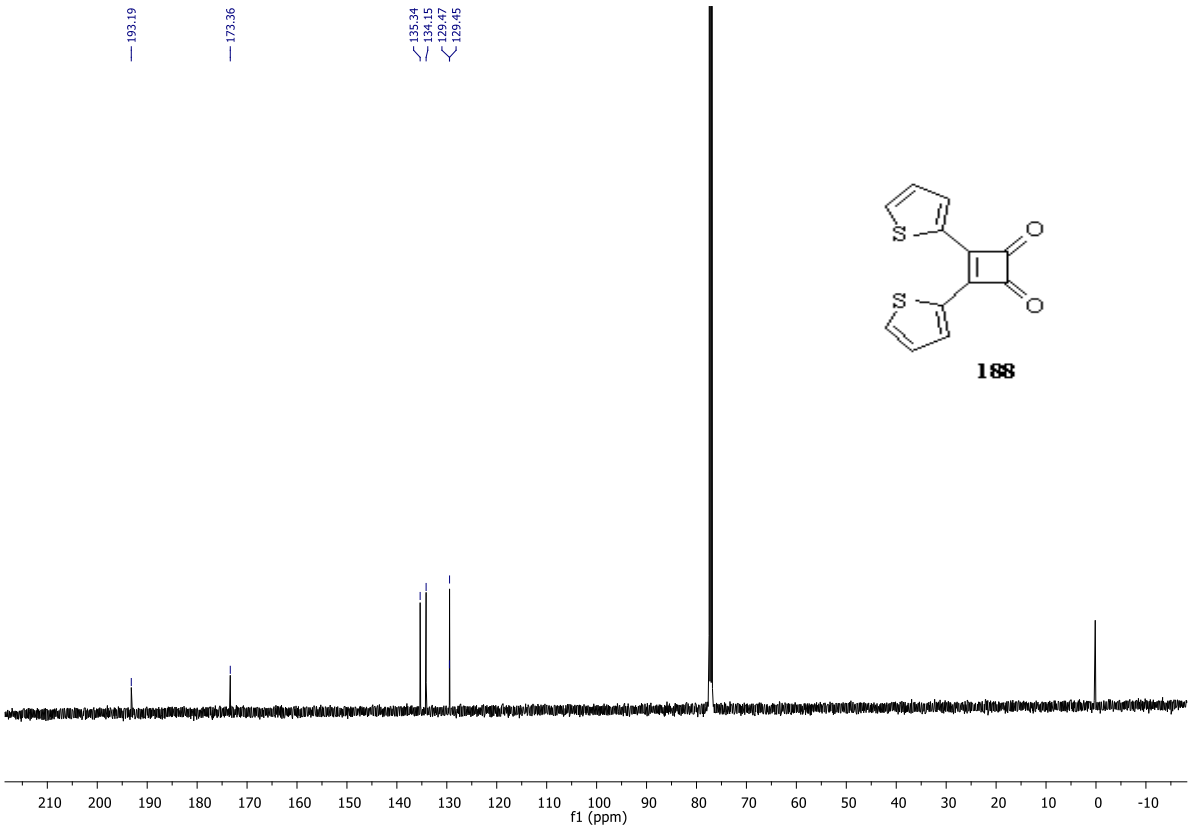
8.43
7.97
7.96
7.39
7.39
7.38
2.00
2.00
2.05
f1 (ppm)

188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134.15
129.47
129.45
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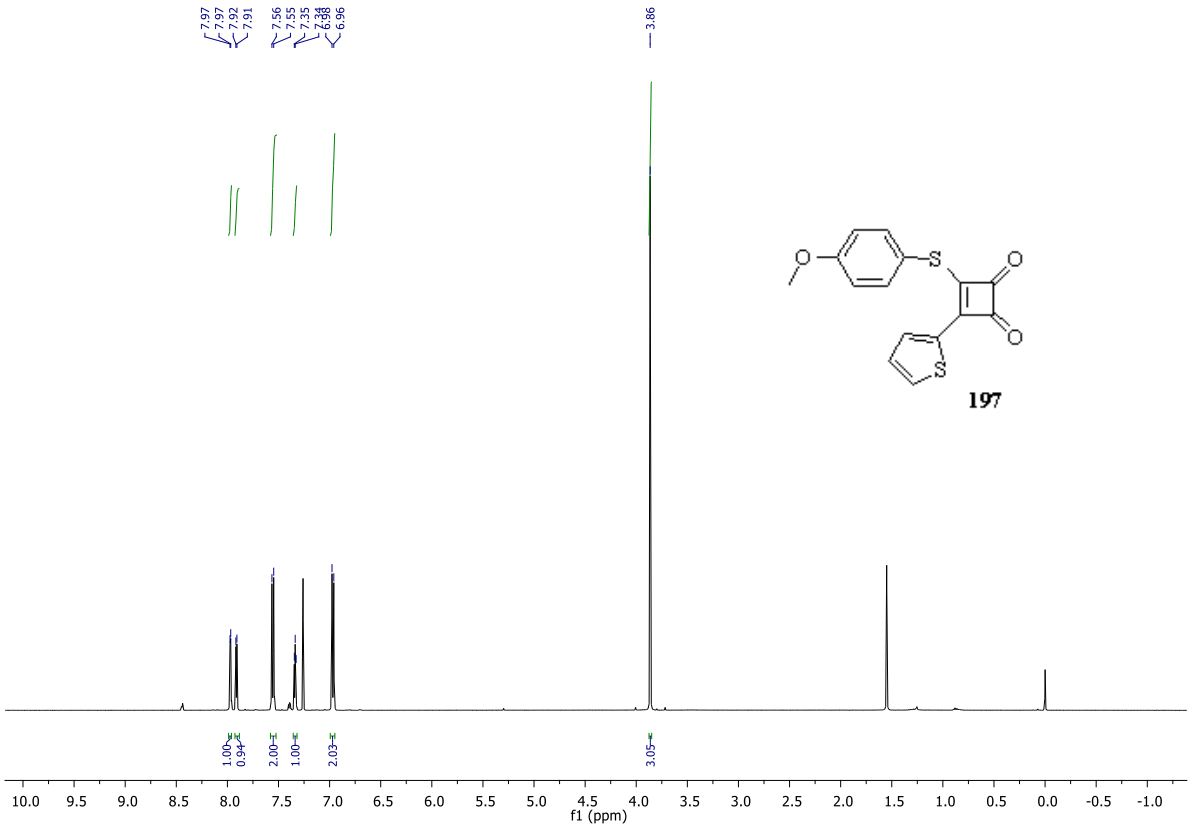
188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7.91
7.56
7.55
7.35
7.34
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6.96
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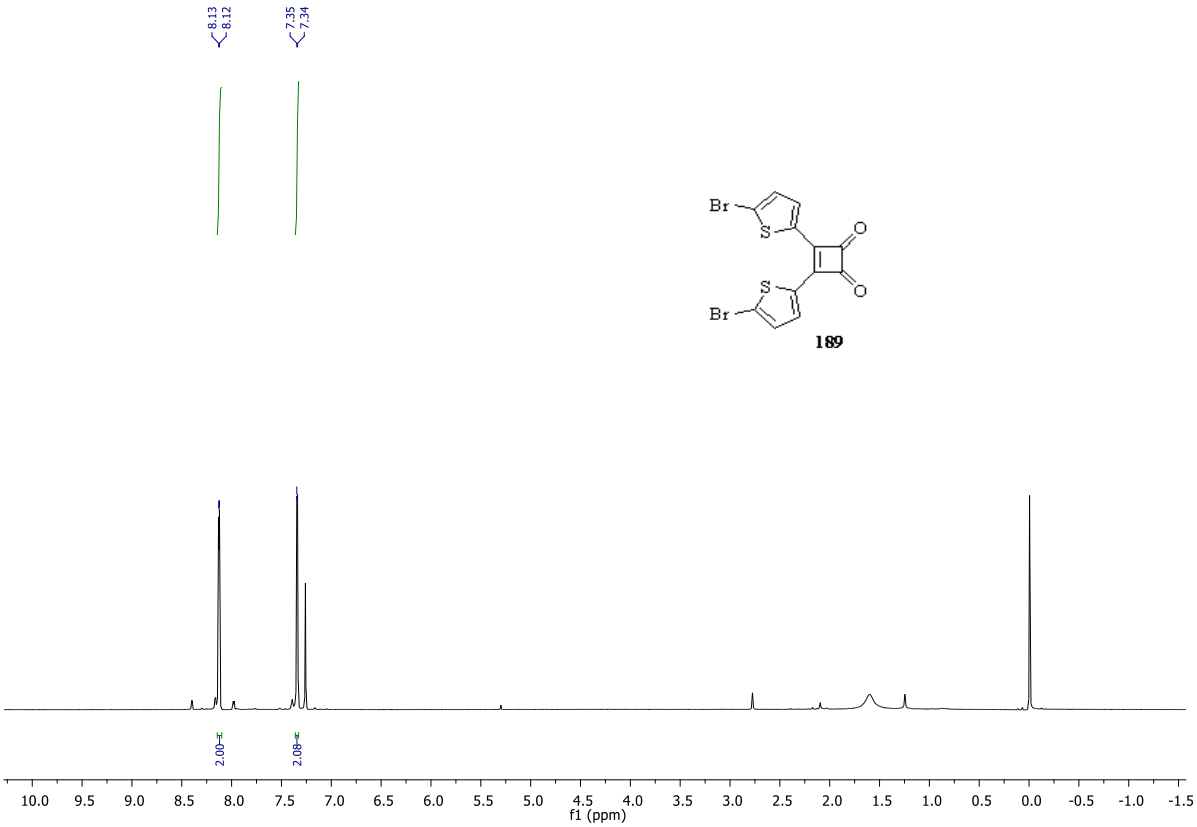
1.00
0.94
2.00
1.00
2.03
3.05
f1 (ppm)

197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7.34
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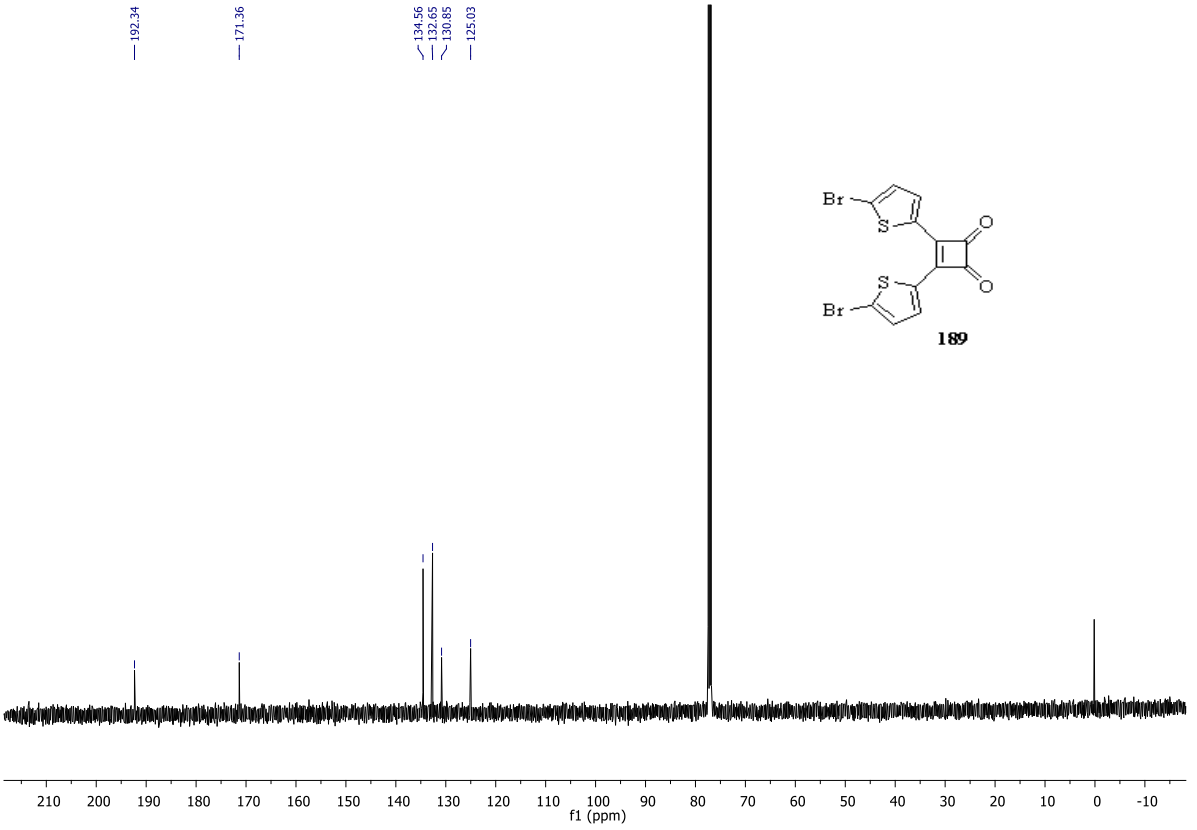
S
S
Br
O
O
189
2.00
2.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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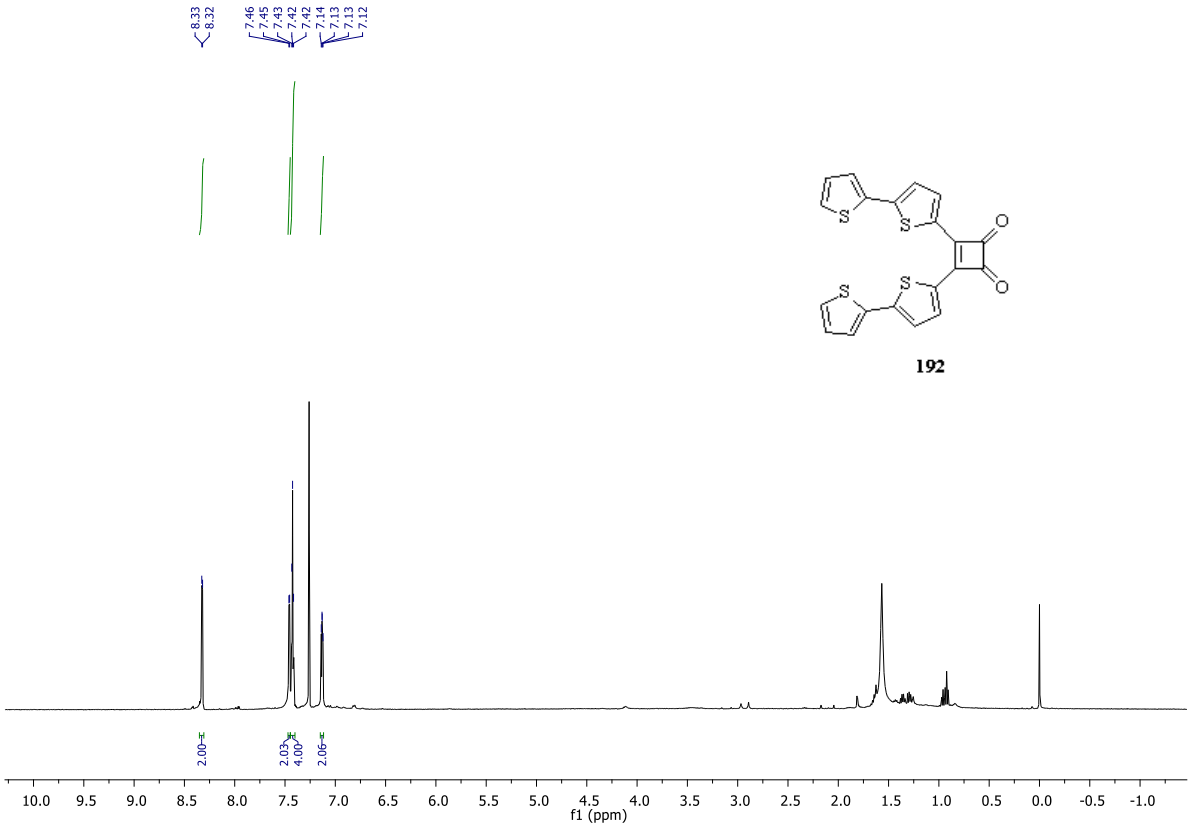
132.65
130.85
125.03
Br
S
S
Br
O
O
189
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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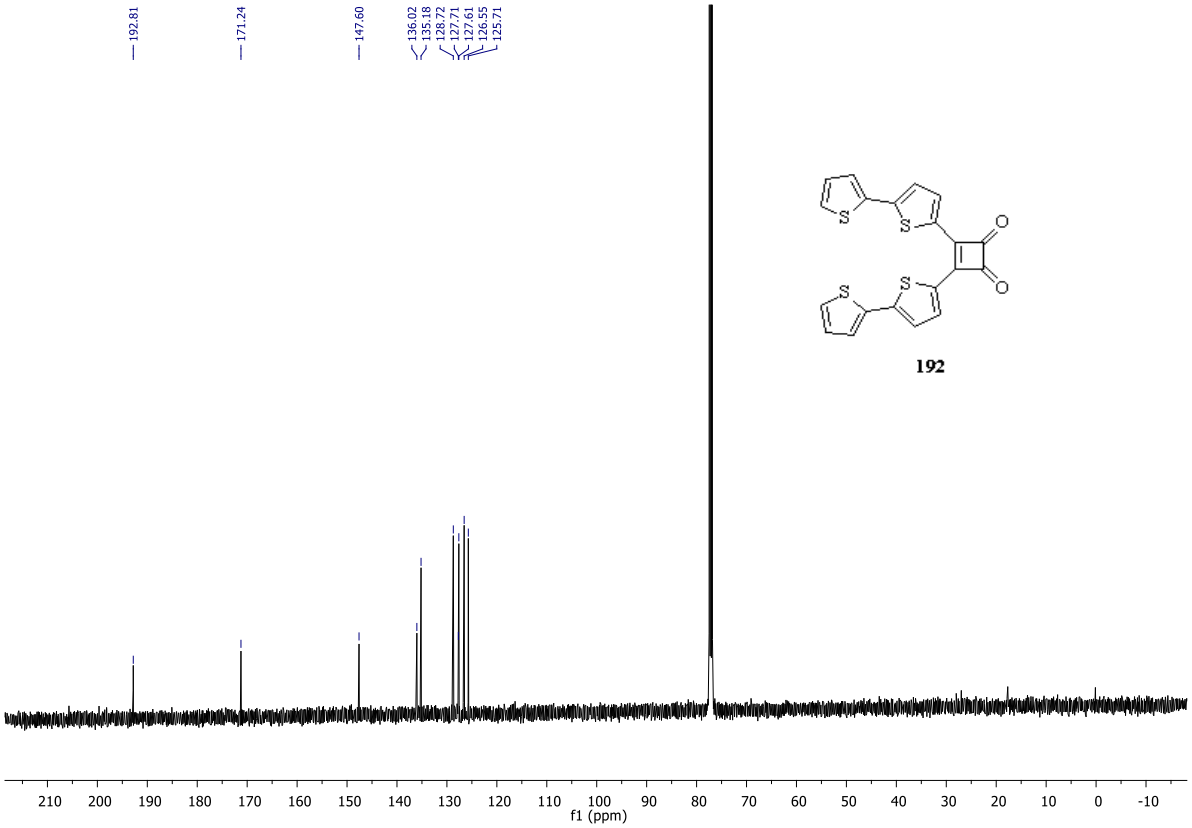
7.45
7.43
7.42
7.42
7.14
7.13
7.13
7.12
2.00
2.03
4.00
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

192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147.60
136.02
135.18
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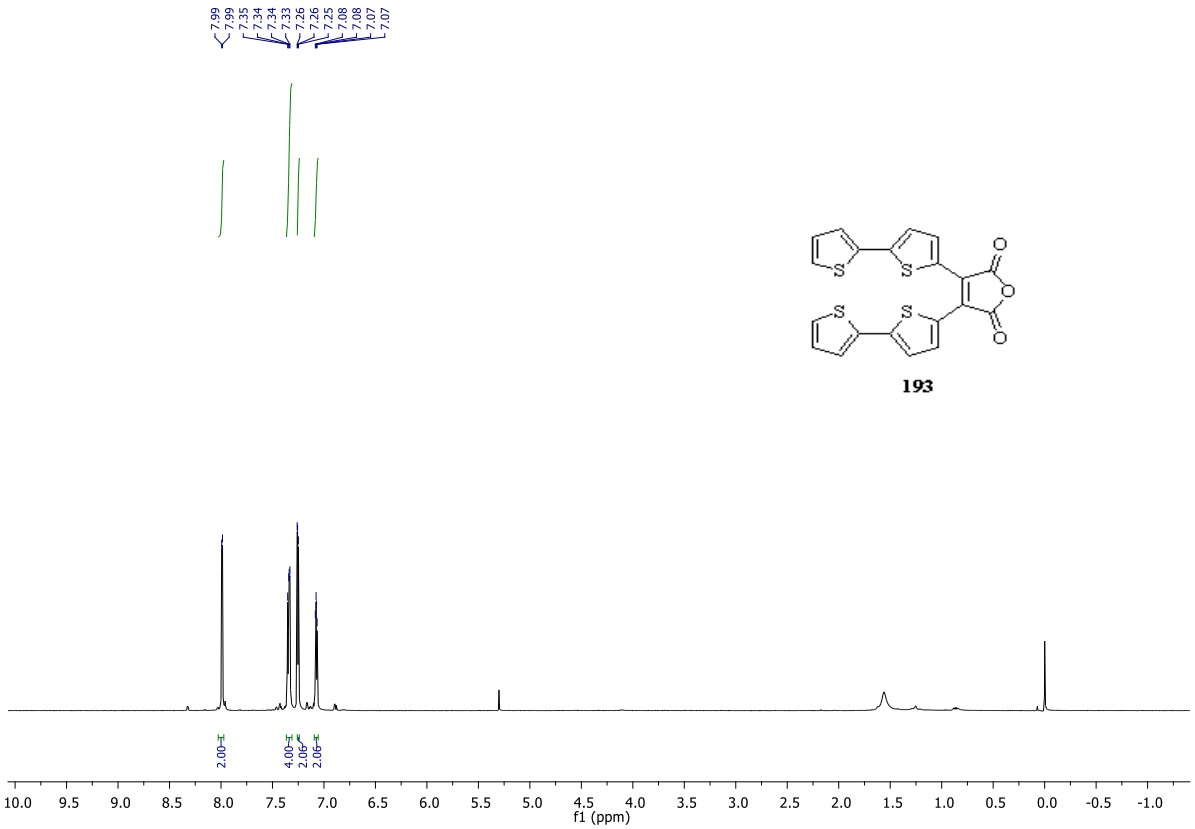
127.71
127.61
126.55
125.71
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

192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7.34
7.34
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7.26
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7.08
7.08
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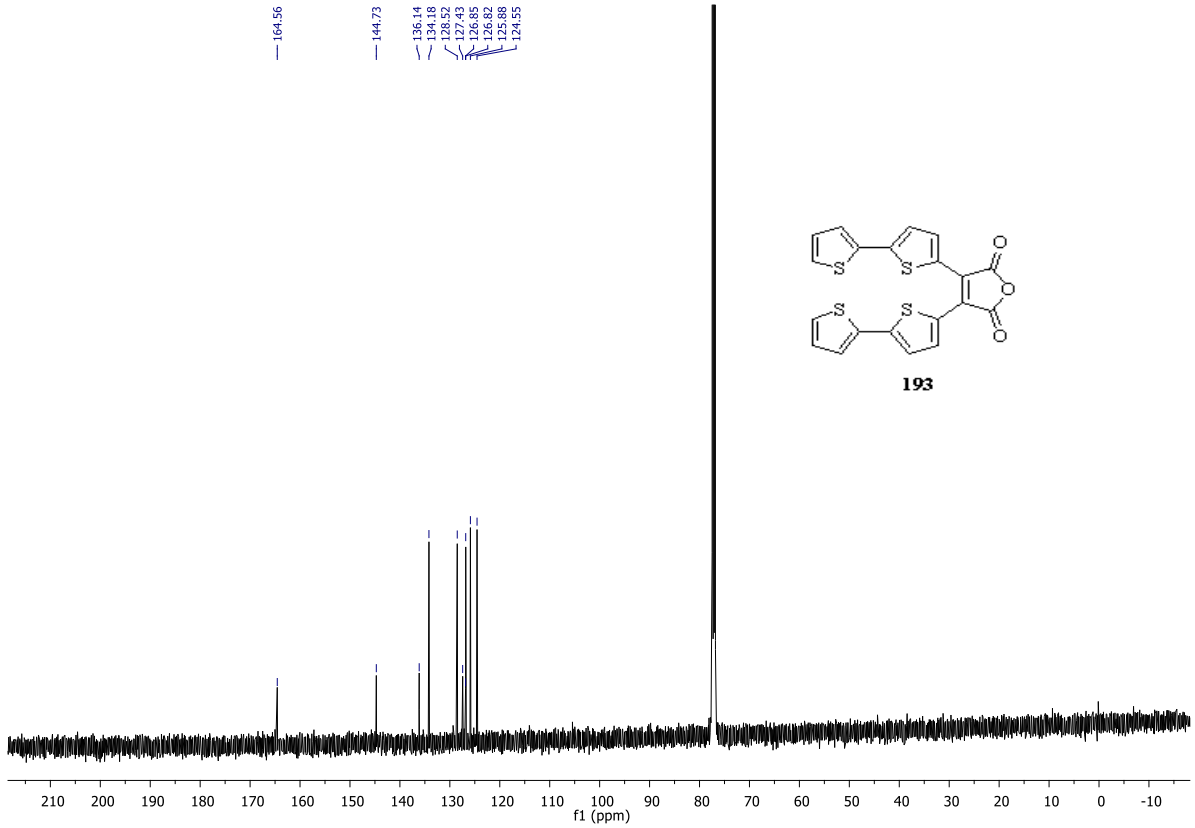
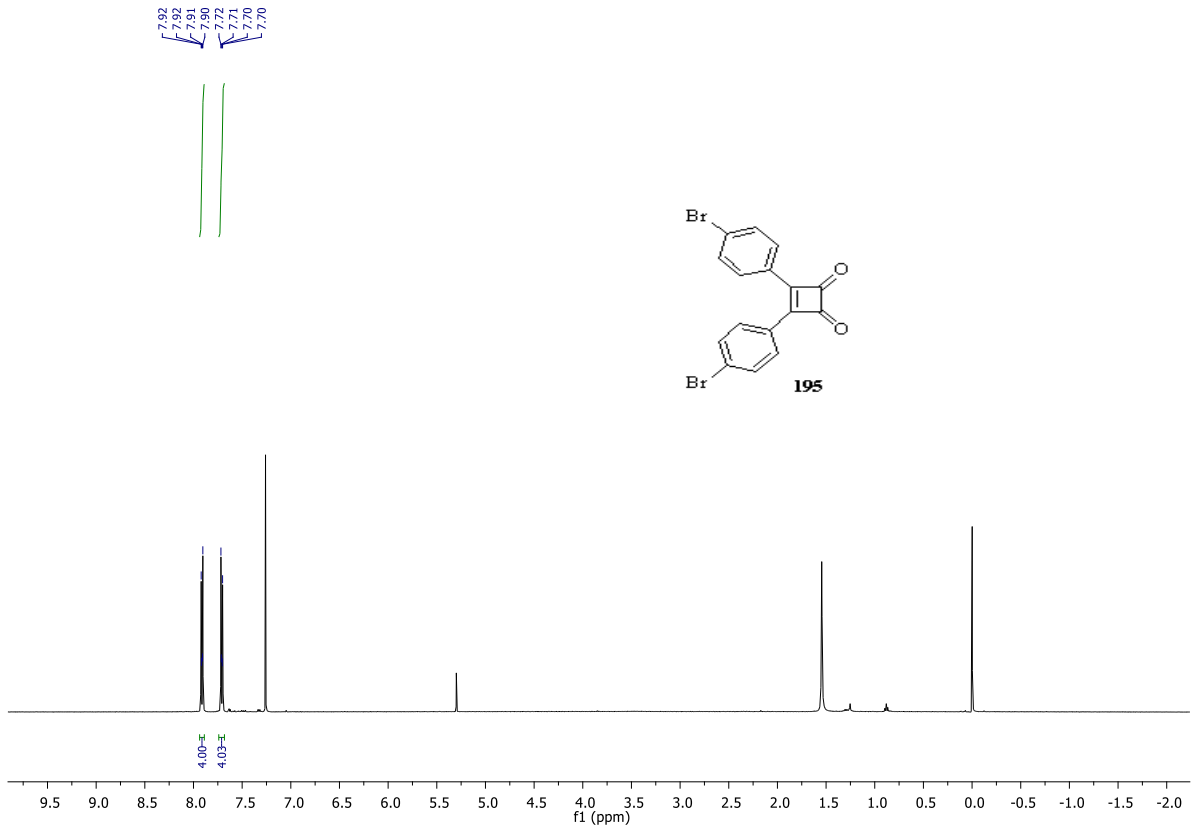
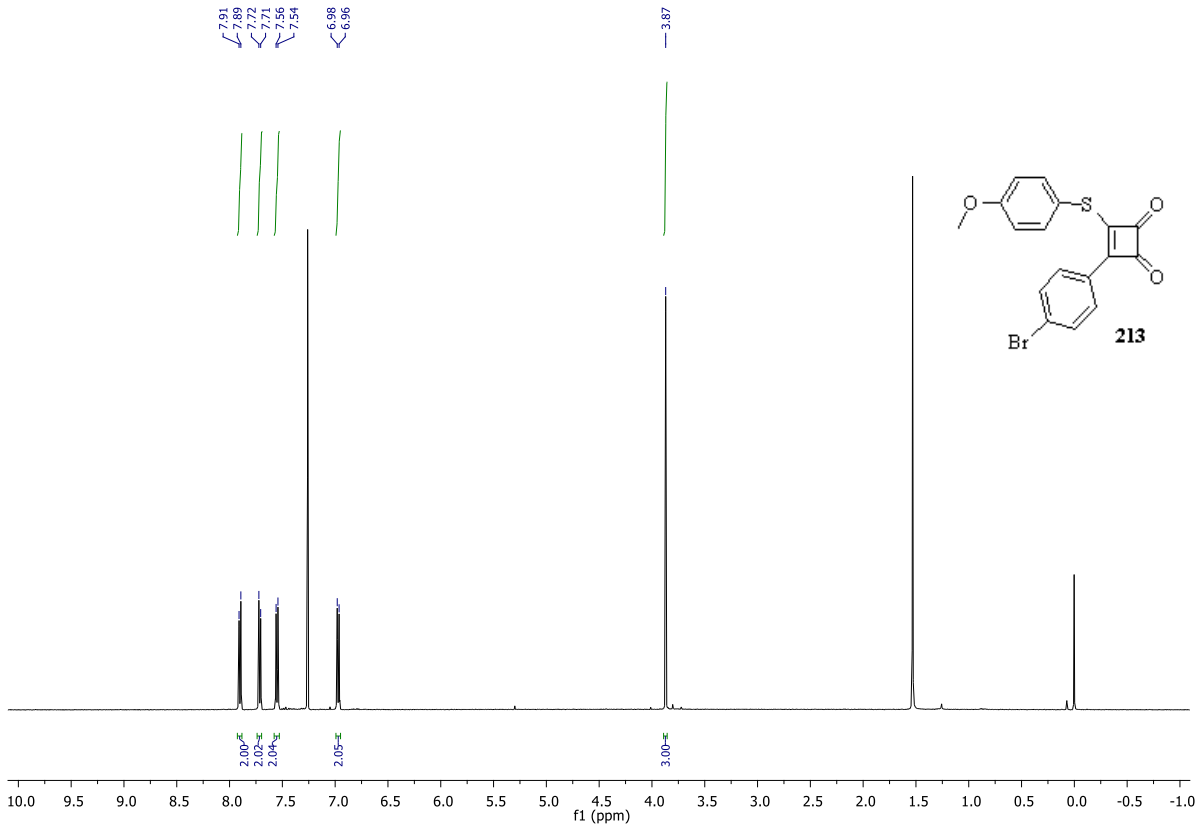
7.07
2.00
4.00
2.06
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

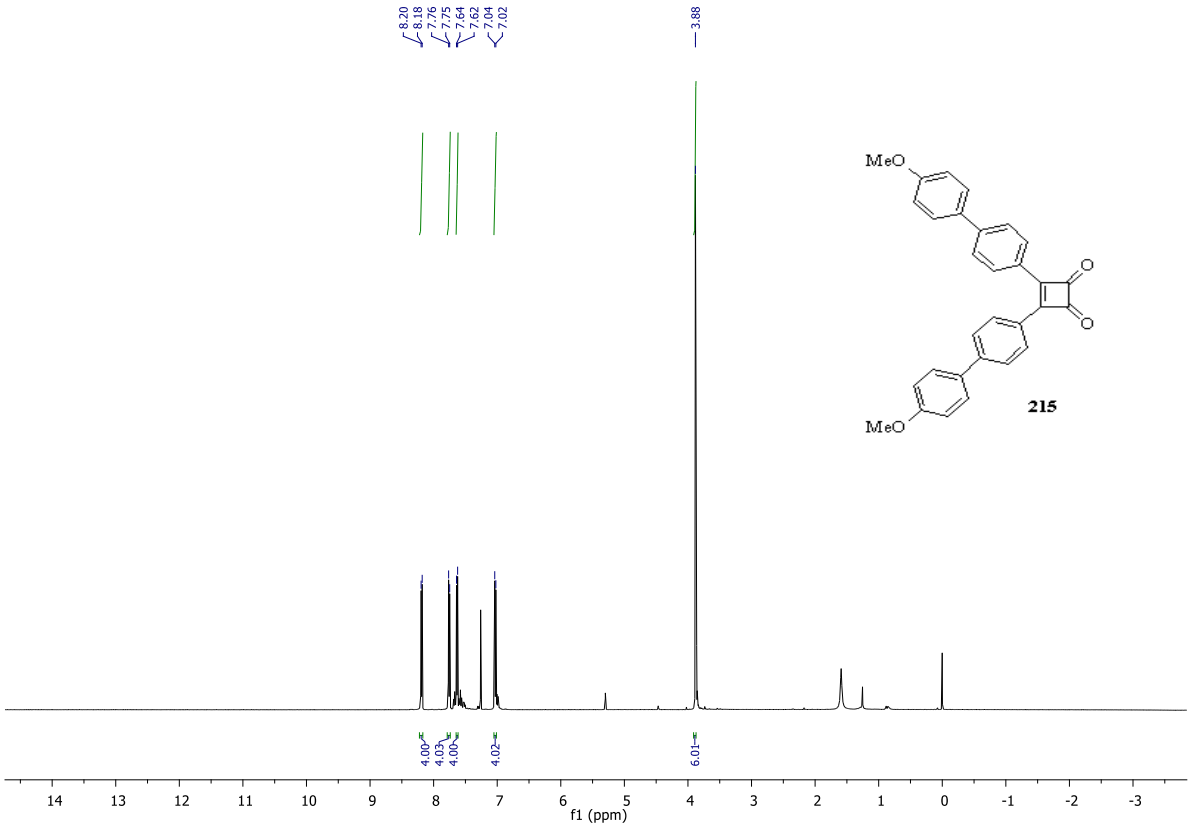
193

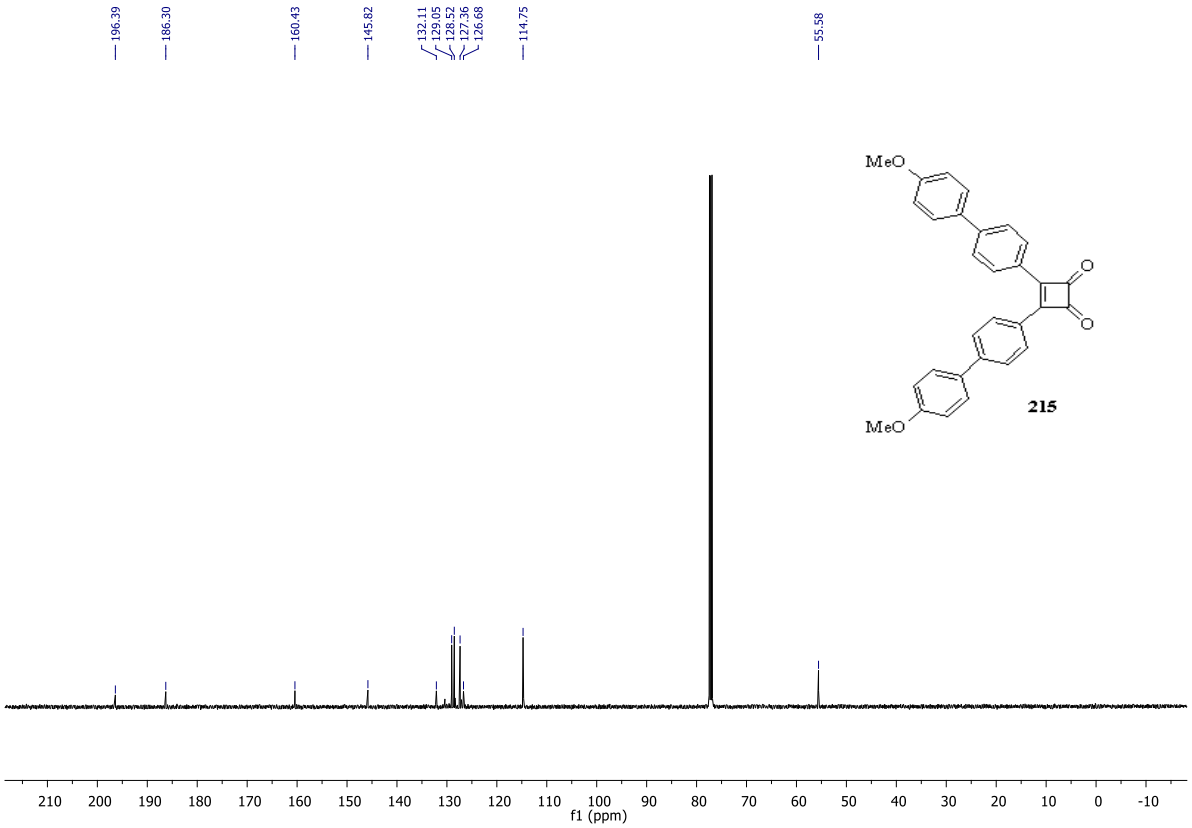

164.56
144.73
136.14
134.18
128.52
127.43
126.85
126.82
125.88
124.55
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

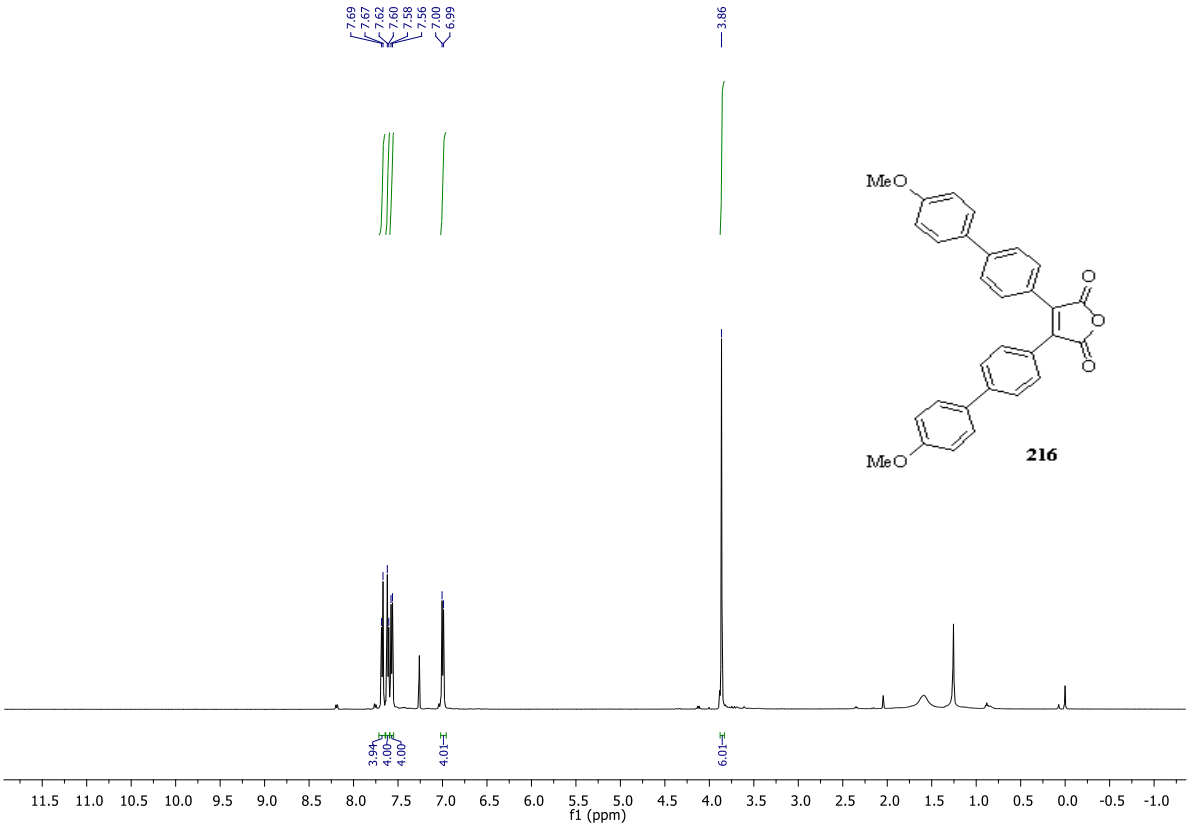
193

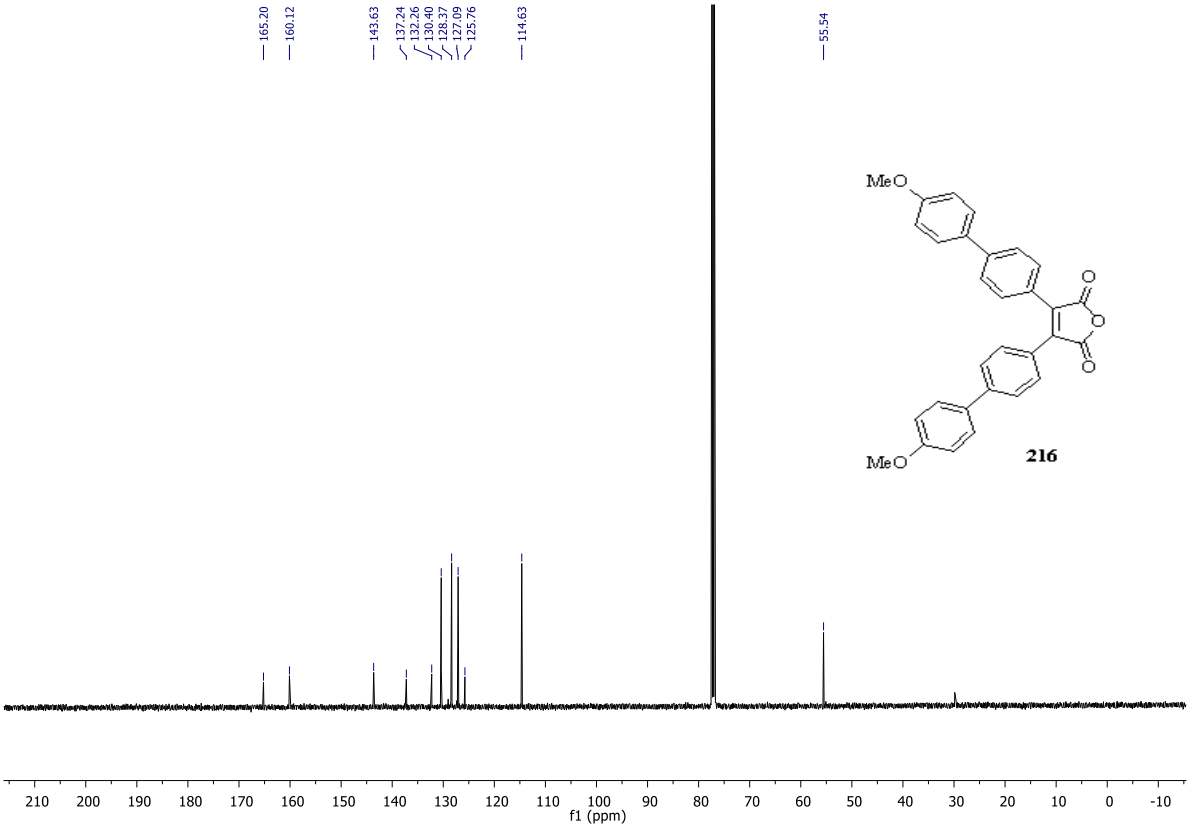

7.92
7.92
7.91
7.90
7.72
7.71
7.70
7.70
Br
O
O
Br
195
4.00
4.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)

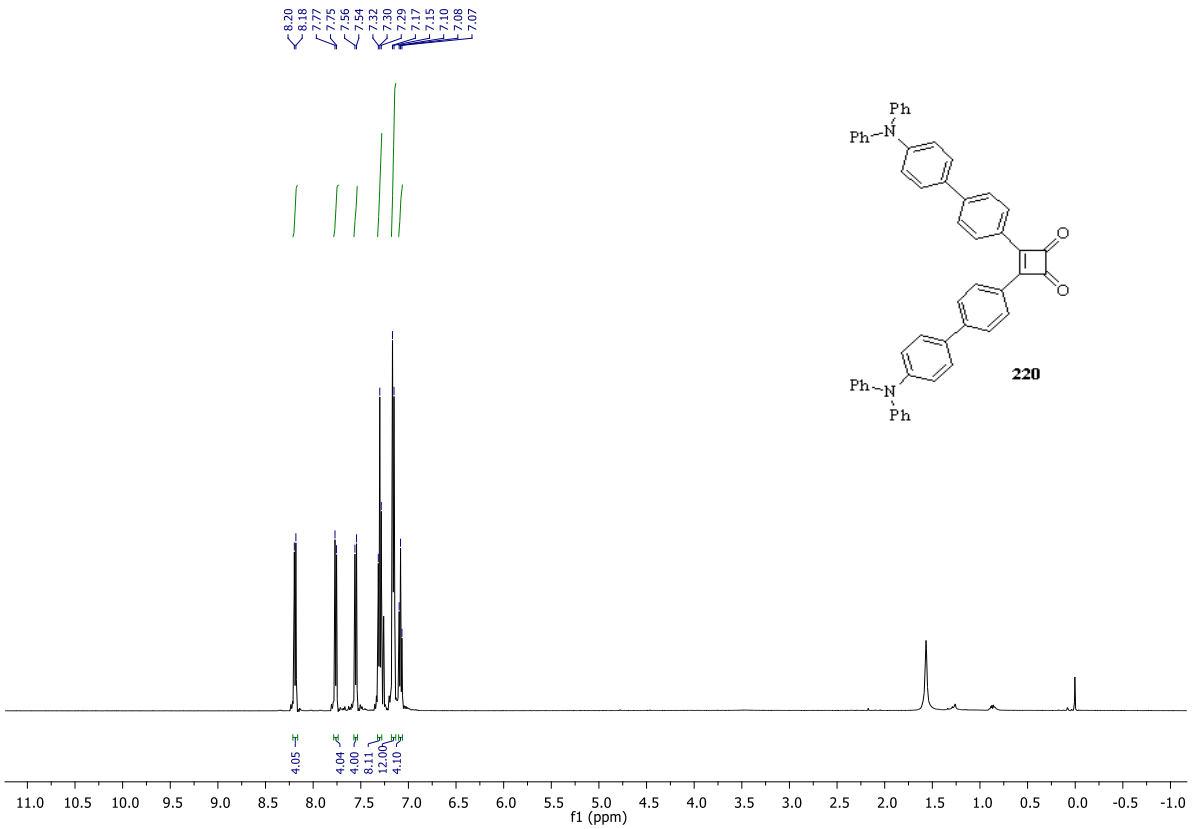

7.91
7.89
7.72
7.71
7.56
7.54
6.98
6.96
3.87
O
S
O
O
Br
213
2.00
2.02
2.04
2.05
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

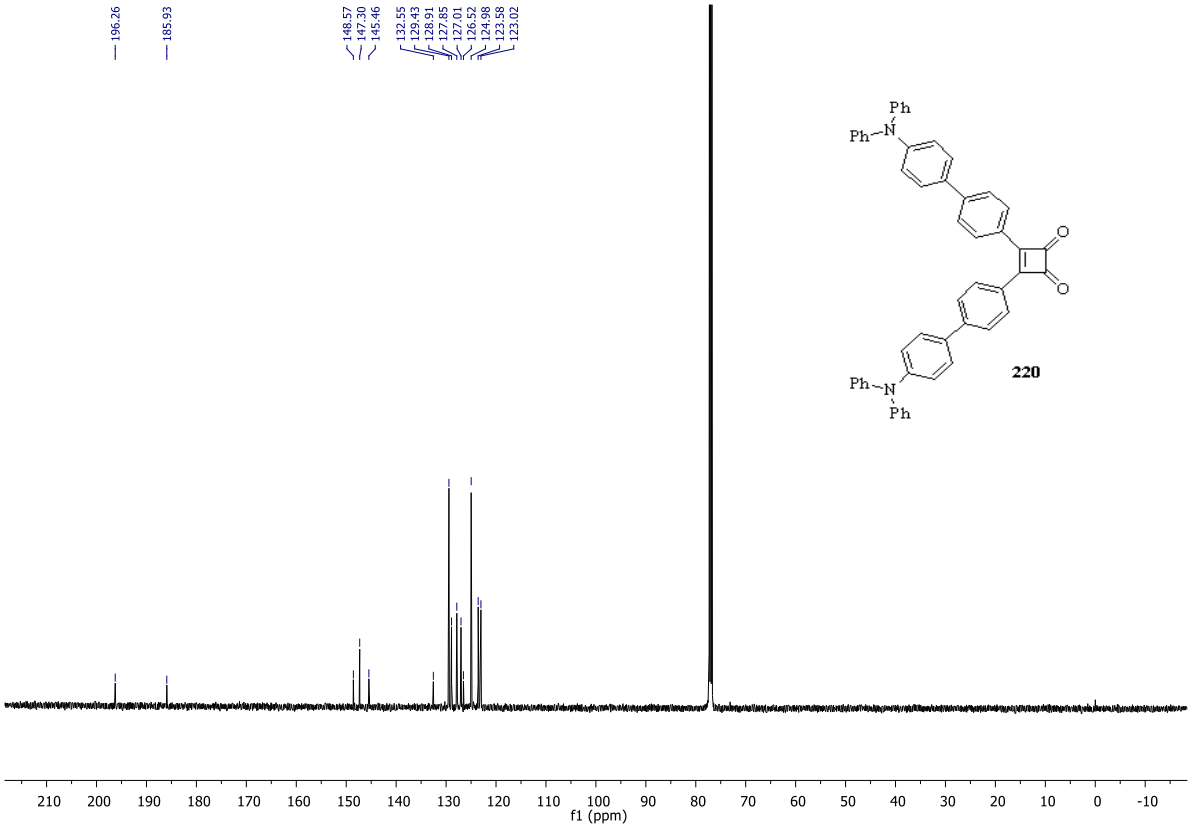

8.20
8.18
7.76
7.75
7.64
7.62
7.04
7.02
3.88
MeO
MeO
215
4.00
4.03
4.00
4.02
6.01
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

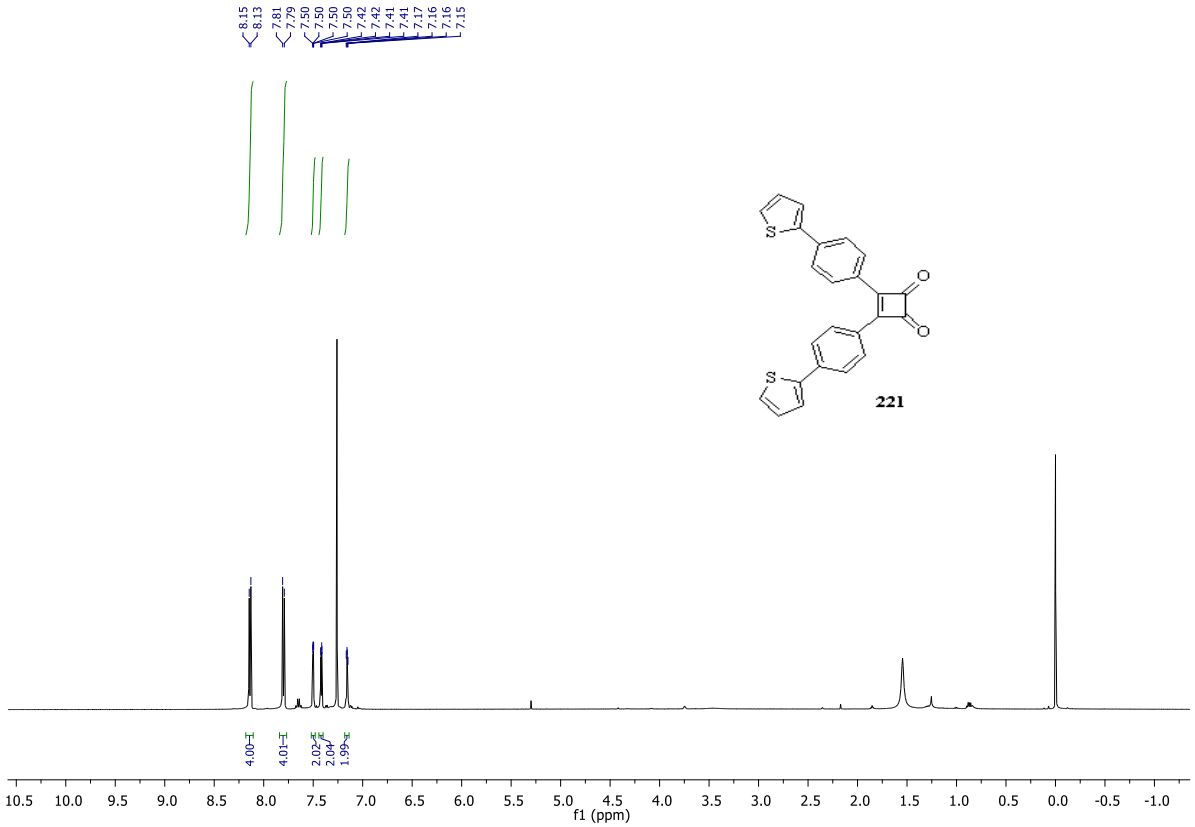

196.39
186.30
160.43
145.82
132.11
129.05
128.52
127.36
126.68
114.75
55.58
MeO
MeO
215
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.69
7.67
7.62
7.60
7.58
7.56
7.00
6.99
3.86
MeO
MeO
O
O
O
216
3.94
4.00
4.00
4.01
6.01
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

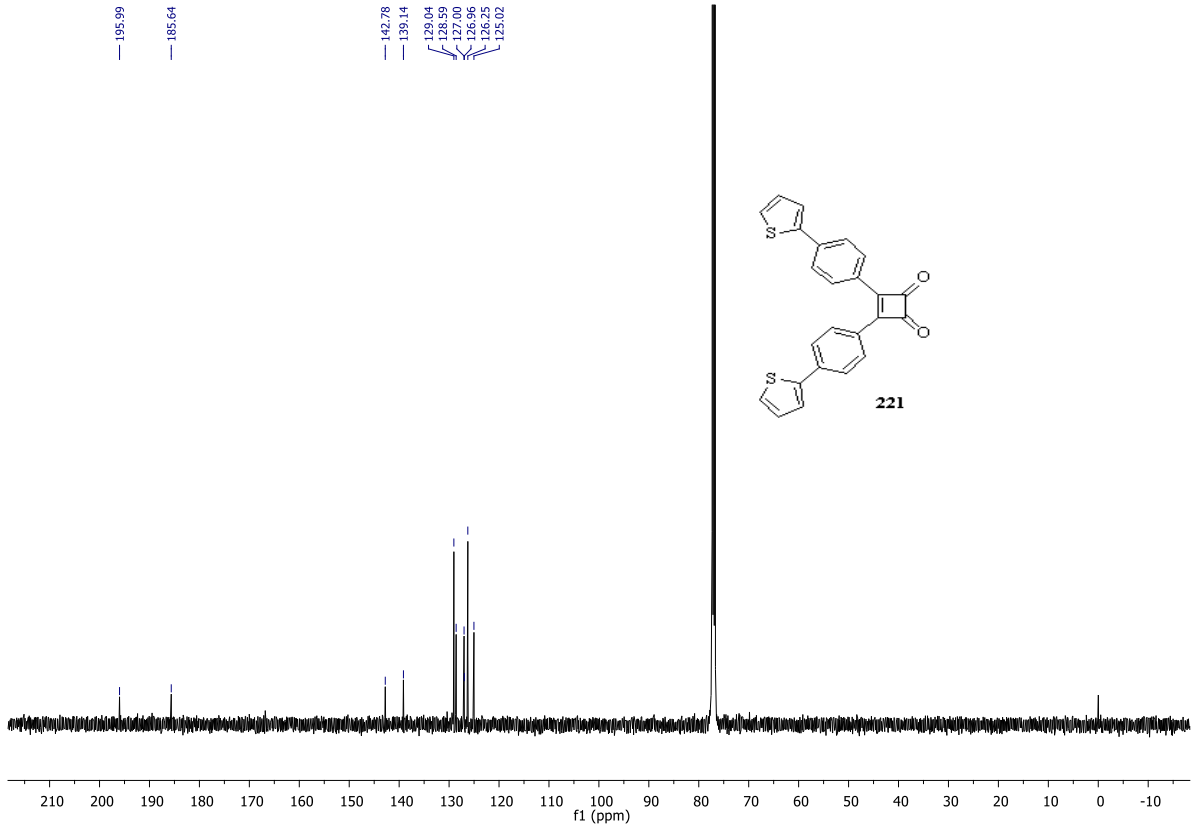

165.20
160.12
143.63
137.24
132.26
130.40
128.37
127.09
125.76
114.63
55.54
MeO
MeO
O
O
O
216
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.20
8.18
7.77
7.75
7.56
7.54
7.32
7.30
7.29
7.17
7.15
7.10
7.08
7.07
Ph
N
Ph
O
O
Ph
N
Ph
220
4.05
4.04
4.00
8.11
12.00
4.10
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

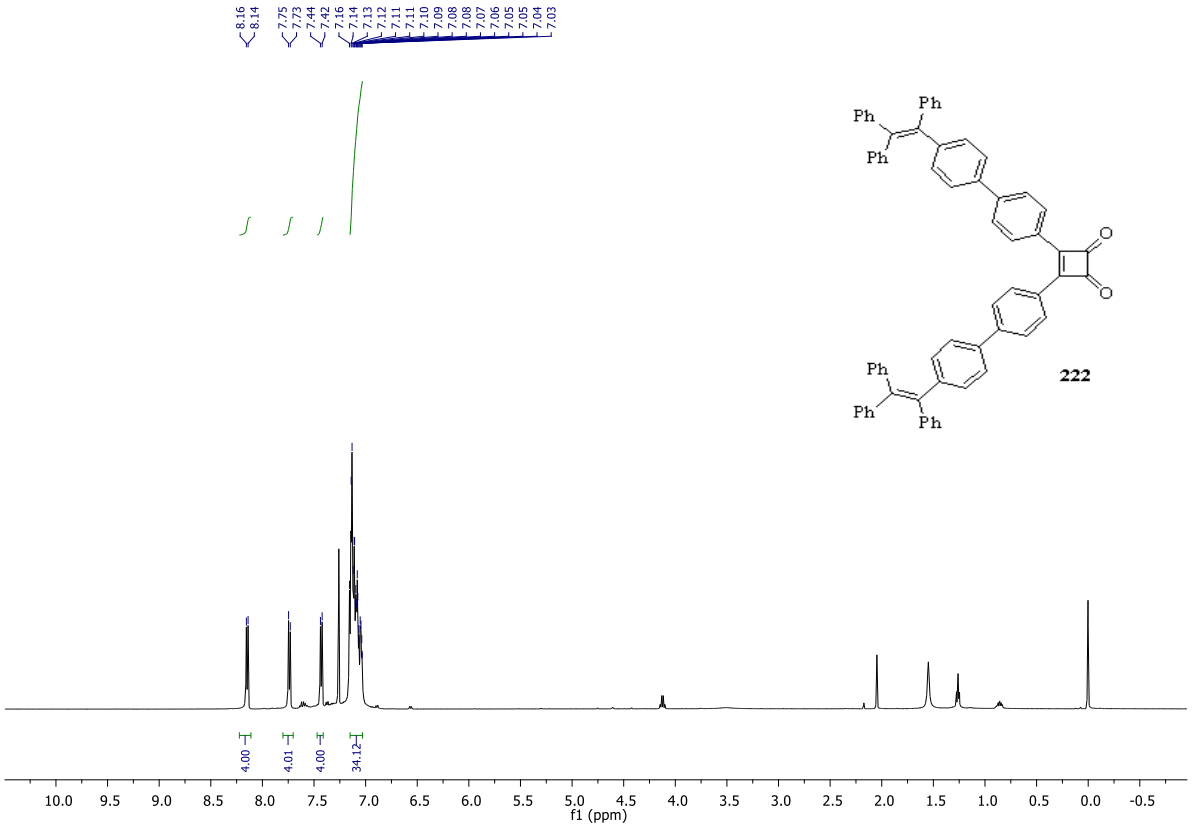

196.26
185.93
148.57
147.30
145.46
132.55
129.43
128.91
127.85
127.01
126.52
124.98
123.58
123.02
Ph
N
Ph
O
O
Ph
N
Ph
220
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

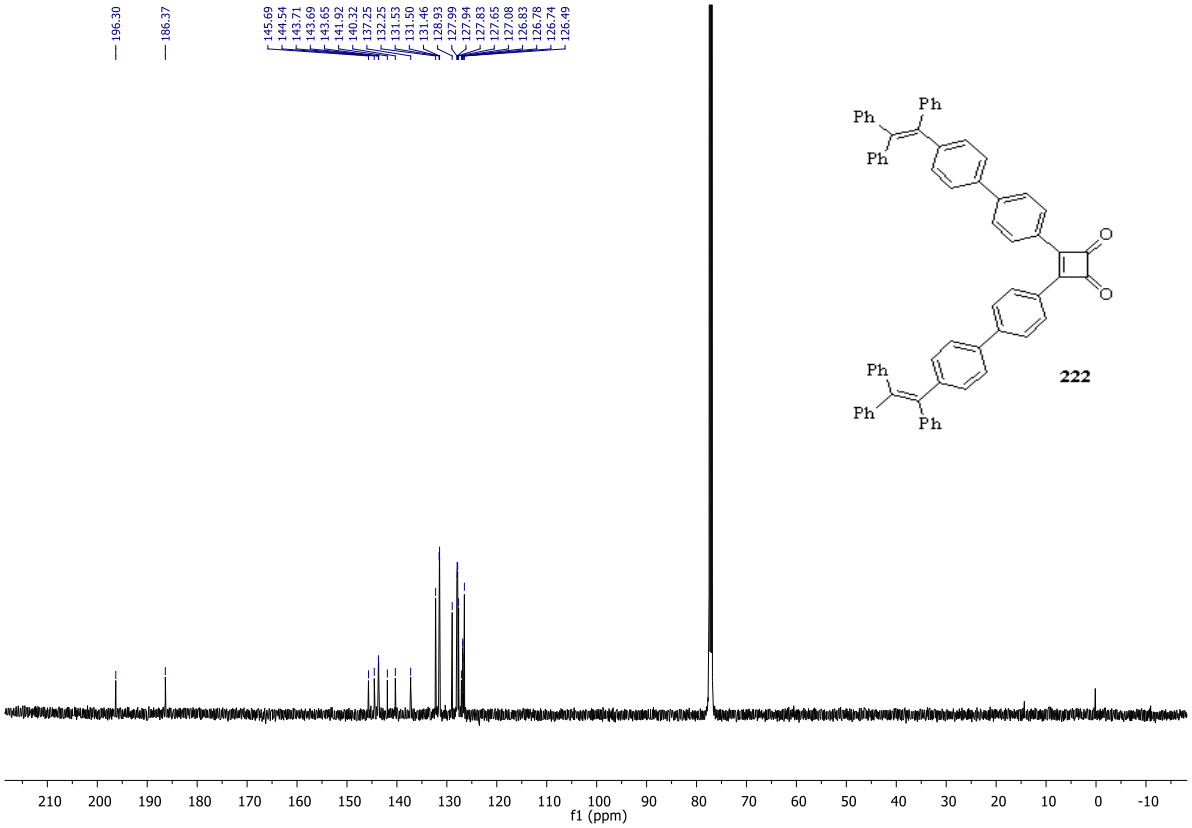

8.15
8.13
7.81
7.79
7.50
7.50
7.50
7.42
7.42
7.41
7.41
7.17
7.16
7.16
7.15
4.00
4.01
2.02
2.04
1.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
S
S
O
O

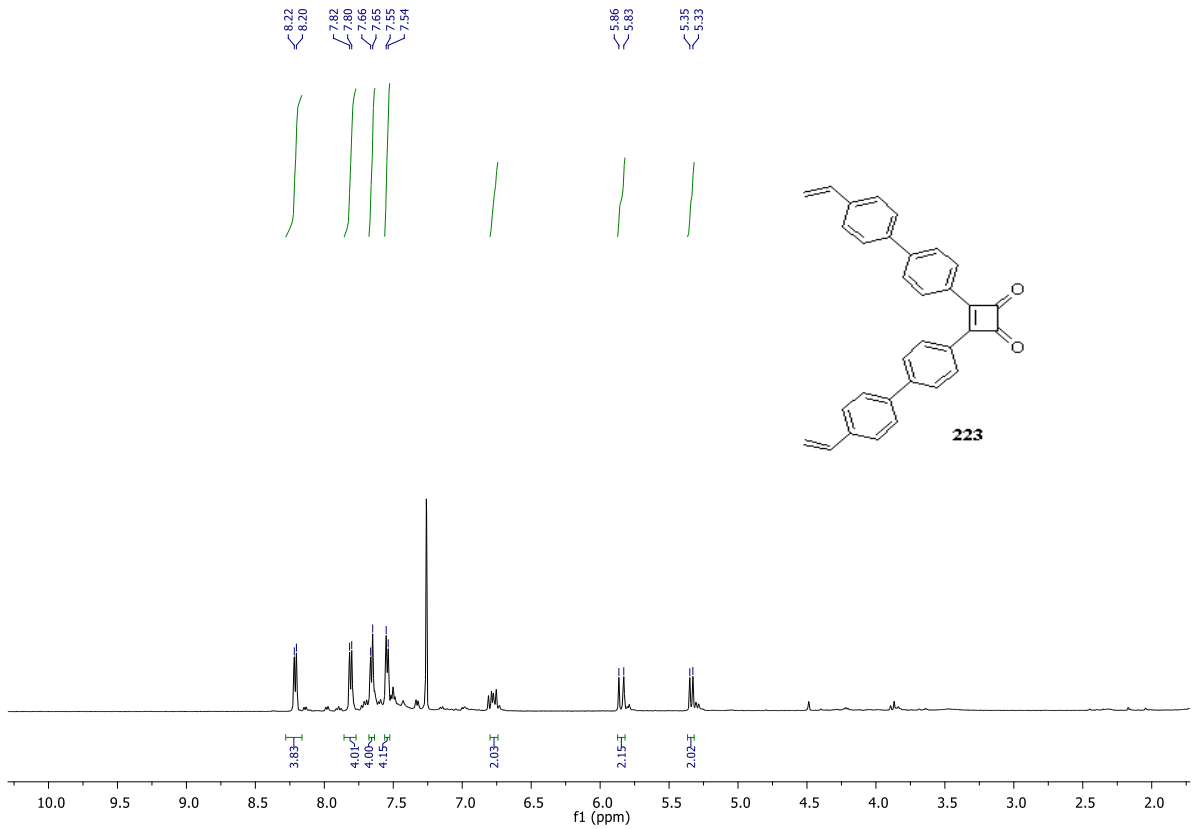
221

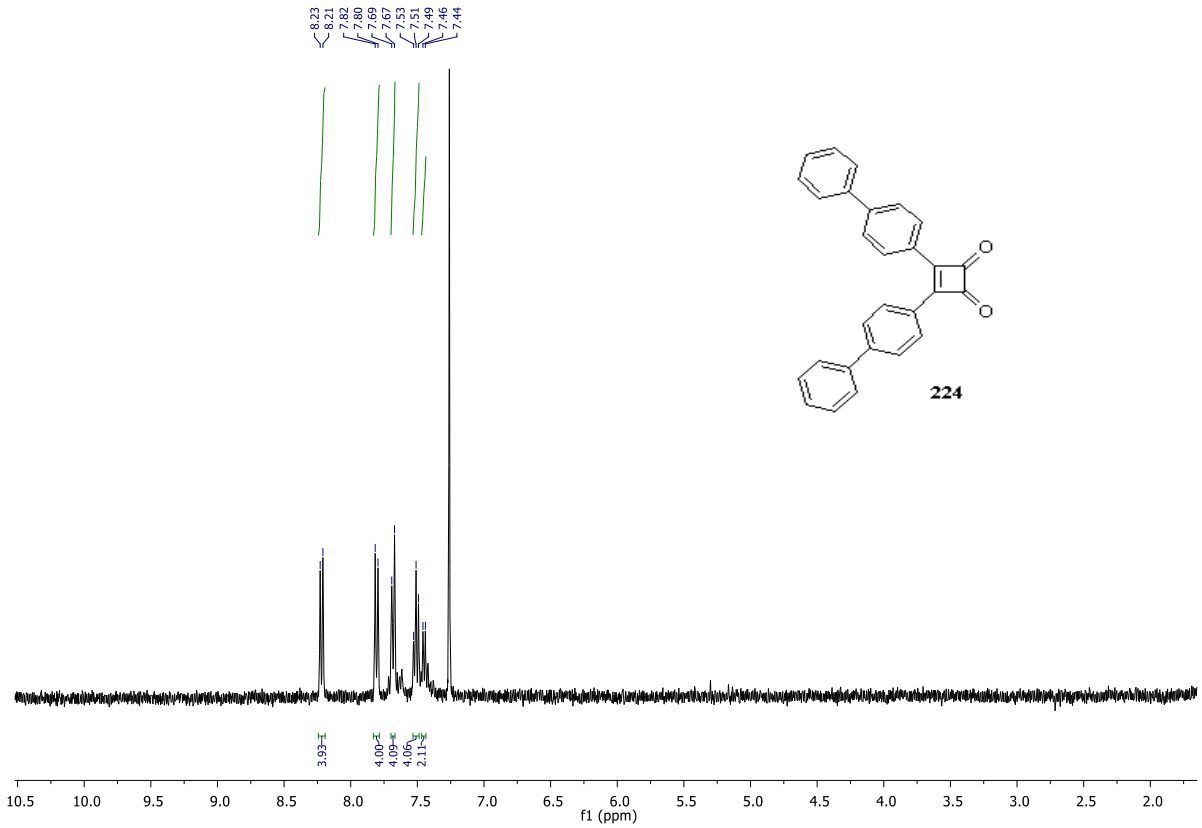

195.99
185.64
142.78
139.14
129.04
128.59
127.00
126.96
126.25
125.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
S
S
O
O

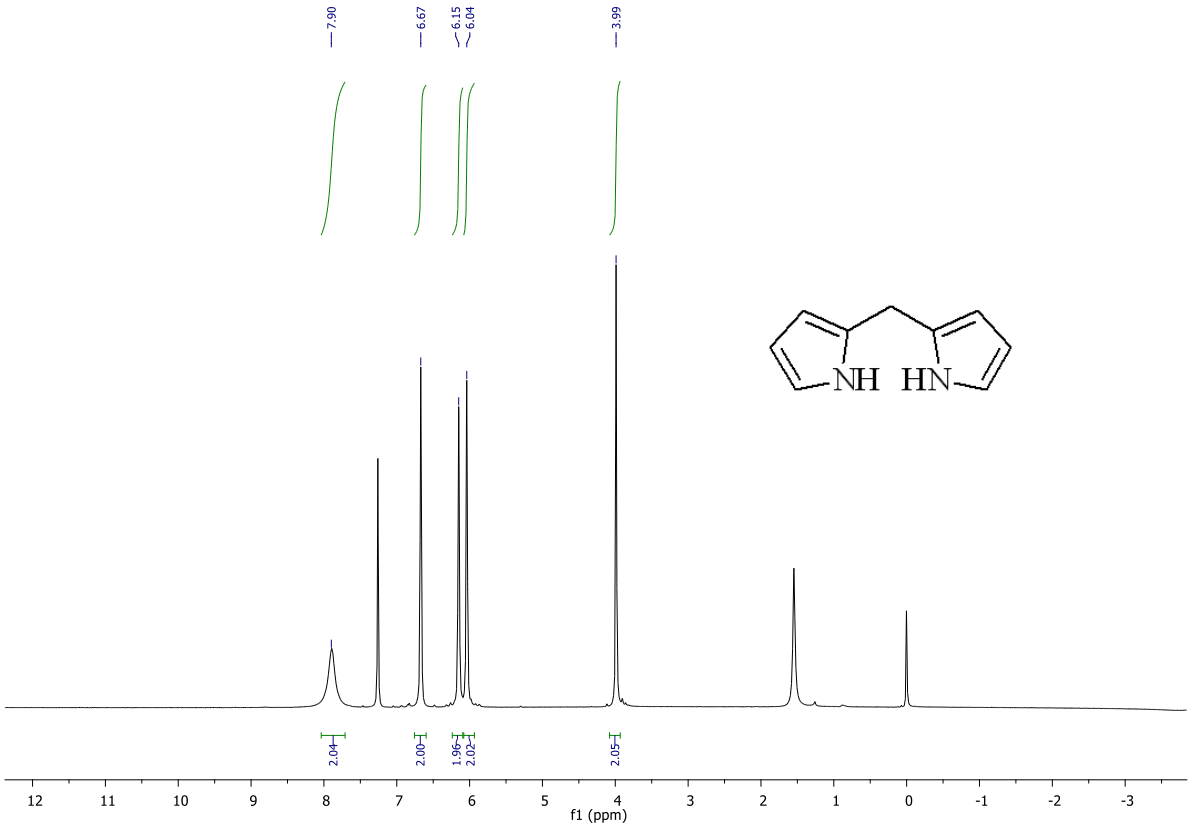
221

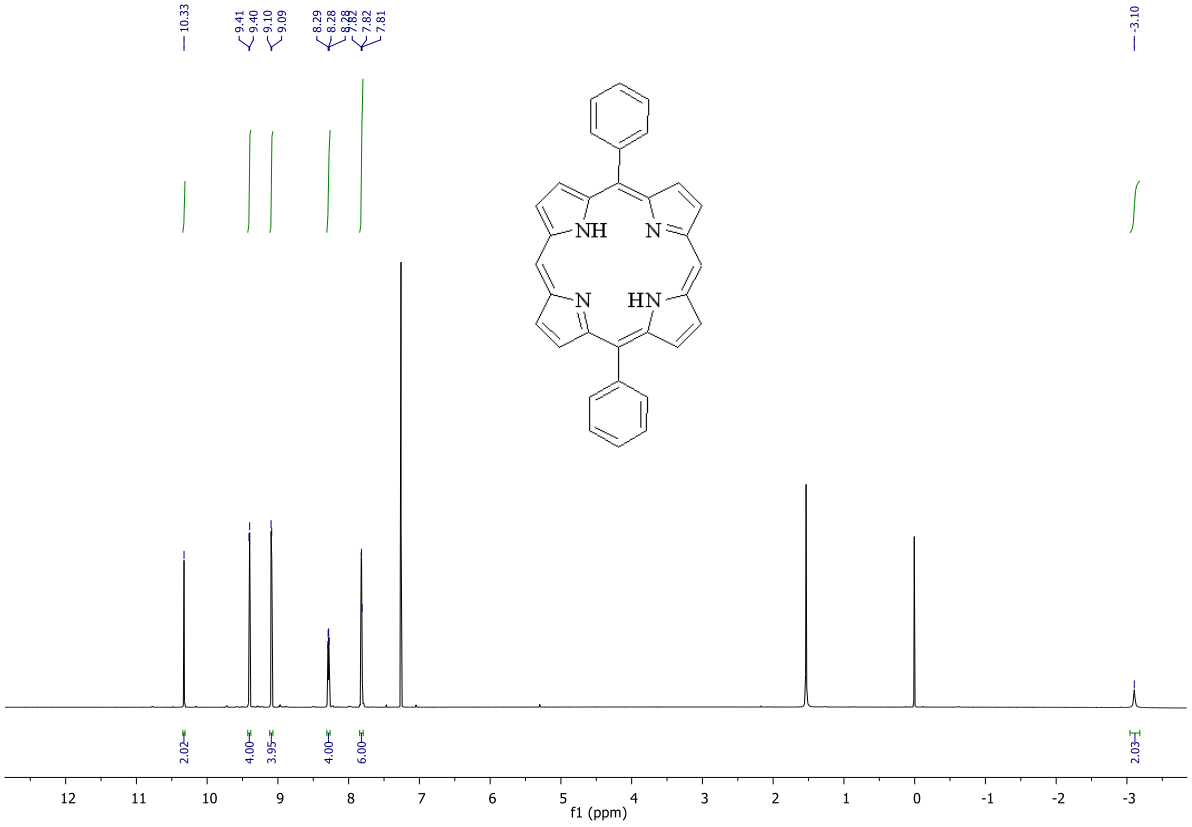

8.16
8.14
7.75
7.73
7.44
7.42
7.16
7.14
7.13
7.12
7.11
7.11
7.10
7.09
7.08
7.08
7.07
7.06
7.05
7.05
7.04
7.03
Ph
Ph
Ph
Ph
O
O
Ph
Ph
Ph
222
4.00
4.01
4.00
34.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

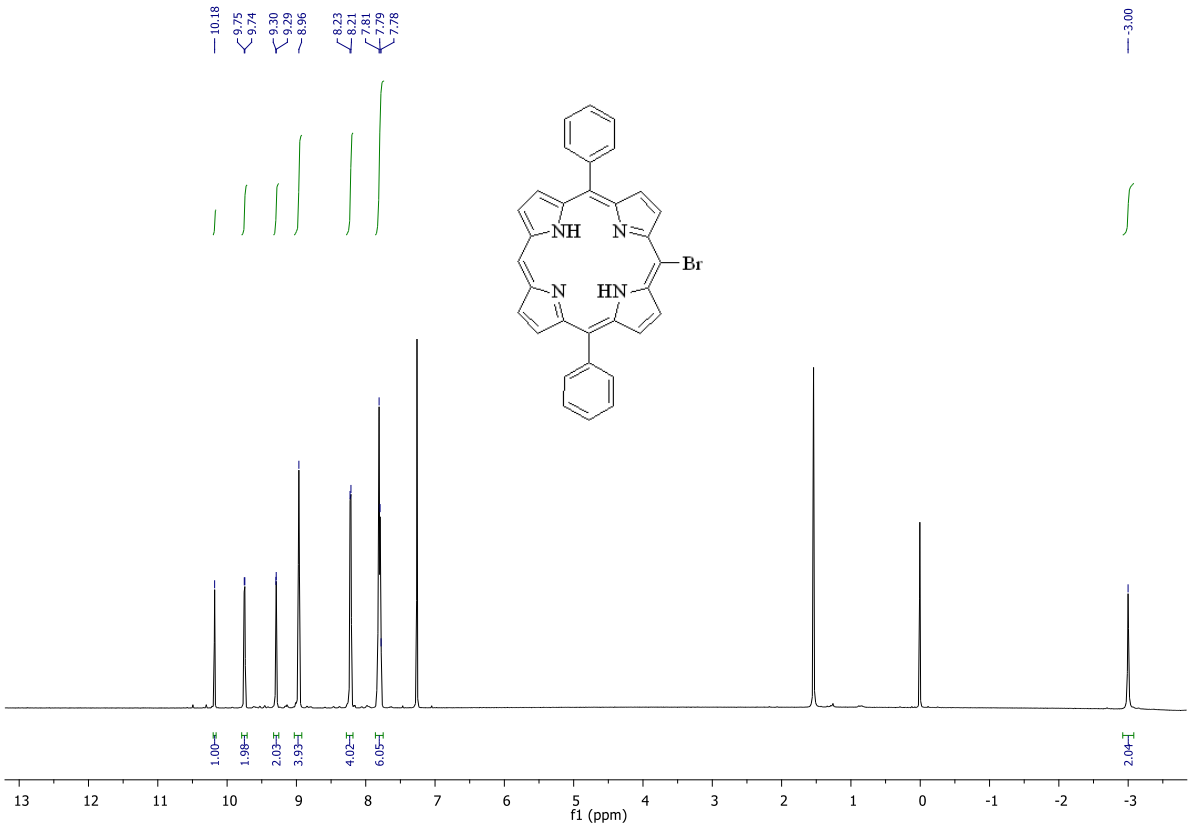

196.30
186.37
145.69
144.54
143.71
143.69
143.65
141.92
140.32
137.25
132.25
131.53
131.50
131.46
128.93
127.99
127.94
127.83
127.65
127.08
126.83
126.78
126.74
126.49
Ph
Ph
Ph
Ph
O
O
Ph
Ph
Ph
222
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

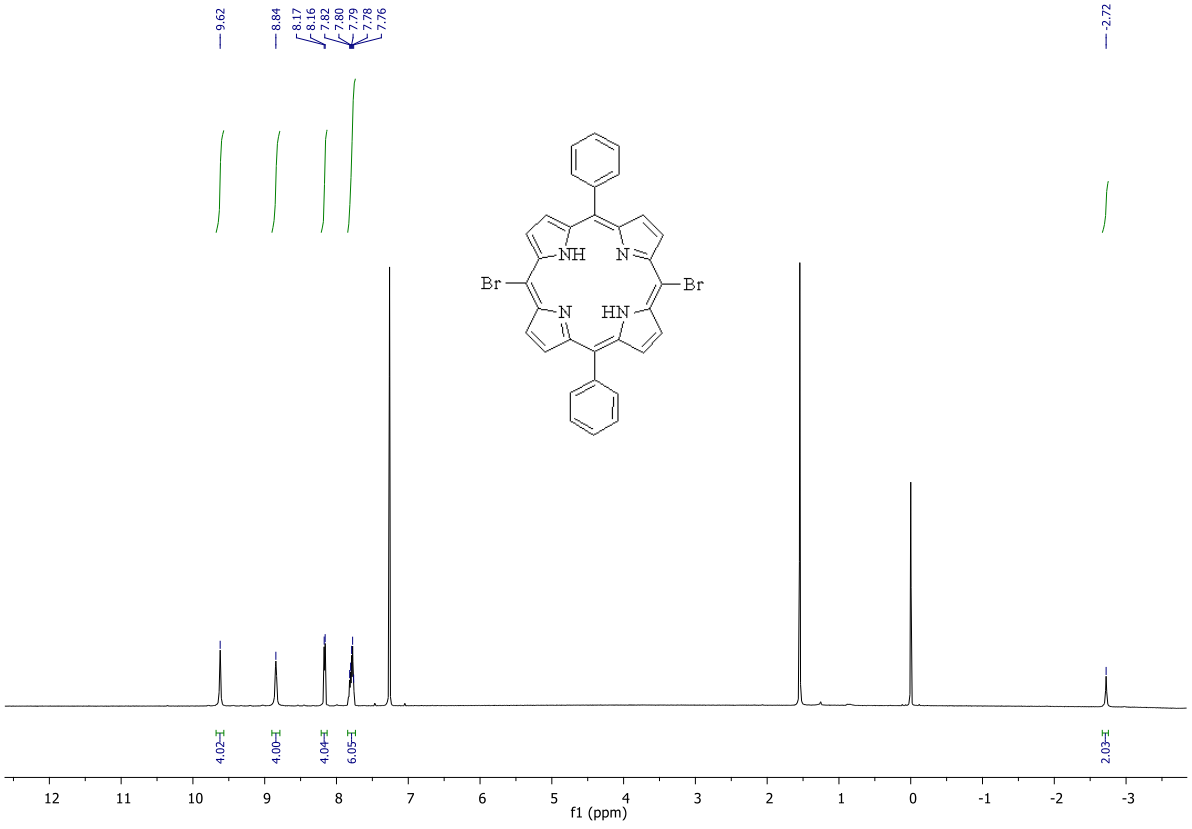

8.22
8.20
7.82
7.80
7.66
7.65
7.55
7.54
5.86
5.83
5.35
5.33
O
O
223
3.83
4.01
4.00
4.15
2.03
2.15
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

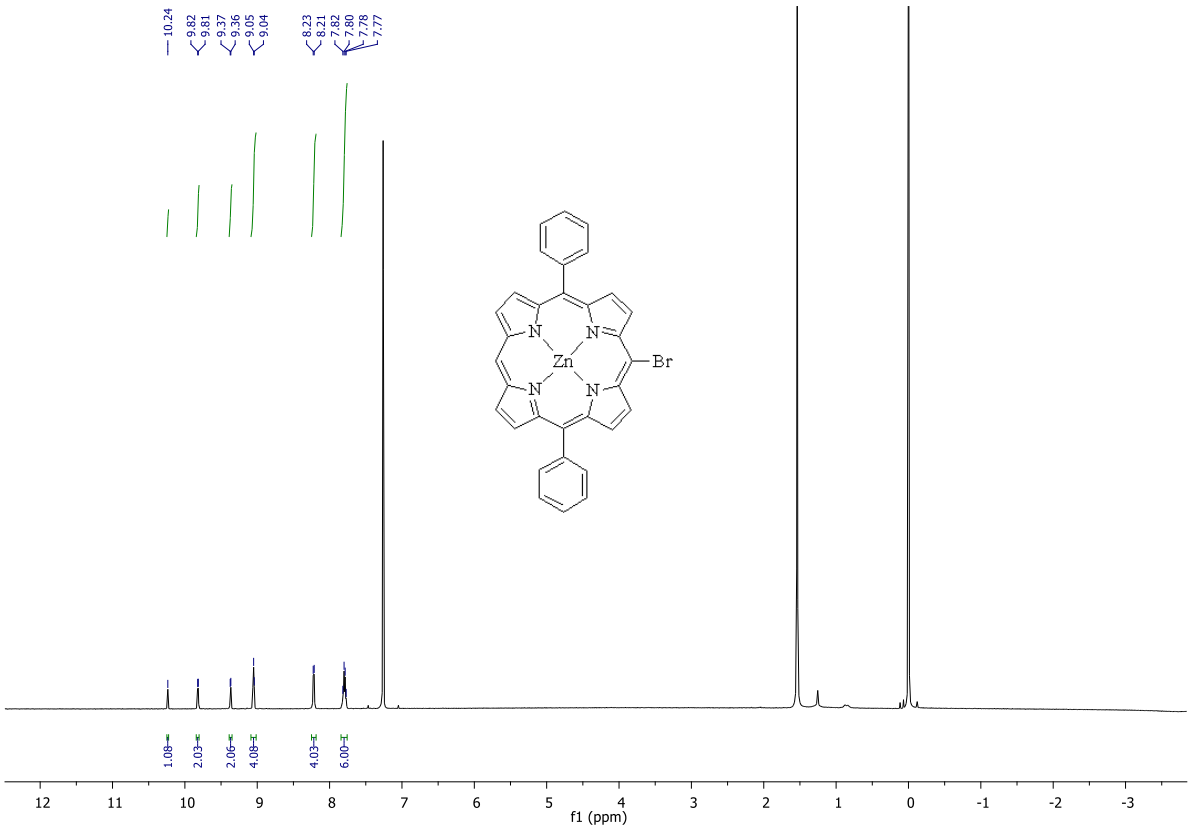

8.23
8.21
7.82
7.80
7.69
7.67
7.53
7.51
7.49
7.46
7.44
O
O
224
3.93
4.00
4.09
4.06
2.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

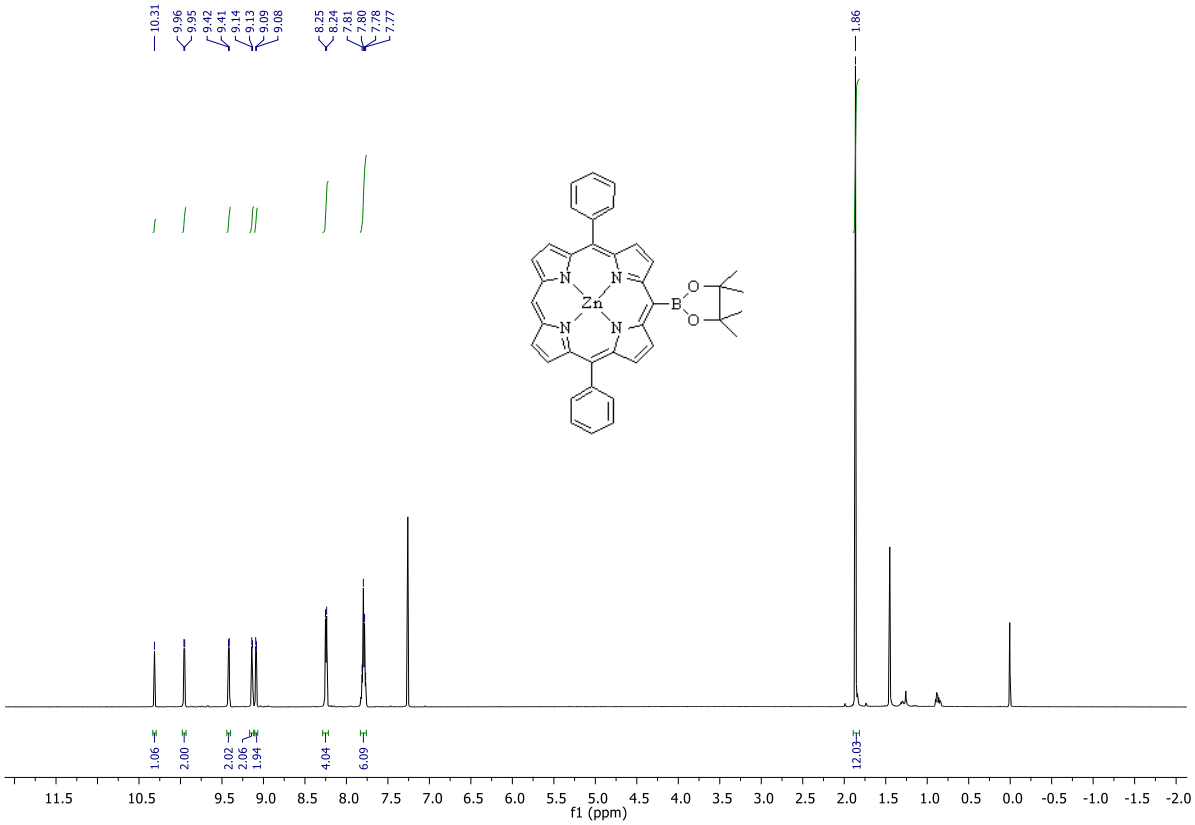

7.90
6.67
6.15
6.04
3.99
NH HN
2.04
2.00
1.96
2.02
2.05
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

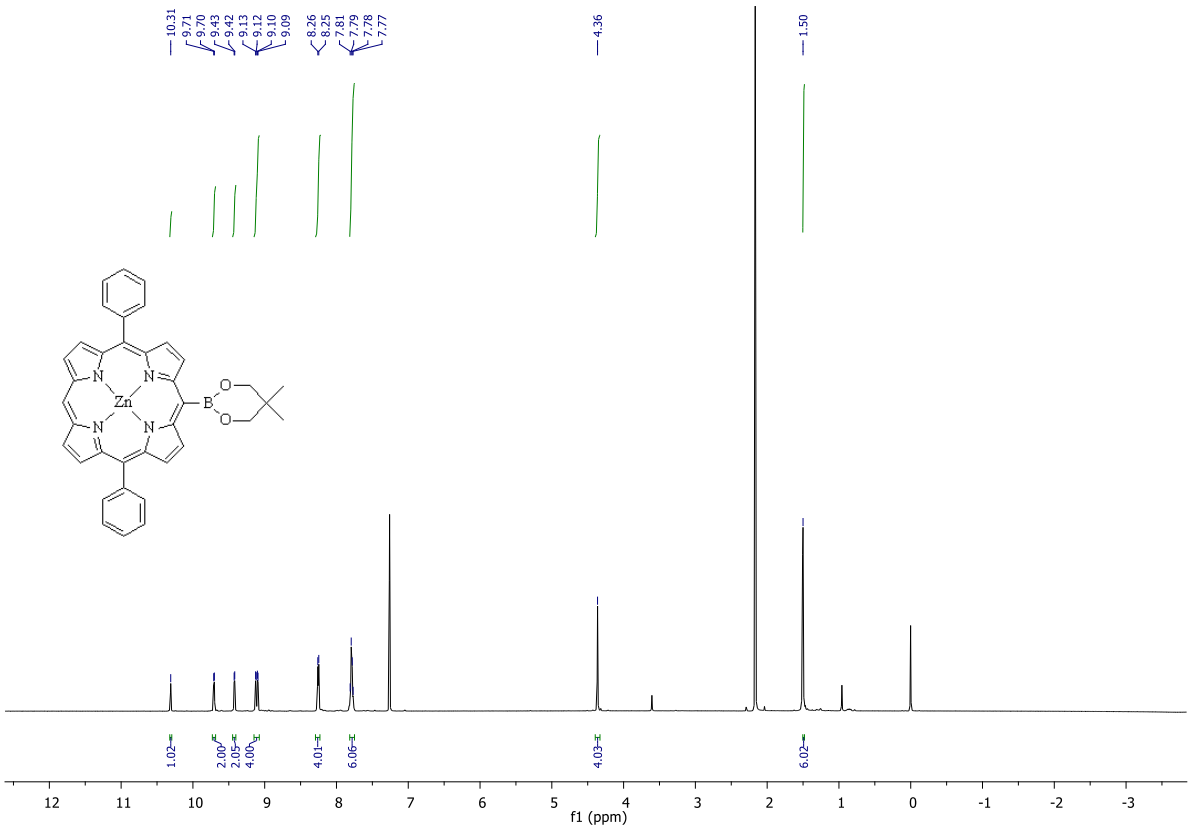

10.33
9.41
9.40
9.10
9.09
8.29
8.28
7.82
7.81
-3.10
NH N
N HN
2.02
4.00
3.95
4.00
6.00
2.03
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


10.18
9.75
9.74
9.30
9.29
8.96
8.23
8.21
7.81
7.79
7.78
-3.00
NH
N
Br
N
HN
1.00
1.98
2.03
3.93
4.02
6.05
2.04
f1 (ppm)


9.62
8.84
8.17
8.16
7.82
7.80
7.79
7.78
7.76
-2.72
NH
N
Br
Br
N
HN
4.02
4.00
4.04
6.05
2.03
f1 (ppm)


10.24
9.82
9.81
9.37
9.36
9.05
9.04
8.23
8.21
7.82
7.80
7.78
7.77
N
N
Zn
N
N
Br
1.08
2.03
2.06
4.08
4.03
6.00
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


10.31
9.96
9.95
9.42
9.41
9.14
9.13
9.09
9.08
8.25
8.24
7.81
7.80
7.78
7.77
1.86
N
N
Zn
N
N
B
O
O
1.06
2.00
2.02
2.06
1.94
4.04
6.09
12.03
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)


10.31
9.71
9.70
9.43
9.42
9.13
9.12
9.10
9.09
8.26
8.25
7.81
7.79
7.78
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1.02
2.00
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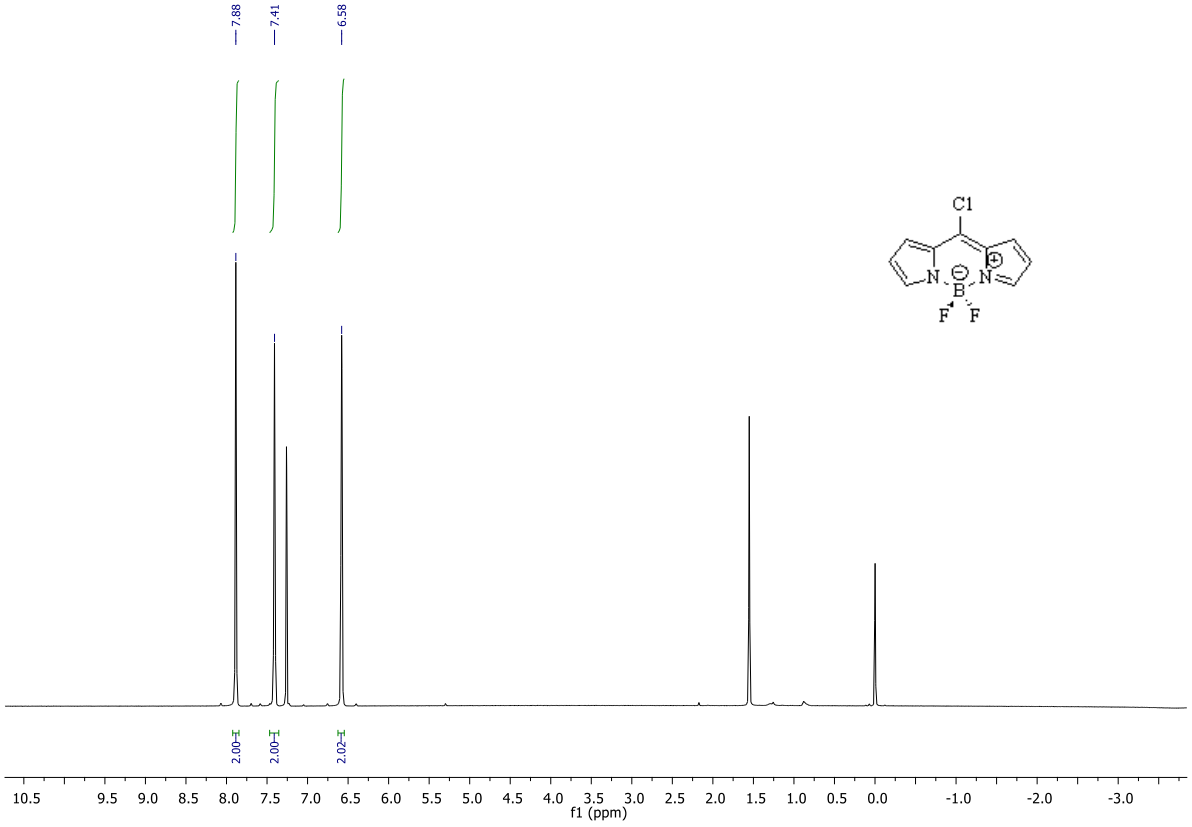
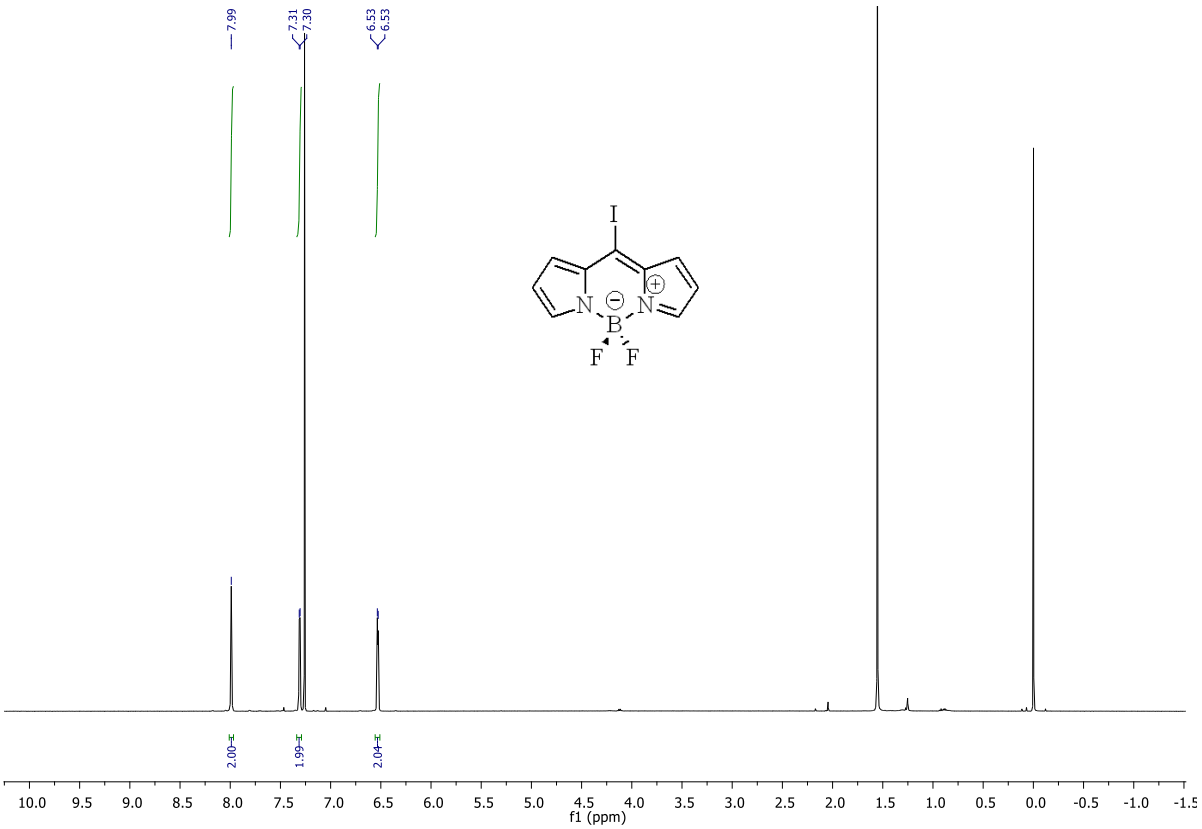
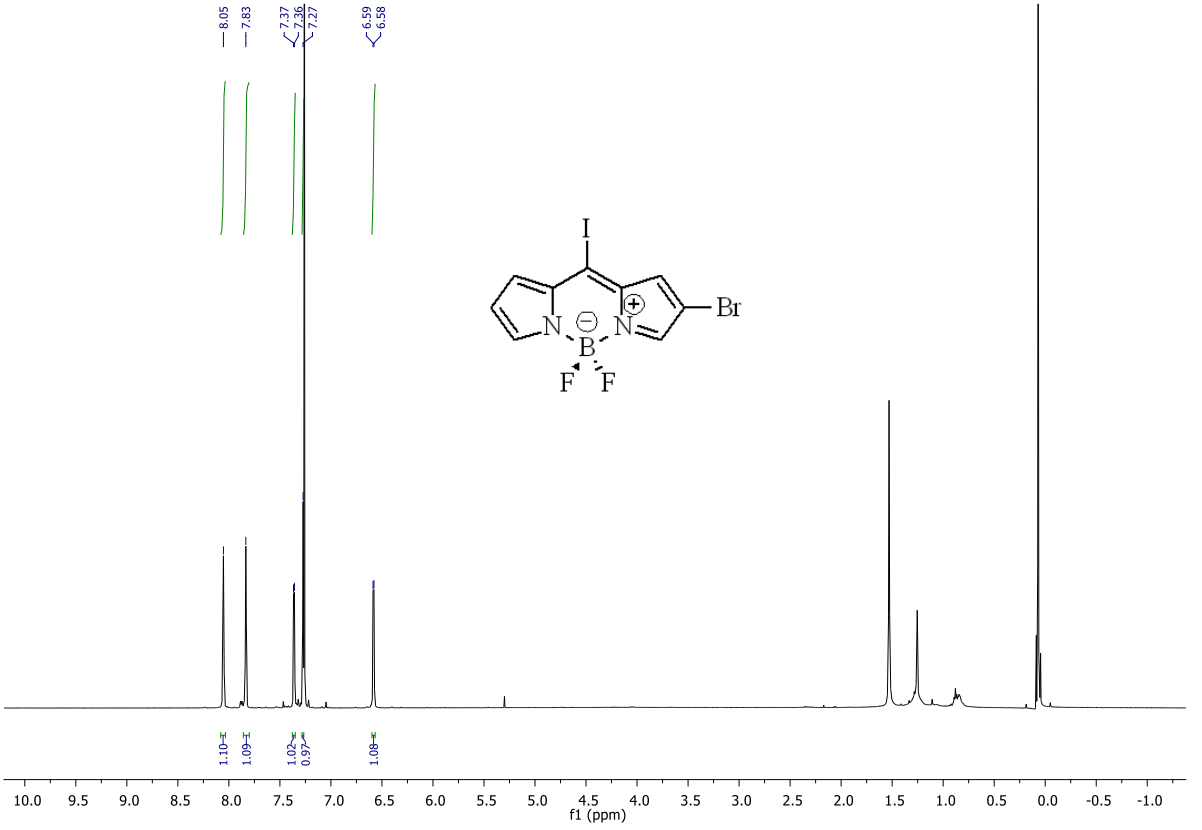
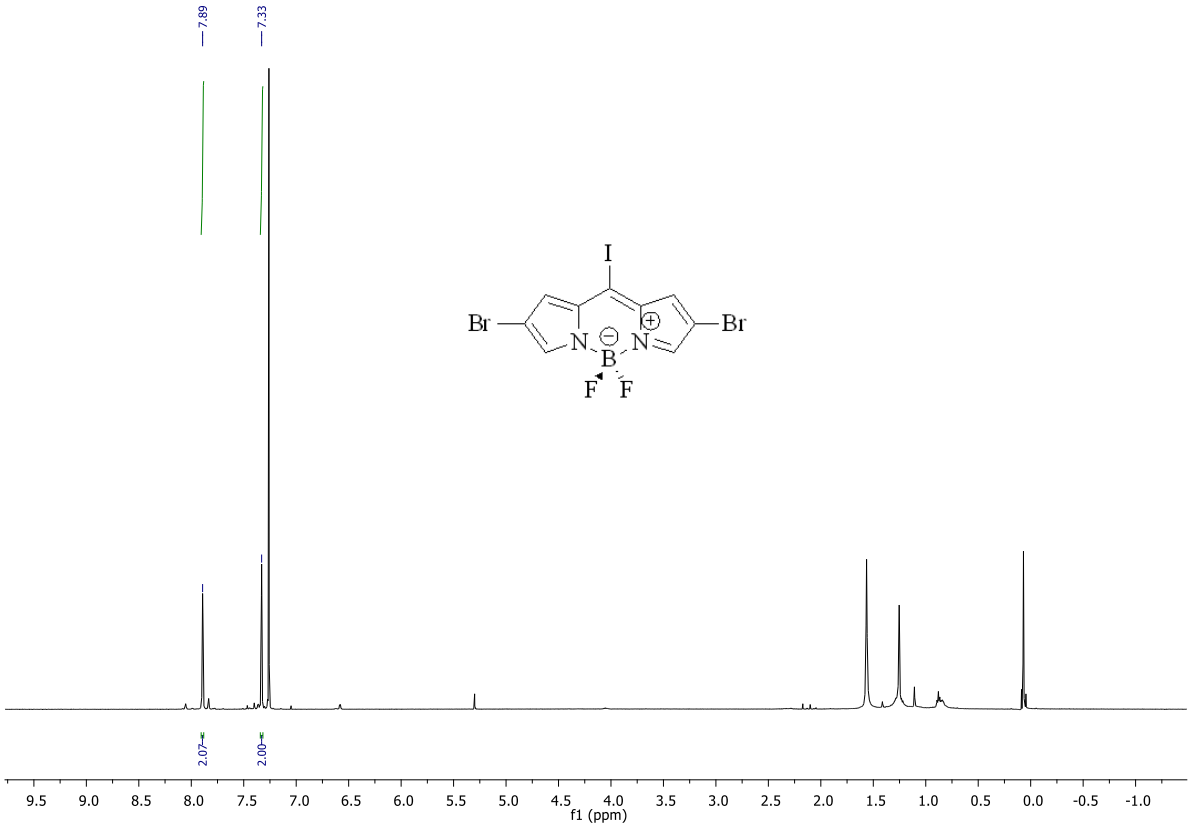
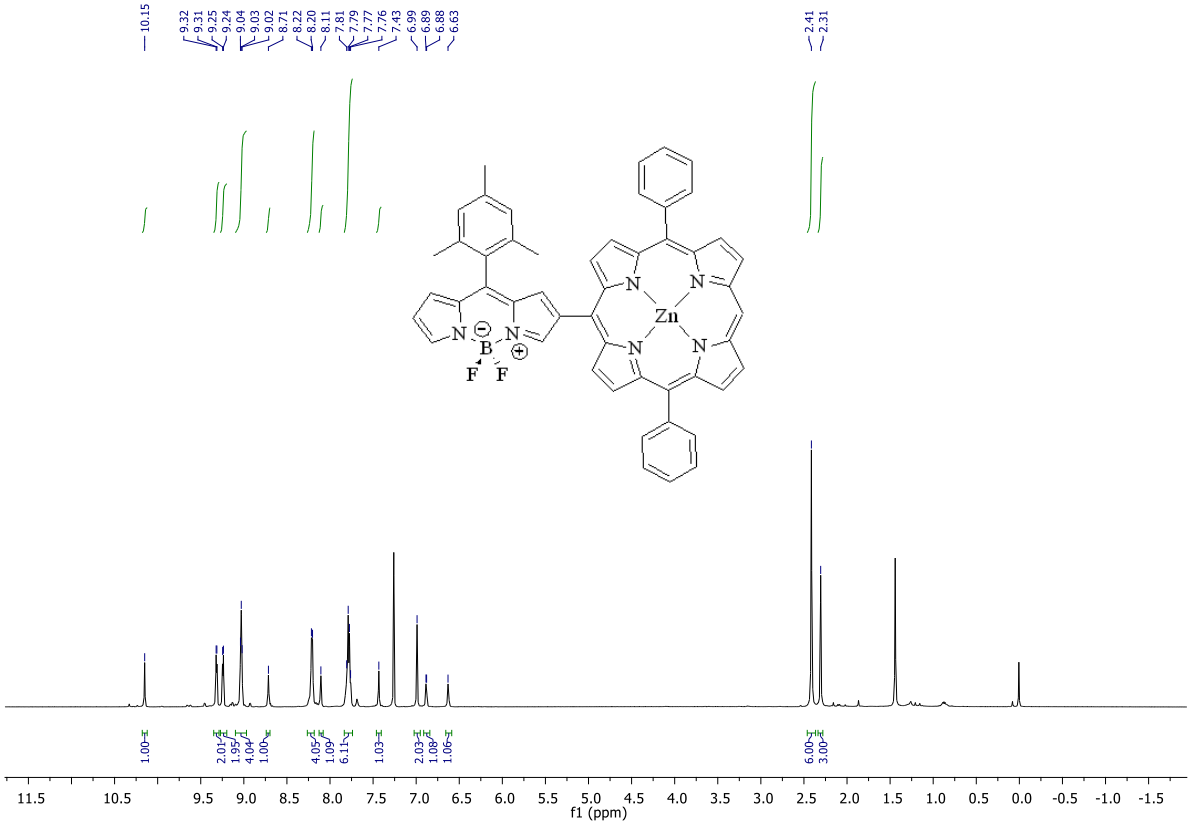
4.06
4.01
6.06
4.03
6.02
f1 (ppm)

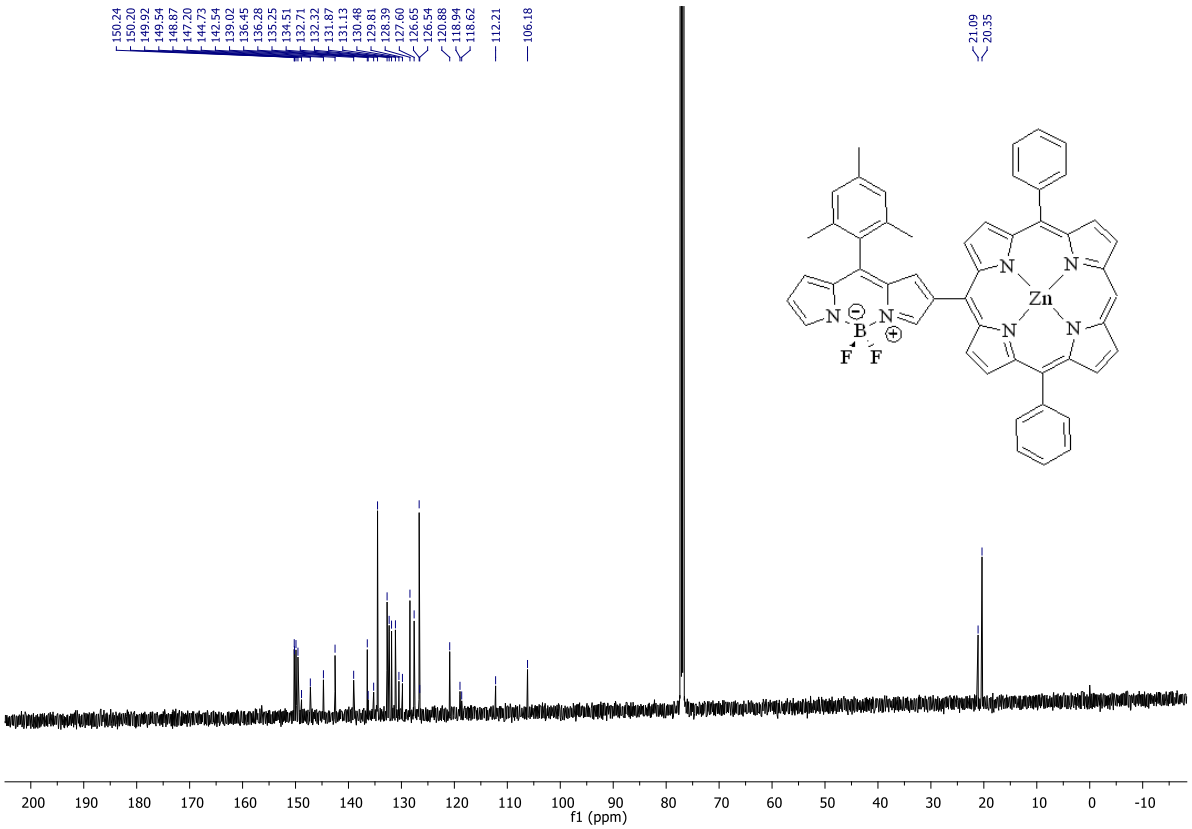

7.88
7.41
6.58
2.00
2.00
2.02
f1 (ppm)

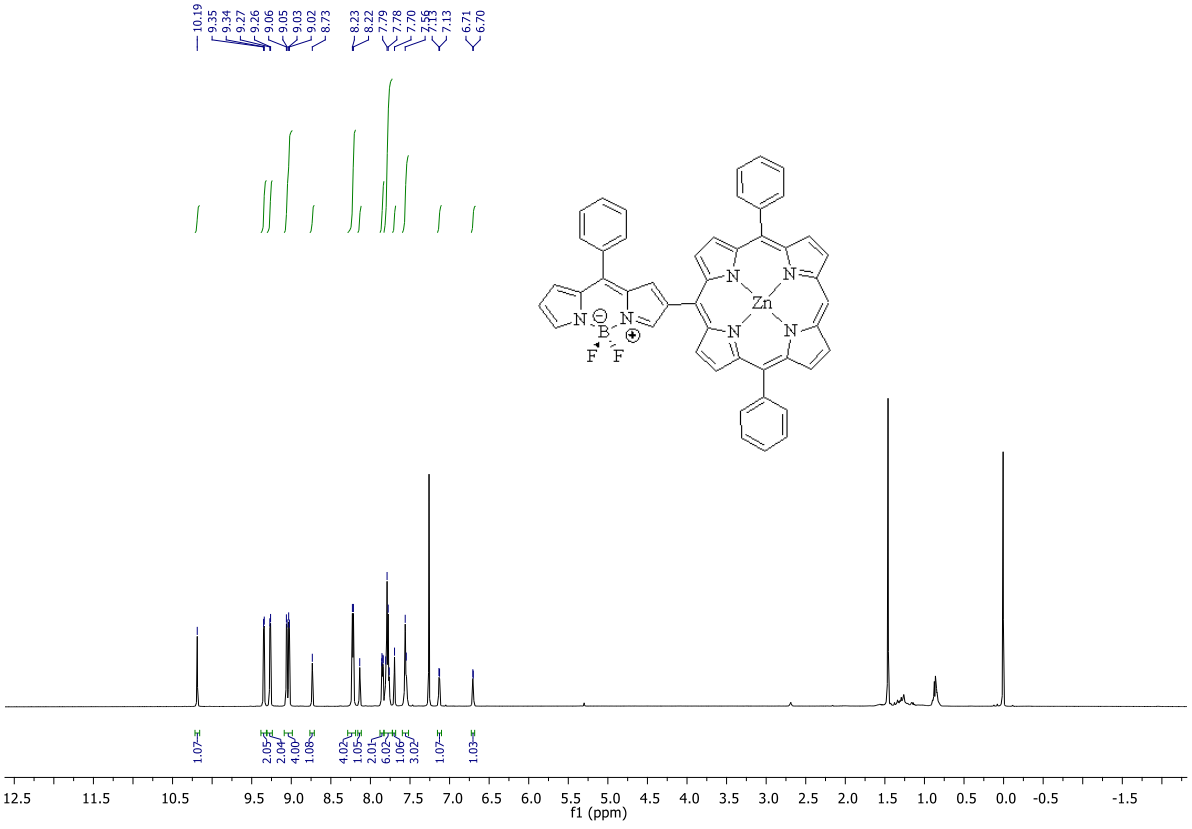

7.99
7.31
7.30
6.53
6.53
I
N
B
N
F
F
2.00
1.99
2.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


8.05
7.83
7.37
7.36
7.27
6.59
6.58
I
Br
N
B
N
F
F
1.10
1.09
1.02
0.97
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


7.89
7.33
I
Br
Br
N
B
N
F
F
2.07
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


10.15
9.32
9.31
9.25
9.24
9.04
9.03
9.02
8.71
8.22
8.20
8.11
7.81
7.79
7.77
7.76
7.43
6.99
6.89
6.88
6.63
2.41
2.31
N
N
Zn
N
N
N
B
N
F
F
1.00
2.01
1.95
4.04
1.00
4.05
1.09
6.11
1.03
2.03
1.08
1.06
6.00
3.00
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


150.24
150.20
149.92
149.54
148.87
147.20
144.73
142.54
139.02
136.45
136.28
135.25
134.51
132.71
132.32
131.87
131.13
130.48
129.81
128.39
127.60
126.65
126.54
120.88
118.94
118.62
112.21
106.18
21.09
20.35
N
N
Zn
N
N
N
B
N
F
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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9.35
9.34
9.27
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9.06
9.05
9.03
9.02
8.73
8.23
8.22
7.79
7.78
7.70
7.56
7.13
6.71
6.70
N
N
Zn
N
N
N
B
N
F
F
1.07
2.05
2.04
4.00
1.08
4.02
1.05
2.01
6.02
1.06
3.02
1.07
1.03
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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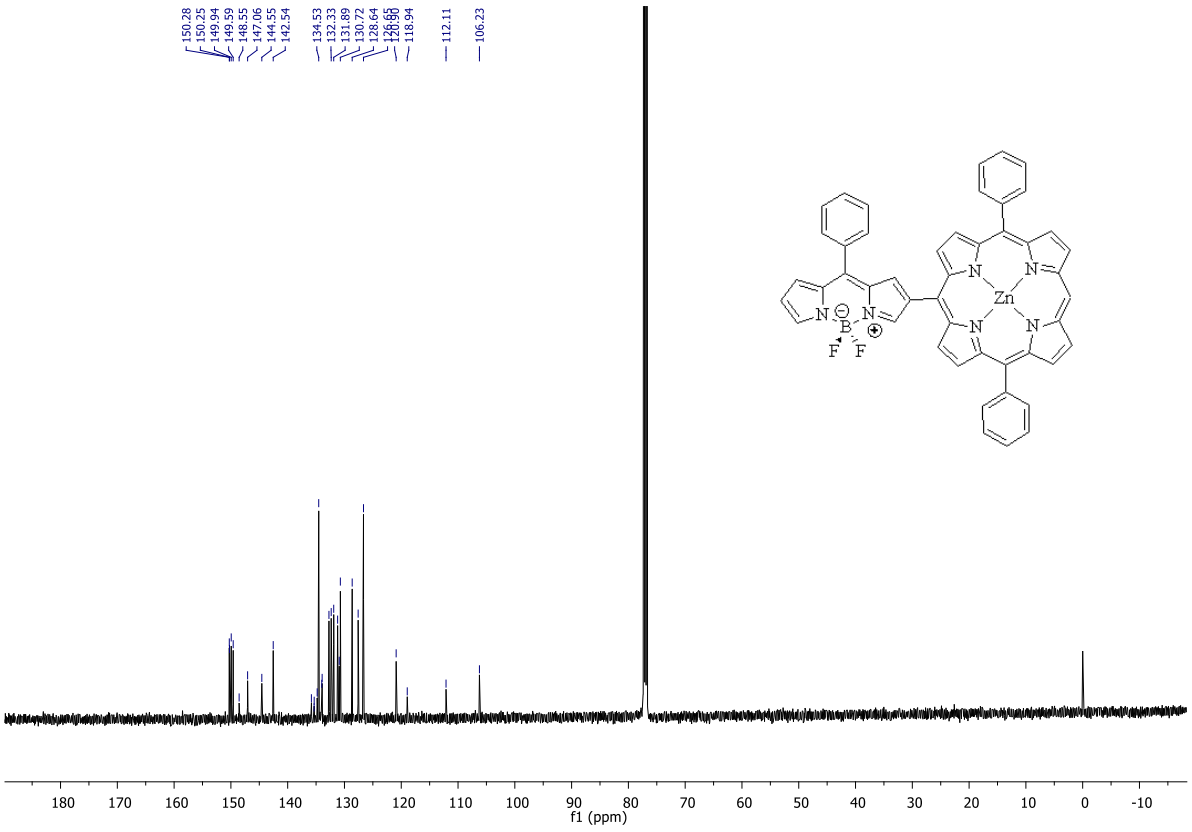
f1 (ppm)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112.11
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F
F
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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Annex B: List of published articles obtained during doctoral study

1. **Kokate, S. V.**; Aguilar-Aguilar, A.; Vázquez-Guevara, M. A.; Luna-Bárcenas, G.; Gimenez, A. J.; Peña-Cabrera, E. *Arkivoc* **2021**, *3*, 76-84. https://doi.org/10.24820/ark.5550190.p011.459

2. Liu, X.; Chi, W.; Qiao, Q.; **Kokate, S. V.**; Peña-Cabrera, E.; Xu, Z.; Liu, X.; Chang, Y. -T. *ACS Sens.* **2020**, *5*, 731-739. https://doi.org/10.1021/acssensors.9b01951

3. Reviriego, F.; Peña-Cabrera, E.; **Kokate, S. V.**; Alkorta, I.; Elguero, J. *Magn. Reson. Chem.* **2020**, *59*, 454-464. https://doi.org/10.1002/mrc.5118

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