IRIDIUM-CATALYZED C-H BOND ACTIVATION AND BORYLATION OF SMALL ORGANIC MOLECULES

THESIS

SUBMITTED TO

BABASAHEB BHIMRAO AMBEDKAR UNIVERSITY
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2021

Dedicated

To

My Father

DECLARATION

I hereby declare that the thesis titled "**IRIDIUM-CATALYZED C-H BOND ACTIVATION AND BORYLATION OF SMALL ORGANIC MOLECULES**" submitted by me for the degree of Doctor of Philosophy, is the record of work carried out by me under the supervision of **Dr. Gajanan Pandey**, Professor, Department of Applied Chemistry, School of Physical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow, India and co-supervision of **Dr. Buddhadeb Chattopadhyay**, Assistant Professor, Department of Molecular Synthesis and Drug Discovery, Centre of Biomedical Research, Lucknow, India and I further confirm that said work has not been submitted anywhere else for the award of any degree, diploma, fellowship, etc. either in this or any other university or other institution of higher learning. I further declare that the material obtained from other sources has been duly acknowledge in this thesis. I, Jagriti Chaturvedi also declare that the thesis submitted by me is essentially free from all kind of plagiarism (checked by URKUND).

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CERTIFICATE

This is to certify that the thesis titled "**IRIDIUM-CATALYZED C-H BOND ACTIVATION AND BORYLATION OF SMALL ORGANIC MOLECULES**" submitted by Ms. **Jagriti Chaturvedi** is an original research work and has not been previously submitted in part or full for the award of any other degree or diploma to this or any other university.

The thesis submitted to Babasaheb Bhimrao Ambedkar University Lucknow satisfies all the requirements as stipulated in the *Doctor of Philosophy (Ph.D.) regulation-1999 as amended in 2008/2010/2013* and it is fit for submission and evaluation for the award of the degree of Doctor of Philosophy of the University.

Date: 20-12-2021

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Head of Department

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Abstract

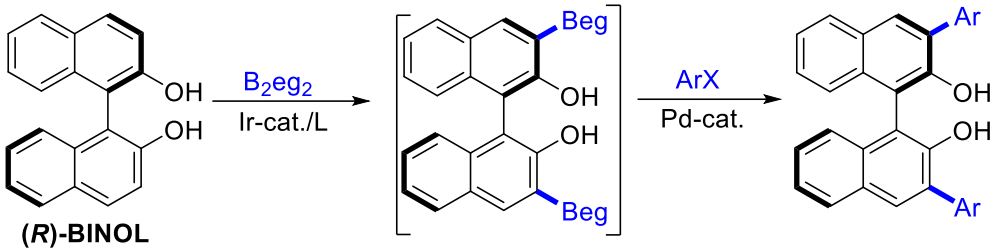
The pursuit for the discovery of new and powerful synthetic methods from simple starting materials to access high-valued organic materials has been at the forefront of synthetic organic chemistry research for more than a century. While traditional synthetic strategies mostly rely on the innate reactivity of functional groups, the introduction of transition metal-catalysts renders innovative strategies to construct covalent bonds, thus offering a great opportunity to derivatize various important molecules with little functionality to synthetically versatile motifs. In this context, transition metal-catalyzed C-H bond activation and subsequent borylation sparked significant interest as a prevalent reaction in synthesis owing to the high synthetic usefulness of the organoboron compounds. Organoboron compounds are a class of multifunctional reagents for the preparation of carbon-carbon and carbon-heteroatom bonds in modern synthetic chemistry. The most challenging task in these C-H borylation reactions is controlling the site selectivity. However, because of the huge efforts of many pioneering research groups, the selectivity problem has now outreached a notable level for both the proximal and distal C-H bond borylation reactions. The work complied in this thesis mainly aims to deliberate and summarize the different strategies and findings related to the invention of the directed proximal *ortho*, distal *meta*/*para*, aliphatic (racemic and enantioselective) borylation reactions.

This thesis is divided into four chapter.

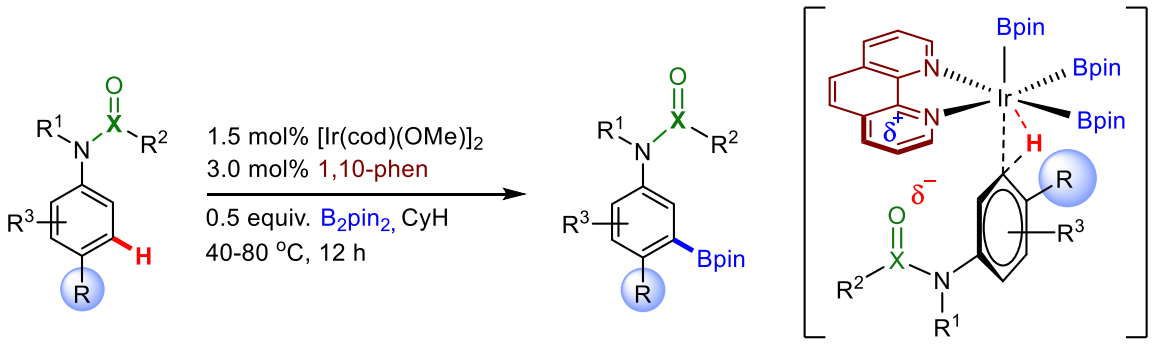
Chapter 1 highlights seminal advances in iridium-catalyzed *ortho*, *meta* and *para*-C-H borylation as well as C(sp^3)-H borylation reaction. Numerous elegant C-H borylation strategies are deliberated including pioneering examples of catalytic C-H borylation, reaction scopes, limitations and its mechanism, directed and noncovalent interaction assisted proximal and distal C-H bond borylation reactions. Beside these, some important application of boron containing molecules towards the synthesis of natural products, therapeutics, and applications in materials chemistry also discussed in this chapter.

Chapter 2 demonstrates a double-fold *ortho* C−H borylation of BINOL derivatives. The proposed mechanisms for *ortho* C−H activation and borylation processes involved an electrostatic interaction. The borylating agent B_2eg_2 (eg = ethylene glycolate) directs the C-H activation at *ortho* positions. The borylation protocol was combined with Suzuki

arylation as a one-pot method for the rapid synthesis of 3,3' diarylbinol derivatives with retention of chirality.

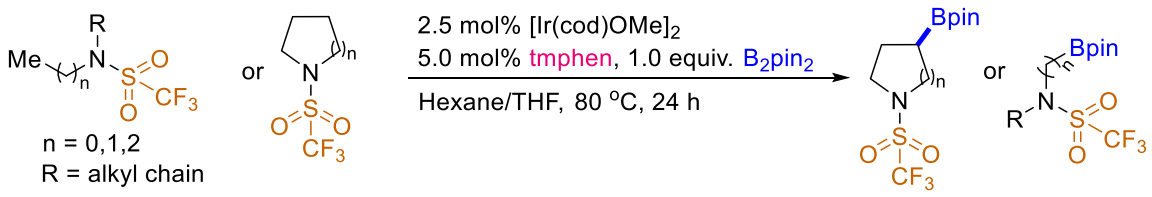


Chapter 3 describes an electrostatically directed *meta* borylation of sterically biased and unbiased substrates. An electrostatic interaction between the partially positive and negative charges between the ligand and substrate controls the *meta*-selectivity of this borylation process. With this protocol, it has been demonstrated that a broad number of challenging substrates, especially 4-substituted arenes can selectively be borylated at the *meta* position.



A variety of unsubstituted substrates displayed excellent *meta* selectivity, especially four substituted substrates, can selectively borylated at the *meta* position. The employment of bench-stable ligand, milder temperature, makes this borylation method more useful in organic synthesis.

Chapter 4 explains C(sp^3)-H borylation of the *N*-protected alkylamines. In this method, a bench stable 3,4,7,8-tetramethylphenanthroline ligand is used for borylation at moderate



reaction temperature. Long chain as well as cyclic substrates are well compatible under these borylation reaction. This C(sp^3)-H borylation strategy will be useful for the synthesis of various alkylboron reagents and would be widely used in pharmaceutical industries, natural product synthesis and drug discovery.

In the last, fifth chapter explains the summary of all the work.

Contents

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Abbreviations

Ar	Aryl
Ac	Acetyl
aq.	Aqueous
acac	Acetylacetonate
$AsPh_3$	Triphenylarsine
8-AQ	8-Aminoquinoline
-Bcat	Catecholate ester of boron, also called Catechol boronate
HBcat	Catechol borane
-Bpin	Pinacolate ester of boron, also called Pinacol boronate
HBpin	Pinacol borane
B_2pin_2	Bis(pinacolato)diborane
$B_2(OH)_4$	Tetrahydroxydiboron
Bn	Benzyl
bpy	Bipyridine
Br	Bromine
Bu	Butyl
B-N	Boron-Nitrogen Bond
Boc	*tert*-butyloxycarbonyl
Beg	Ethyleneglycolatoboron
BDE	Bond Dissociation Energy
BEt_3	Triethylborane
$EtB(OEt)_2$	Diethyl ethylboronate
^tBu	Tertary butyl also called tert-Butyl
^oC	Degree Celsius

Abbreviations

Cp*	Pentamethyl Cyclopentadienyl
C-B	Carbon-Boron Single Bond
C-C	Carbon-Carbon Single Bond
C=C	Carbon-Carbon Double Bond
C-H	Carbon-Hydrogen Single Bond
C-F	Carbon-Fluorine Single Bond
C-O	Carbon-Oxygen Single Bond
C-TM	Carbon bonded to transition metal
C-X	Carbon singly bonded to any halogen
CMD	Concerted Metalation Deprotonation
C-Si	Carbon-Silicon Single Bond
cod	Cyclooctadiene
coe	Cyclooctene
$CHCl_3$	Chloroform
CyH	Cyclohexane
Cl	Chlorine
CHO	Aldehyde Functional Group
CF_3	Trifluoromethyl Group
$CDCl_3$	Deuterated Chloroform, NMR solvent
D	Deuterium
d	doublet (peak in NMR spectrum)
dd	doublet of doublet (peak in NMR spectrum)
DG	Directing group
DCM	Dichloromethane

Abbreviations

DMSO	Dimethyl sulfoxide
DMF	*N*,*N*-Dimethylformamide
DMAP	Dimethylaminopyridine
DME	1,2 Dimethoxyethane
dtbpy	4,4' Di-tert-butyl-2,2'-bipyridine
dppe	1,2-Bis(diphenyl phosphine)ethane
dmpe	Dimethyl phosphinoethane
DoM	Directed *Ortho* Metalation
EAS	Electrophilic Aromatic Substitution
EDG	Electron Donating Group
EI	Electron Impact
ESI	Electron Spray Ionization
Et_3N	Triethylamine
EtOAc	Ethylacetate
EtOH	Ethanol
et al	et alia (and others)
EWG	Electron Withdrawing Group
equiv.	Equivalent
er	Enantiomeric Ratio
ee	Enantiomeric Excess
F	Fluorine
FG	Functional Group
Fe	Iron
GC	Gas Chromatography

Abbreviations

GC-FID	Gas Chromatography with Flame Ionizing Detector
GC-MS	Gas Chromatography with Mass Spectrometer
H	Hydrogen atom
h	Hour
Hz	Hertz (cycles per second)
HRMS	High Resolution Mass Spectroscopy
HPLC	High-Performance Liquid Chromatography
H_2SiEt_2	Diethylsilane
$HSiEt_3$	Triethylsilane
-I	Inductive effect
Ir	Iridium
$[Ir(cod)(OMe)]_2$	Bis(η^4-1,5-cyclooctadiene)-di- -methoxy-diiridium(I)
$[Ir(cod)Cl]_2$	Cyclooctadiene iridium(I) chloride dimer
$[Ir(cod)_2]BF_4$	Bis (1,5-cyclooctadiene)iridium(I) tetrafluoroborate
$[Ir(cod)(OH)]_2$	Hydroxy(cyclooctadiene)iridium (I)dimer
$[Ir(coe)_2Cl]_2$	Chlorobis (cyclooctene)iridium (I)dimer
^{i}Pr	Isopropyl
J	NMR Coupling Constant
KIE	Kinetic Isotope Effect
KOAc	Potassium Acetate
K_2CO_3	Potassium Carbonate
KOH	Potassium Hydroxide
LA	Lewis Acid
LB	Lewis Base

Abbreviations

LCMS	Liquid Chromatography Mass Spectroscopy
$LiAlH_4$	Lithium Aluminium Hydride
m	Multiplet Peak in NMR Spectrum
***m*-**	Meta- Substituted or directing to the meta position
M	Metal atom
M+	Molecular Ion peak in Mass Spectrum
m/z	Mass divided by Charge of an Ion in Mass Spectroscopy
Me	Methyl
Mol	Mole
mg	Milligram
mmol	Millimole
mL	Milliliter
MHz	Megahertz
MeOH	Methanol
MOM	Methoxy methyl ether
Mg	Magnesium
Me_4phen	3,4,7,8-tetramethyl-1,10-phenanthroline
N	Nitrogen atom
NMR	Nuclear Magnetic Resonance
NMe_2	*N*,*N*-Dimethylamine
NMP	*N*-methyl pyrrolidone
Nu	Nucleophile
NH_4Cl	Ammonium Chloride
o	Ortho

Abbreviations

o/p	Directing to ortho or para position
P	Phosphorous Atom
PCy_3	Tricyclohexyl Phosphine
Pd	Palladium
$Pd_2(dba)_3$	Tris(dibenzylidene acetone)dipalladium (0)
$Pd_2(dba)_3 \cdot CHCl_3$	Tris(dibenzylidene acetone)dipalladium (0) chloroform adduct
$PdCl_2 \cdot dppf$	1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(PPh_3)_4$	Tetrakistriphenylphosphine palladium(0)
P(*o*-tolyl)$_3$	Tri(*ortho*-tolyl)phosphine
Ph	Phenyl
PMe_3	Trimethyl Phosphine
PPh_3	Triphenyl Phosphine
***p*-xylene**	Paraxylene
Pd/C	Palladium on carbon
Pt	Platinum
Py	Pyridine
PtO_2	Platinum(IV) oxide
PhH	Benzene
PhMe	Toluene
Piv	Pivaloyl group
Phen	1,10-Phenanthroline
rt	Room Temperature
rds	Rate Determining Step

Abbreviations

Ru	Ruthenium
Rh	Rhodium
[Ru(*p*-cymene)Cl_2]	Dichloro(p-cymene)ruthenium(II)dimer
s	Singlet Peak in NMR Spectrum
s	Second
S	Sulphur
SiO_2	Silica Gel
SMAP	Silica-constrained monodentate trialkyl phosphine
THF	Tetrahydrofuran
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
TMP	3,4,7,8-tetramethyl-1,10-phenanthroline
^{t}BuONO	Tert-Butyl nitrile
TON	Turnover Number
tol	Toluene
TMEDA	Tetramethyl ethylenediamine
TM	Transition Metal
TS	Transition State
Ts	Tosyl
TFA	Trifluoroacetic Acid
TLC	Thin Layer Chromatography
Tf	Triflate

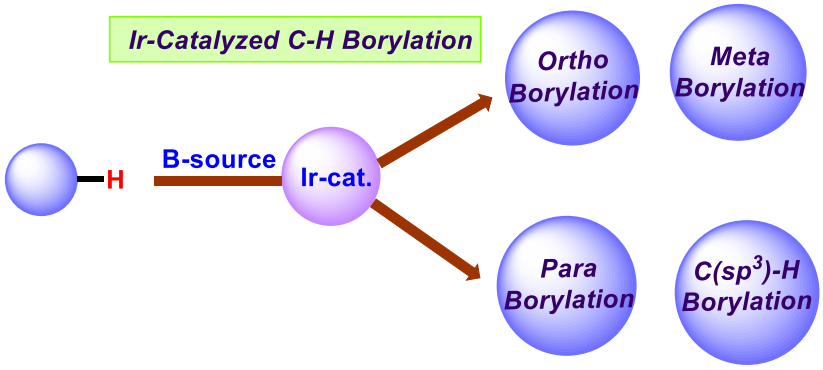
Abbreviations

Greek Letters:

α	Alpha
β	Beta
γ	Gamma
δ	Delta

CHAPTER 1

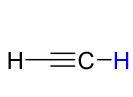
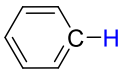
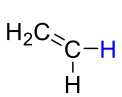
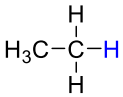
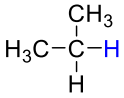
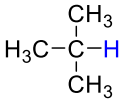
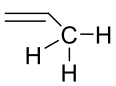
Iridium-Catalyzed C-H Bond Activation and Borylation of Aromatic and Aliphatic Molecules



1.1 Introduction

Last few decades have witnessed significant growth in the designing and development of step economical and environmentally benign organic synthesis that could provide a straight forward route for the preparation of high-valued organic compounds.[1] Usually, conventional organic synthesis reaction requires multistep, various hazardous reagents as well as pre-functionalized substrate. Often, this method produces stoichiometric amount of undesired by-products. Hence, this method is neither environmentally friendly nor economically workable. To address the aforementioned difficulties, it would be highly intriguing to develop new substitute synthetic strategy with improved atom and step economical process. In order to solve the above-mentioned limitations, organic synthesis has gradually shifted in the direction of a catalytic path. In this context, direct C-H bond activation and subsequent functionalization[2] could substantially reduce the lengthy synthetic path and also minimize the production of hazardous waste. In fact, transition metal-catalyzed carbon hydrogen activation/functionalization method is an attractive recipe to forge challenging carbon-hetero and carbon-carbon bonds.[3] The major challenge in this chemistry is the controlling the regioselectivity. If someone is planning to activate a C-H bond of a particular molecule selectively, one must be aware about the challenges linked with this method. Despite these challenges, many researchers have made tremendous developments to functionalize unreactive C-H bonds selectively. It is noteworthy that C-H activation/functionalization method can introduce a new functional group into the organic compounds by avoiding pre-functionalized substrate.[4]

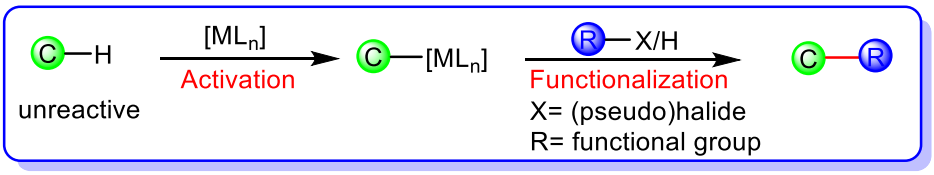
A non-acidic carbon-hydrogen bond in a molecule is very unreactive due to large kinetic

Type of C-H	C(sp)	$C(sp^2)_{aromatic}$	$C(sp^2)_{vinyl}$	$C(sp^3)_1{}^o$	$C(sp^3)_2{}^o$	$C(sp^3)_3{}^o$	$C(sp^3)_{allylic}$
Structure							
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
p*Ka*	25	43	44	50	50	50	43

Scheme 1.1: Bond Dissociation Energies and p*Ka* Values of Selected C-H Bonds

barrier associated with the carbon-hydrogen bond breakage. The bond dissociation energy and acidity of various types of C-H bonds are illustrated in **Scheme 1.1**. **Scheme 1.1** explains that although the BDE decreases from $1^o \rightarrow 2^o \rightarrow 3^o$ $C(sp^3)$-H bond, the p*K*a of corresponding C-H bonds follow the opposite trend.[5]

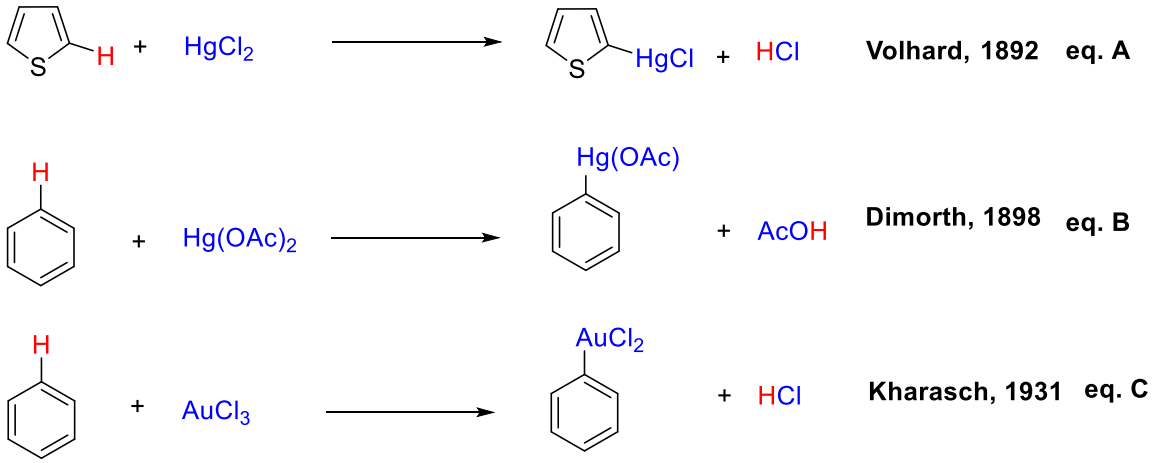
Generally, C-H bond activation refers to a reaction in which an unreactive C-H bond of aliphatic and aromatic molecules is cleaved in presence of a transition metal complex to produce a metal-carbon (M-C) bond. The selective activation of C-H bond followed by its functionalization into C-R bond (R = various functional group.) is called C-H functionalization[6] **(Scheme 1.2)**.



Scheme 1.2: General Representation of C-H Activation and Functionalization

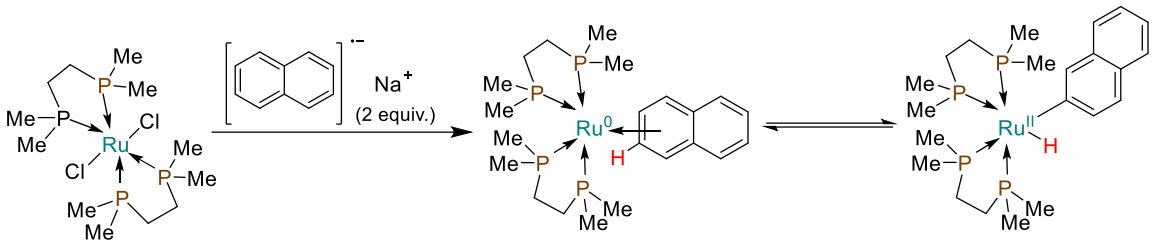
1.2. Historical Overview

The first example of metal-catalyzed C-H activation was reported by Volhard[7] in 1892 **(Scheme 1.3, eq. A)**. Authors reported the reaction between thiophene and mercury (II) chloride to prepare chloromercurythiophen. Later, in 1898, Dimorth[8] synthesized a series of arylmercury acetates from $Hg(OAc)_2$ and aromatic hydrocarbons **(Scheme 1.3, eq. B)**. Afterward, in 1931, Kharasch and co-worker[9] reported the reaction of Gold (III) chloride and benzene to synthesize chlorobenzene and gold chloride after isolation of $PhAuCl_2$ **(Scheme 1.3, eq. C)**.



Scheme 1.3: Pioneering Reports on Electrophilic C-H Metalation

In 1965, Chatt discovered a novel method for metal-catalyzed C-H bond activation by using ruthenium (0) complex (**Scheme 1.4**).[10] A new series of hydrido (aryl)-complexes were obtained from the reduction of trans-[RuCl(dmpe)] by "negatively charged arene" (i.e., benzene, naphthalene, anthracene, and phenanthrene) negative ions.

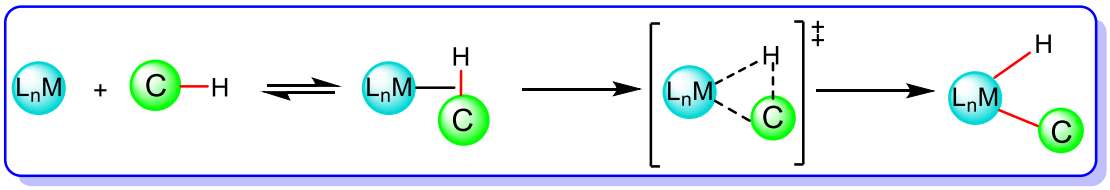


Scheme 1.4: Chatt's Pioneering Work on C-H Activation of Naphthalene

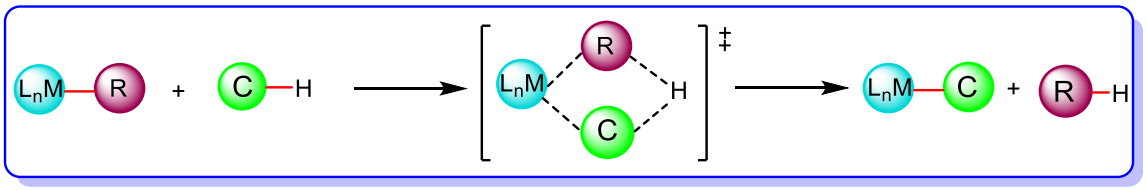
1.3 Mechanism of C-H Bond Activation

To realize the metal-catalyzed C-H bond activation process, it is essential to understand the basic mechanism of C-H activation reaction.[11] Depending on the employed reaction conditions, there are following mode of C-H activation described in literature.

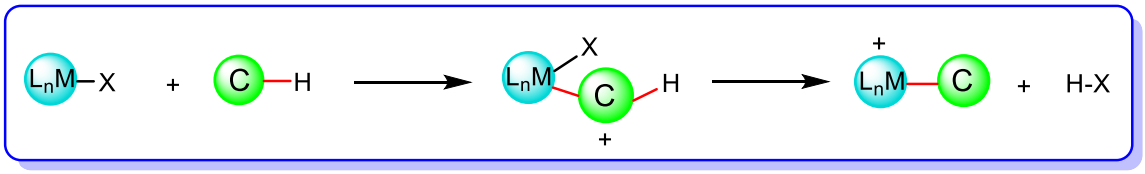
(i) Oxidative Addition: It is common for low valent electron rich transition metal complexes. Oxidative addition is the most general step for the metal-catalyzed C-H bond activation reaction, in which M-C and M-H bonds are formed after breakage of C-H bond. The steric, electronic environment of the metal centre as well as substrate play a crucial role for this oxidative addition step. It is generally favoured by electron donating ligands such as *N*,*N*-bidentate, triphenylphosphine and *N*-heterocyclic carbene.[11a]



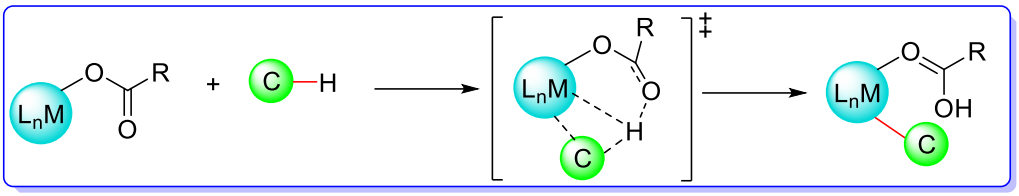
(ii) Sigma Bond Metathesis: Usually this type of mechanism is observed for those metal complexes of group 3 and 4, lanthanides and actinides, where an oxidative addition is not possible prefer this pathway. The mechanism of sigma bond metathesis involves bond breaking and bond formation in concerted manner. Sigma bond metathesis is also observed in late and post transition metals like Pd^{2+}, Pt^{2+}, Hg^{2+} etc.[12]



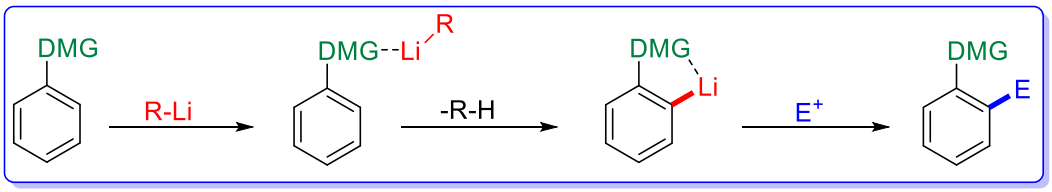
(iii) Electrophilic Substitution Mechanism: This pathway is suitable for electron poor late transition metal complexes. In this mechanism, at first, metal centre coordinates with the C-H bond and then in presence of an external anion, H-atom abstraction occurs.[13]



(iv) Base-Assisted Metallation: In this mechanism, carbon-hydrogen bond activation takes place in presence of a carboxylic acid or carbonate that likely proceeds via a concerted cyclic six membered transition state (known as "concerted metalation deprotonation", or CMD process).[14]



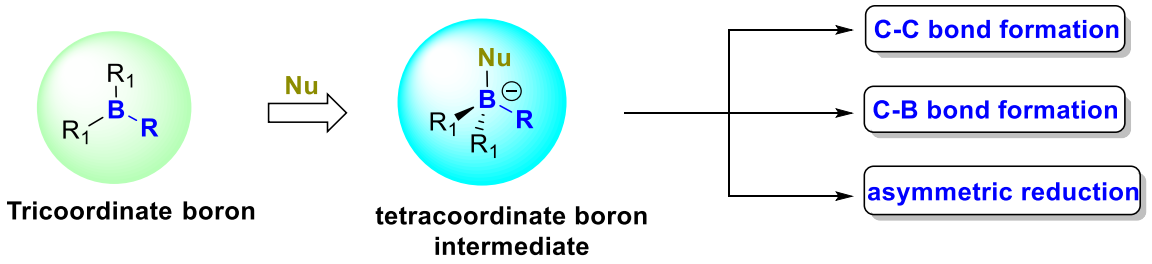
Another pathway is the directed ortho metalation, in which alkali metals activate the ortho position of an arene and in the presence of electrophile ortho position get functionalized. A diverse class of compounds have been metalated by divergent organometallic compounds in several way. The concept of directed *ortho* metalation was developed by Snieckus *et al.*[15,16]



1.4 Introduction of Organoboron Compounds and its Applications

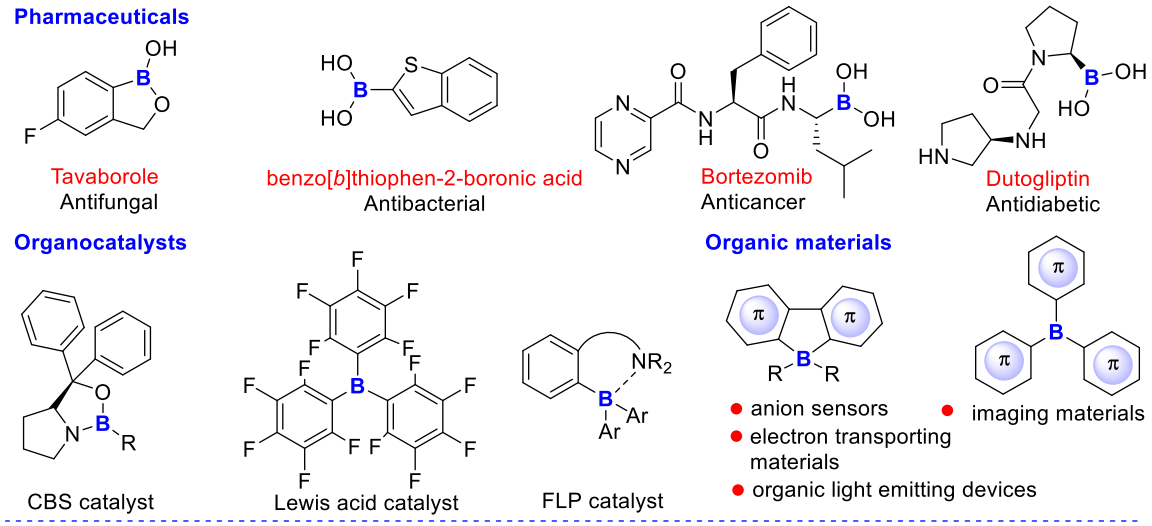
The chemical compounds of carbon and boron are known as organoboron compounds. They are the organic derivatives of BH_3. Last few decades have seen tremendous development of organoboron chemistry particularly in the field of organic synthesis. It deserves stating that the organoboron compounds are used both as catalysts and as reagents in many interdisciplinary research fields. In contrast to other organometallic reagents, organoborane reagents are less toxic, less sensitive as well as eco-friendly and easy to use in the laboratory. On the other hand, due to the availability of an empty p-orbital, tricoordinate boron atom acts as a Lewis acid. Due to this unique property, boron atom can easily accept an external nucleophile and converted into a nucleophilic centre. This nucleophilic boron centre participates in many synthetic transformations like as carbon-carbon, carbon-boron bond formation reaction, asymmetric reduction and many more

(**Scheme 1.5**). Notably, this donor-acceptor properties make organoboron compound an efficient catalyst in organic synthesis. [17]



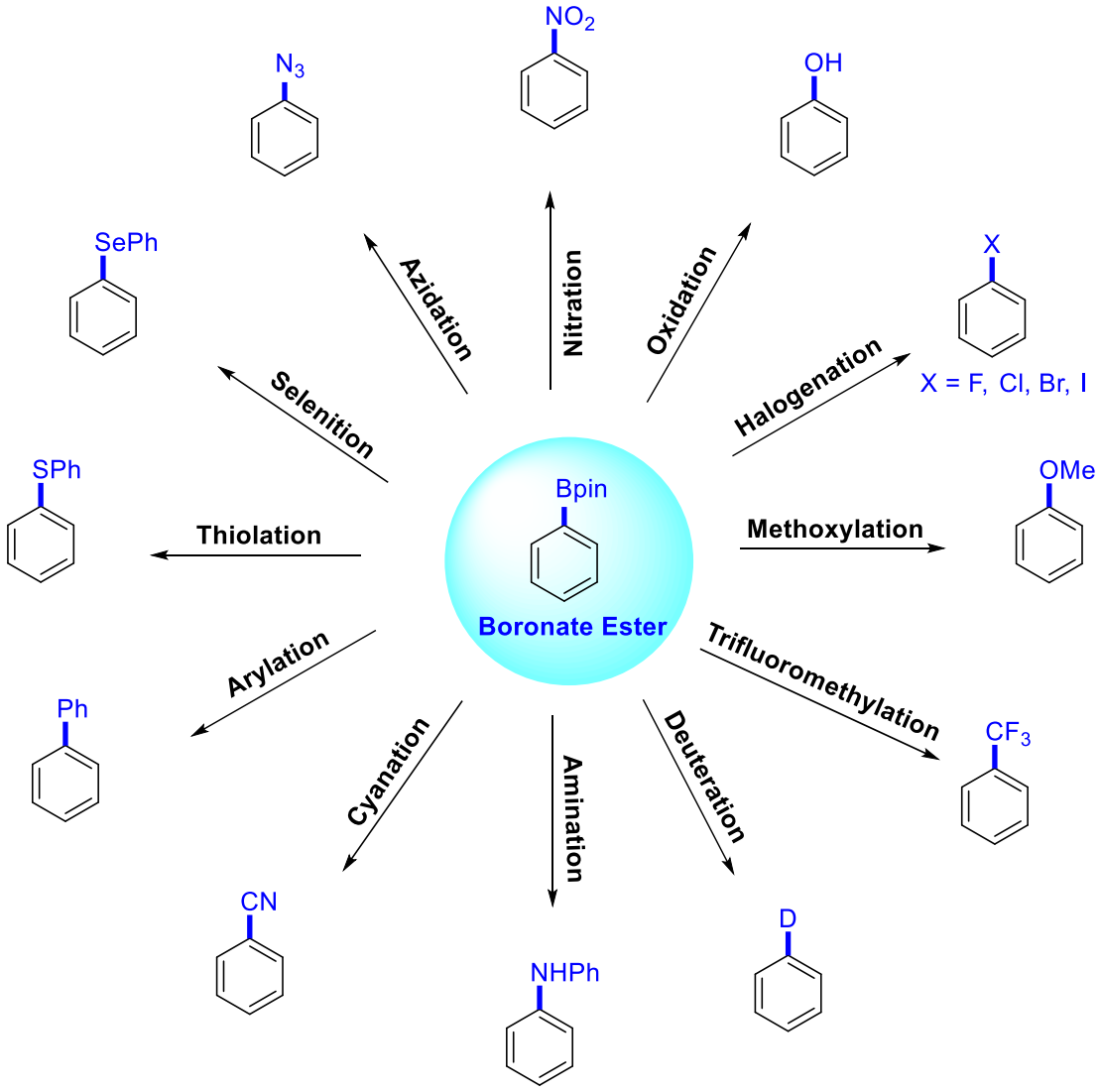
Scheme 1.5: Transformation of Tetracoordinated Organoborane Compounds

Recently, organoborane compounds have received considerable attention from synthetic organic chemist due to their widespread application in pharmaceuticals,[18] catalysis[19] and materials sciences[20] **(Scheme 1.6)**. Boron bearing drugs such as Tavaborole (antifungal), Bortezomib (anticancer), Dutogliptin (antidiabetic) are well known in pharmaceutical industry.[21] Several boron containing catalysts like CBS catalyst, $B(C_6F_5)_3$, FLP catalyst are widely used in organocatalysis reaction.[22] However, in material sciences[20] also, boron atom is used in many purposes.



Scheme 1.6: Organoborane Compounds in Pharmaceuticals, Organocatalysis and Organic Materials

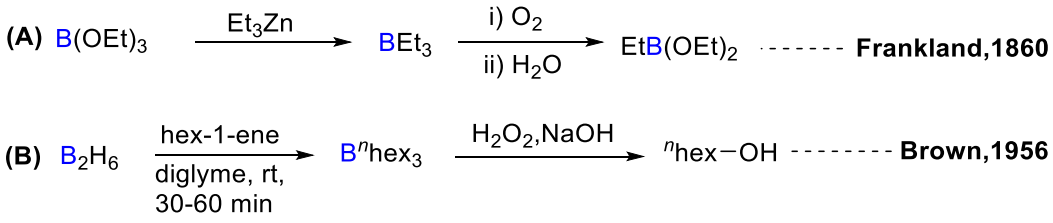
Owing to the versatility and unique reactivity, one can achieve many synthetic transformations using organoborane esters. Several notable transformations[23] illustrated in **Scheme 1.7** such as cross-coupling, amination, bromination, iodination, chlorination, etherification, oxidation, deuteration, azidation, carboxylation, nitration, alkylation and many more can be accomplished from boronate esters.



Scheme 1.7: Synthetic Transformations of Boronate Ester

1.4.1 Synthesis of Organoboron Reagents

The first synthesis of organoborane compound was reported by Frankland in 1860. He synthesized triethyl borane i.e., Et_3B and diethyl ethyl borate **(Scheme 1.8, A)**.[24]

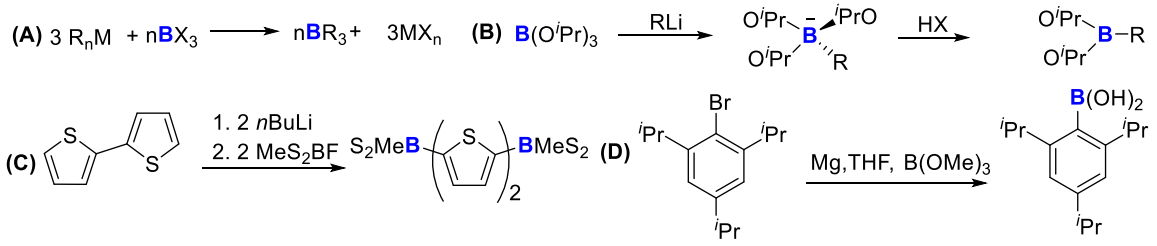


Scheme 1.8: Pioneering Reports of Organoborane Synthesis

After that, almost after 100 years, in 1956, Brown discovered hydroboration of alkene system using diborane reagent **(Scheme 1.8, B)**.[25] Brown *et al.* transformed the corresponding trialkyl borane reagent into alcohol using alkaline peroxide reagent. This

nobel prize winning reaction is known as a major contributor in the field of organoboron chemistry. Although, in literature several transformations are available for the preparation of organoboron compounds, in this section I will discuss some of the vital methods i.e. (i) transmetallation reaction, (ii) hydroboration of C=C system and (iii) C-H activation approach.

(i) Transmetallation Reaction: Transmetallation reaction presents a straightforward strategy to access organoborane compounds.[26] Basically, the reaction between organometallic reagent like organolithium species and borane BX_3 yielded desirable organoborane compounds along with the corresponding metal salts **(Scheme 1.9, A)**.

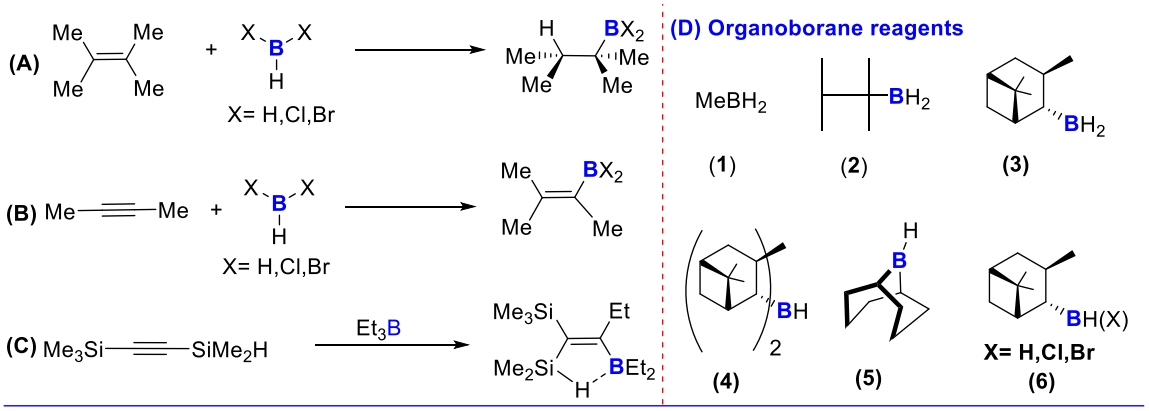


Scheme 1.9: Transmetallation Method for the Synthesis of Boronate Esters

Among many organometallic reagents, organolithium and Grignard reagents are most valuable and extensively used reagents for the preparation of boronic acid or ester derivatives. Few examples of organoborane synthesis using organolithium reagents and Grignard reagents respectively are exemplified in **Scheme 1.9**. As shown in **Scheme 1.9,** one can synthesize the organoborane compounds using organolithium reagents by two step processes. Various boronic acid derivatives can be prepared applying above lithiation strategy after acidic work up. It has been found that triisopropyl borate and dimethylaminodihaloborane afforded good selectivity. Plenty of diorgano and triorganoboranes could be accessed using the above-mentioned established protocols. Undoubtedly, this traditional transmetallation method is extremely beneficial due to the use of inexpensive reagent, operationally simple protocol as well as suitability in large scale, there are many disadvantages which limit its synthetic benefit such as: (i) high reactivity of reagents lead to reaction with solvent like ethers (ii) selectivity issues in case of other types of boron derivatives for example RBX_2, R_2BX, R_3B etc. (iii) need of stoichiometric amount of bases (iv) necessity of severe cryogenic conditions (v) incompatibility of various substrate and functional groups also.

(ii) Hydroboration Reaction: Hydroboration is one of the most competent and useful protocol for the preparation of organoboron compounds. This reaction was discovered by

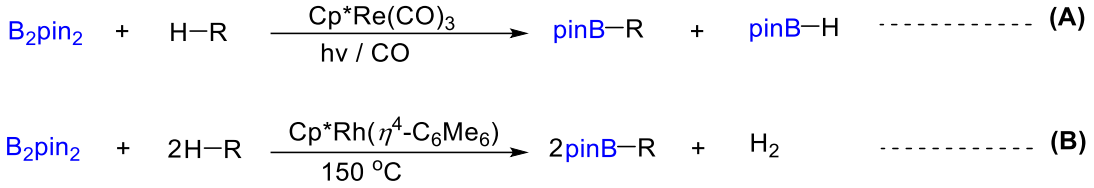
Brown *et al.* in 1956.[25] Mechanistically, in hydroboration reaction, the boron and H atoms added to the C=C bond and C-C triple bonds in cis-fashion. Notably, boron atom added to the less substituted site following the anti-Markovnikov addition. However, in case of strong electron poor substitution (e.g., F substitution), the addition of borane reagent occurred at more substituted site (called Markovnikov addition). In literature, detailed mechanistic investigations of the hydroboration reactions are reported.[17] Generally, in hydroboration reaction, a 4-membered **TS** is formed and reaction pathway is concerted. Some typical examples of hydroboration reaction and borane reagents are illustrated in **Scheme 1.10**.



Scheme 1.10: Examples of Hydroboration Reaction and Organoborane Reagents

(iii) C-H Activation: An elegant and straightforward strategy to access organoboron compounds is the direct C-H activation. Over the time, plenty of carbon-hydrogen bond activation strategies (stoichiometric and catalytic) have been developed around the world by many researchers.[27] One of the major advantages of the C-H activation strategy is that it can functionalize inert C(sp^2)-H and C(sp^3)-H bonds in single step. Due to this unique property, C-H activation strategy has demonstrated itself as one of the most efficient, step and atom economy as well as eco-friendly method over others reported methods. In the literature, most of the borylation reactions had been achieved using diborane reagent i.e., $B_2(OR)_4$, albeit in some cases $HB(OR)_2$ also used as the boron source. Early report on borylation of hydrocarbon systems using Rhenium-boryl complexes [$Cp^*Re(CO)_2(Bpin)_2$] was disclosed by Hartwig *et al.* in 1995.[28] In this study, authors have shown that metal-boryl complexes can selectively borylate the aliphatic pentane chain to corresponding 1-borylpentane under the developed conditions. Four years later (1999), same group discovered a catalytic aliphatic C-H borylation reaction using $Cp^*Re(CO)_3$ under the

photochemical conditions (**Scheme 1.11, A**).[29] Moreover, in 2000, Hartwig and co-worker developed a Rh-catalyzed C-H borylation reaction of alkane system **(Scheme 1.11, B)**.[30]

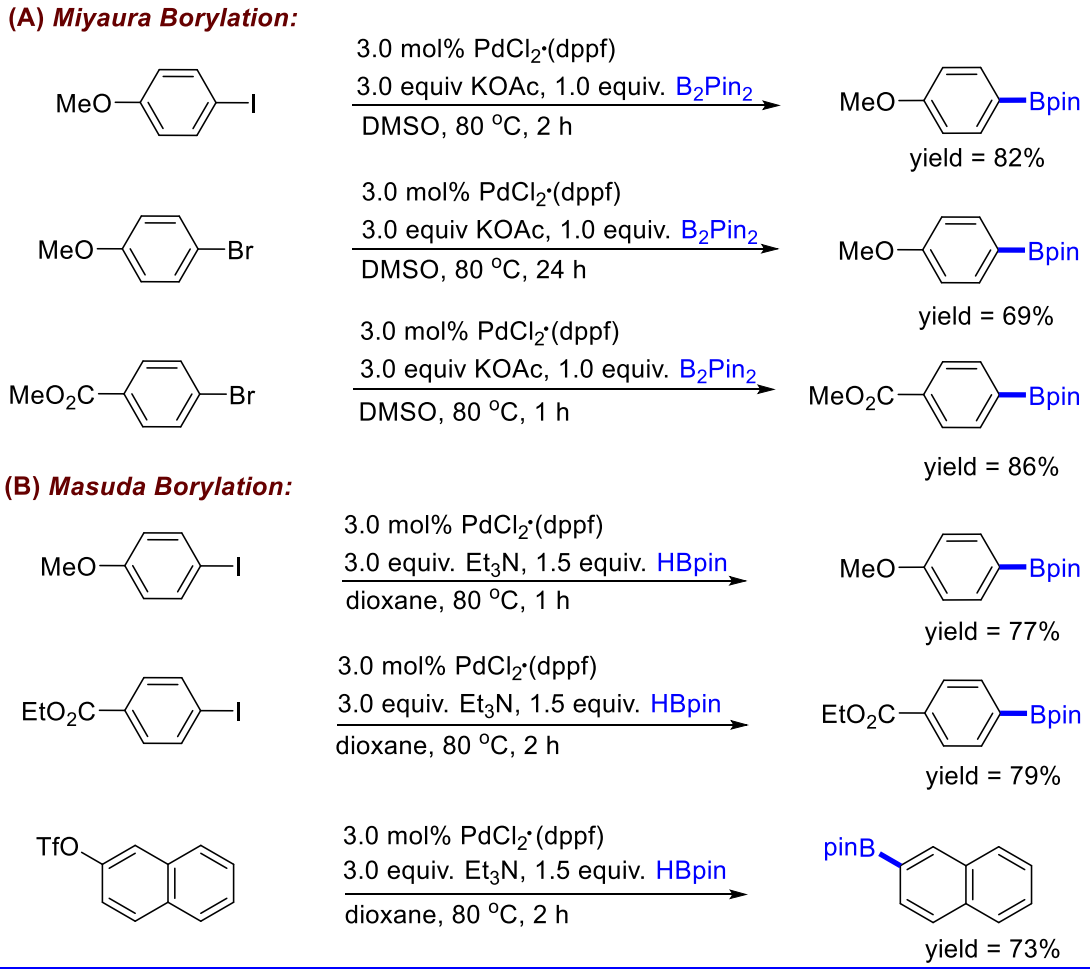


Scheme 1.11: Borylation Using C-H Activation Strategy

However, pioneering examples of C-H borylation reaction, discovery of new catalytic systems, complete mechanistic studies of borylation reaction will be discussed in detail in borylation section.

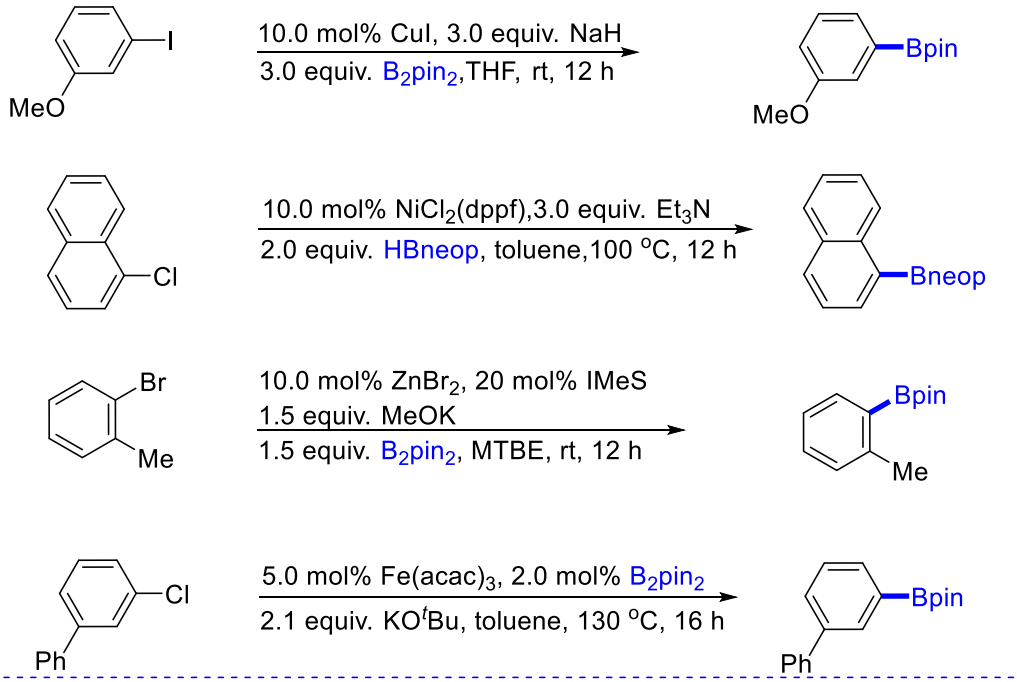
1.4.2 Other Methods for the Synthesis of Organoboron Compounds

(i) Cross Coupling Reaction: Owing to the high synthetic efficacy of aryl boronic acids and esters in organic synthesis, the strategies that produced boronate esters significantly desired more to be investigated.



Scheme 1.12: Pd-Catalyzed Borylation of Aryl Halide

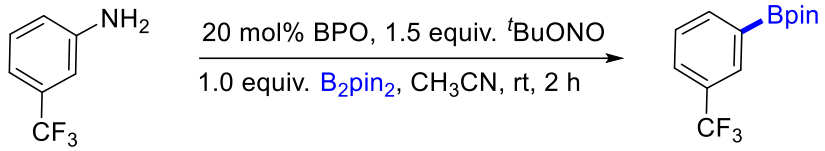
Though, conventional transmetallation approach is well known for the synthesis of organoboranate esters, employment of harsh cryogenic conditions and high reactivity of Grignard and alkyl lithium reagents allow the chemical community to find a new alternative route. For instance, transition-metal catalysts could be more convenient because of their lenient reaction conditions and broad compatibility of functional groups. The cross-coupling reaction of boron nucleophile with aryl electrophile is one of the most elegant strategies for the preparation of $RB(OH)_2$ and $RB(OR)_2$. In 1995, Miyaura *et al.* reported Pd-catalyzed cross-coupling reaction of bis(pinacolato)diboron (B_2pin_2) with aryl halide or pseudohalide (**Scheme 1.12, A**).[31] In this reaction, they have used $PdCl_2$.(dppf) as catalyst along with base. It has found that aryl iodide showed higher reactivity compared to the aryl bromides. Whereas, electron poor substrates are well suited for this coupling reaction, electron donating substrate also underwent borylation reaction, albeit long period of time is necessary. Later, an extension of Miyaura's Pd-catalyzed reaction was reported by Masuda *et al.* (**Scheme 1.12, B)**.[32] In this study, they substituted the previously developed borylating agent from B_2pin_2 by HBpin. In addition to Pd-catalyzed Miyaura borylation, other transition-metals (such as Cu, Ni, Zn, and Fe) catalyzed borylation using aryl halides precursors are illustrated in **Scheme 1.13**.[33]



Scheme 1.13: Transition Metal-Catalyzed Borylation of Aryl Halides

(ii) Transition Metal-Free Borylation Reaction

Numerous metal-free protocol for the synthesis of boronate esters have been reported in the literature. In 2010, Wang group first discovered the metal-free borylation reaction using aryl amines. Diazotization of aryl amine using BPO and ^{t}BuONO followed by borylation in presence of B_2Pin_2 afforded the corresponding boronate ester at room temperature, shown in **Scheme 1.14**.[34]

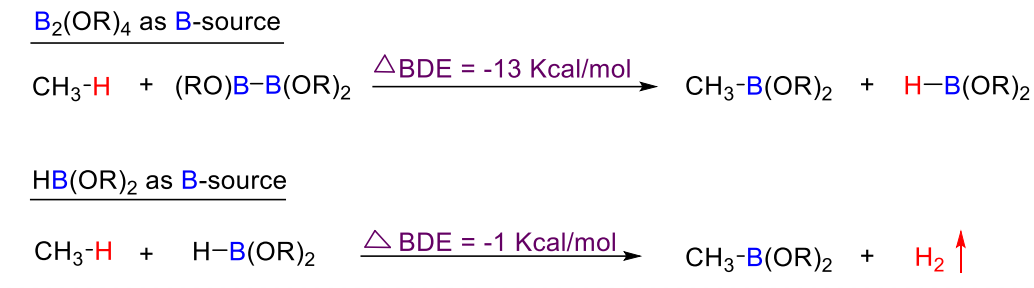


Scheme 1.14: Metal-Free Borylation

However, transition metal-free borylation methods using carbon-nitrogen, carbon-halogen bonds are also available in the literature.[35] Notably, the major limitation of metal-free borylation is the requirement of pre-functionalized arene, which has to be prepared from their hydrocarbon analogue or from the parent functional group.

1.5 C-H Borylation

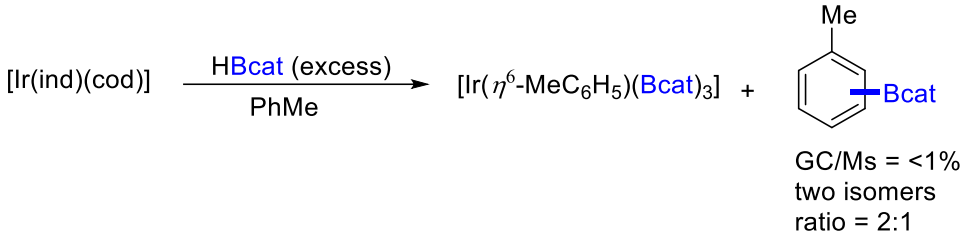
In synthetic organic chemistry, functionalization of a particular carbon-hydrogen bond of organic molecules is challenging. Many scientists have contributed significantly towards selective transformation of arene C-H bonds to C-X (X = O, N, F, Cl, Br & I) bonds.[36,37] In this context, direct functionalization of carbon-hydrogen bond to carbon-boron bond is a growing area in organic chemistry. Remarkable developments have been observed toward the process that catalyzes the borylation reactions of carbon-hydrogen bonds in aromatic and aliphatic molecules with high selectivity and reactivity. It deserves mentioning that the C-H borylation chemistry is studied by several research groups because of their high usefulness in natural product synthesis, chemical synthesis and materials science.[18-20] The calculated bond energies for the formation of carbon-boron bond from carbon hydrogen bond (disclosed by Hartwig *et al.* in 1994) reveals that the reaction is thermodynamically and kinetically favourable, shown in **Scheme 1.15**.[38-40] It has been stated that transition state of carbon hydrogen bond breakage is stabilized due to the presence of lowest unoccupied molecular orbital i.e., p_z-orbital on the boryl group.



Scheme 1.15: Thermodynamics of Methane Borylation

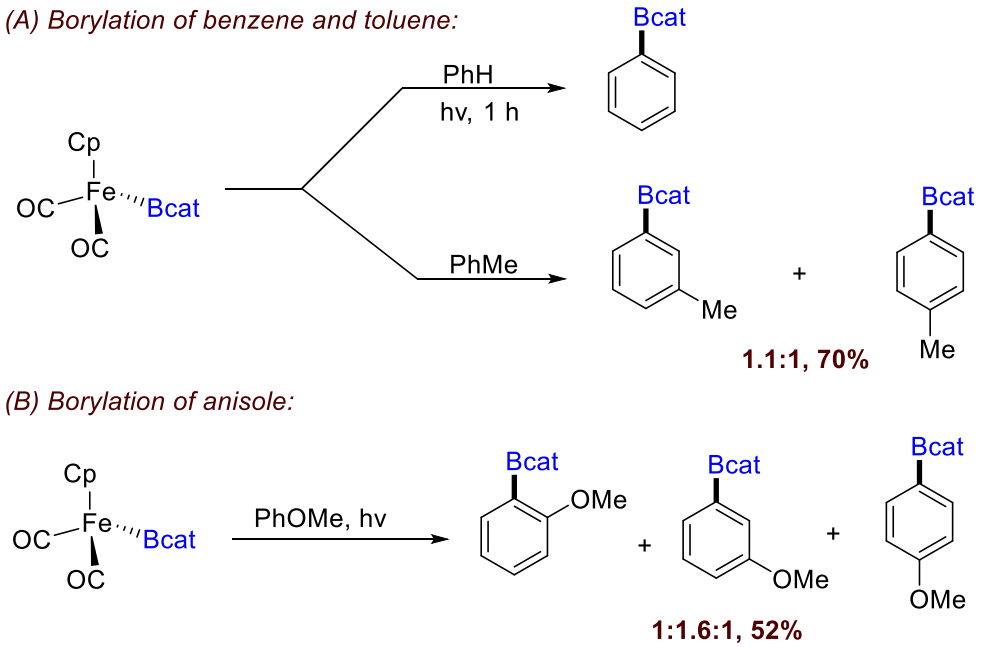
1.5.1 Stoichiometric C-H Borylation

In 1993, Marder group first discovered the synthesis of trisboryl iridium complex i.e., [Ir(η^6-MeC$_6$H$_5$)(Bcat)$_3$].[41] They found that the borylation of toluene gave very less amount (<1% yield) of two regioisomer of tolylboronate ester analyzed by GC/MS (**Scheme 1.16**).



Scheme 1.16: The First Stoichiometric Aromatic C-H Borylation

However, performing the same reaction in deuterated benzene solvent, same outcome i.e., two regioisomers were observed. Notably, this protocol was failed to borylate the arenes.

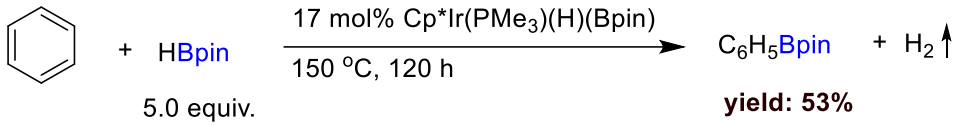


Scheme 1.17: Photocatalytic Borylation Catalyzed by Iron Boryl Complex

In 1995, Hartwig and his co-worker demonstrated a photochemical reaction using metal boryl complexes.[42] The authors obtained 87% yield of PhBcat by irradiation of $CpFe(CO)_2(Bcat)$ in C_6H_6 solution. Monosubstituted arenes like toluene produced a regioisomeric mixture (*m* & *p*) of arylboronate esters. Moreover, it was also found that the anisole afforded the corresponding borylated product in the ratio 1.0:1.6:1.1 (*o*, *m* & *p*) under the established reaction conditions (**Scheme 1.17**).

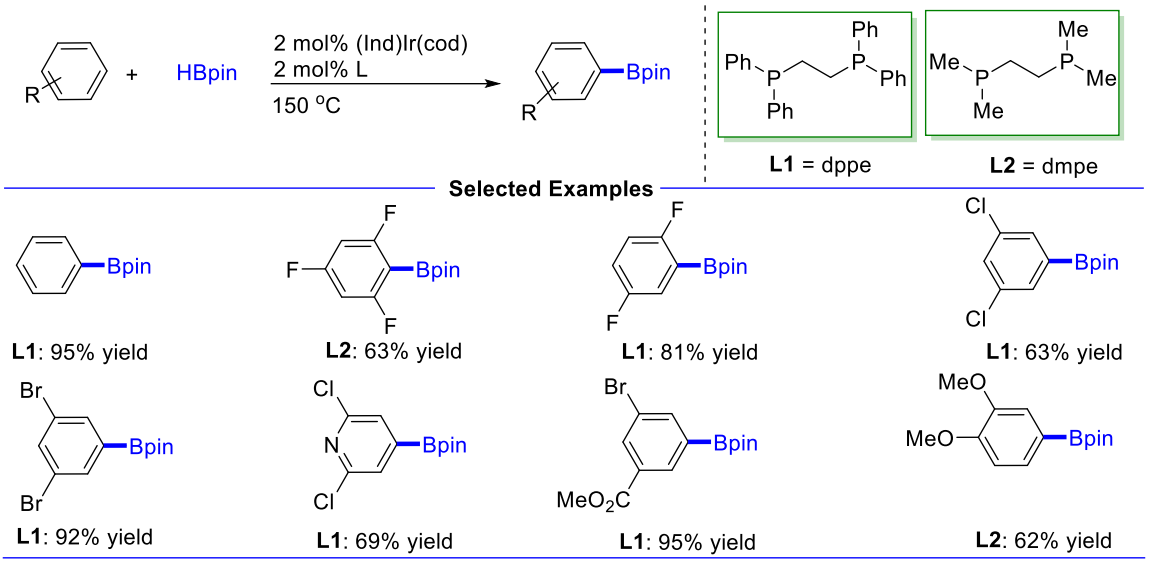
1.5.2 Catalytic C-H Borylation

In 1999, Smith *et al.* for the first time reported a catalytic reaction of HBpin with $Cp^*Ir(PMe_3)(H)(Bpin)$ in deuterated benzene (C_6D_6) at 150 °C, which afforded the C_6D_5Bpin in 53% yield (ca. turnover no = 3). The reaction was also performed on a larger scale in C_6H_6, resulted in C_6H_5Bpin with 53% isolated yield.[43]



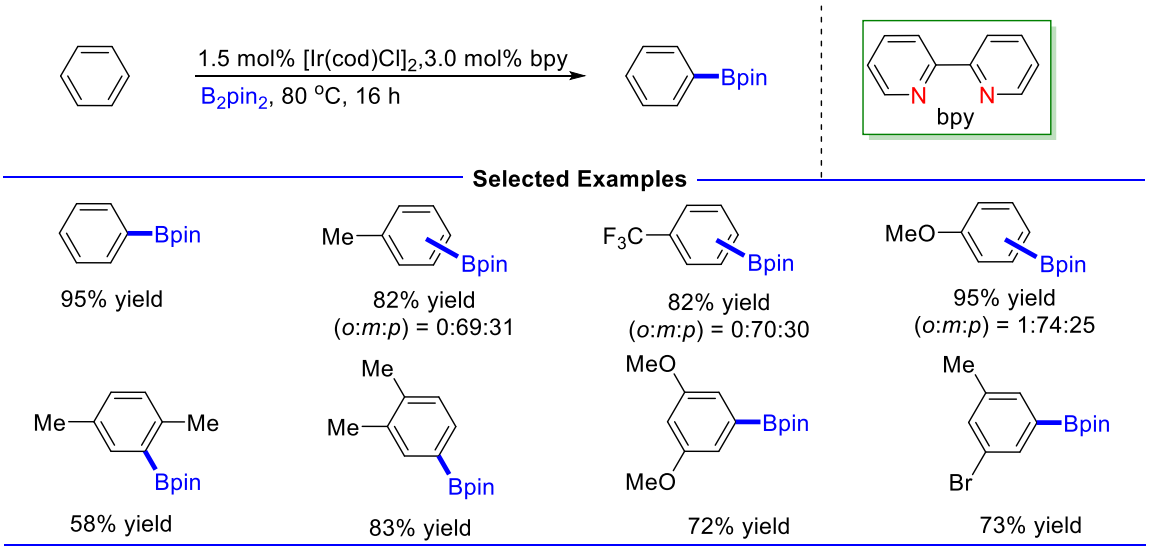
Scheme 1.18: First Report for Thermal Catalytic Borylation

In order to develop a competent catalytic system, the same group discovered an iridium-based catalytic system using phosphine and nitrogen-based ligands (e.g., trimethyl phosphine, dmpe, dppe) for the borylation of arenes (**Scheme 1.19**).[44] For this study, they have used (Ind)Ir(cod) as a catalyst and HBpin as a boron source. Authors observed that this modified strategy promoted the C-H borylation reaction at faster rates in comparison to their previously developed strategy and afforded high yield of the corresponding boronate esters. For example, the reaction between benzene and HBpin at 150 °C in presence of (Ind)Ir(cod) and trimethylphosphine ligand produced phenylboronate ester with 88% yield. Replacing the PMe_3 ligand by the dppe, it resulted in 95% yield of PhBpin after 2 hours of the reaction. The selectivity of this borylation reaction is governed by steric factor. For instance, borylation of 1,3-disubstituted arenes preferred at less hindered position i.e., 5-position of arenes.



Scheme 1.19: (Ind)Ir(cod) and Phosphine Ligands Catalyzed Borylation of Arenes

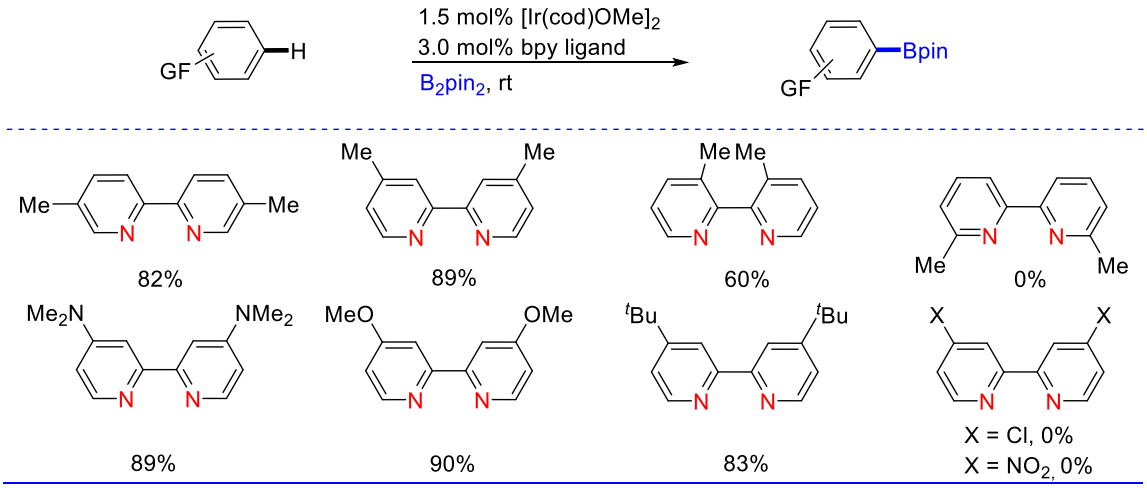
In 2002, Ishiyama, Miyaura, Hartwig and co-workers demonstrated an Ir-catalyzed borylation of arene systems using bipyridine (bpy) and di-tert-butylbipyridine (dtbpy) ligands.[45] In contrast to the previously developed borylation systems using phosphine ligand (represented in **Scheme 1.19),**[44] this borylation method was found to be more suitable. The reaction catalyzed by $[Ir(cod)Cl]_2$ and bipyridine or di-tert-butylbipyridine in presence of B_2pin_2 at 80 °C delivered moderate to good yields of the borylated products. It is also observed that the HBpin can also use as a workable boron source for these reactions. Steric effect controlled the selectivity of Ir/dtbpy-based borylation reactions and the results are depicted in **Scheme 1.20**.



Scheme 1.20: Ir/dtbpy-Catalyzed Borylation of Arene Systems

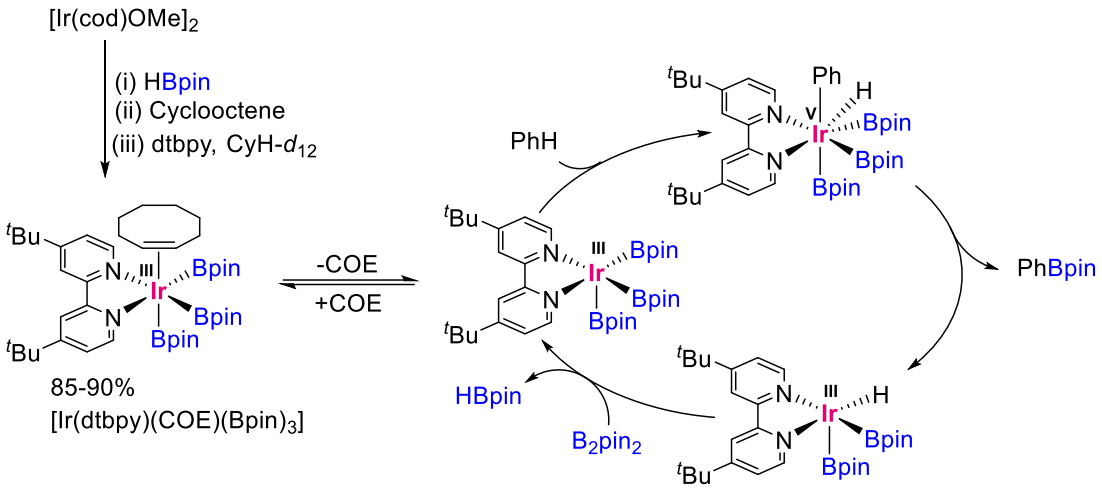
In borylation reaction, the monosubstituted substrates like $PhCF_3$, PhMe and PhOMe gave statistical mixture of *meta* and *para* borylated products, even though very less amount (1%) of *ortho* borylated product was observed. Moreover, the reaction of 1,3- and 1,4-disubstitued symmetrical substrates afforded exclusively one isomer.

To improve the catalytic efficiency, authors performed a systematic study by developing various bpy ligands and Ir-catalyst.[46] After screening various catalyst, they found that $[Ir(cod)OMe]_2$ is the most reactive catalyst among other Ir-based catalysts. However, their study revealed that the steric of methyl group in bipyridine ring influenced the outcome of the borylation reaction. To test this hypothesis, they carried out a borylation reaction benzene substrate in presence of Ir-catalyst, 6,6'-dimethyl-2,2'-bipyridine and B_2pin_2. However, the reaction yielded no borylated products. This is on account of the steric crowding of this Me group around the nitrogen atom which does not allow the iridium catalyst to come closer to the bipyridine N atom. Authors also mentioned that the electron rich group on bipyridine showed more catalytic activity in comparison to the electron poor group (**Scheme 1.21**).



Scheme 1.21: Ir-Catalyzed Borylation of Arenes Using Different Bipyridine Ligands

In 2005, Hartwig *et al.* disclosed a detailed mechanistic investigation for the arene C-H borylation (**Scheme 1.22**).[47] At first, they synthesized active catalytic intermediate $[Ir(dtbpy)(COE)(Bpin)_3]$ using $[Ir(cod)OMe]_2$, HBpin and cyclooctene along with dtbpy with 85-90% of isolated yield. The addition sequence is very much important for higher yield of the active catalyst.



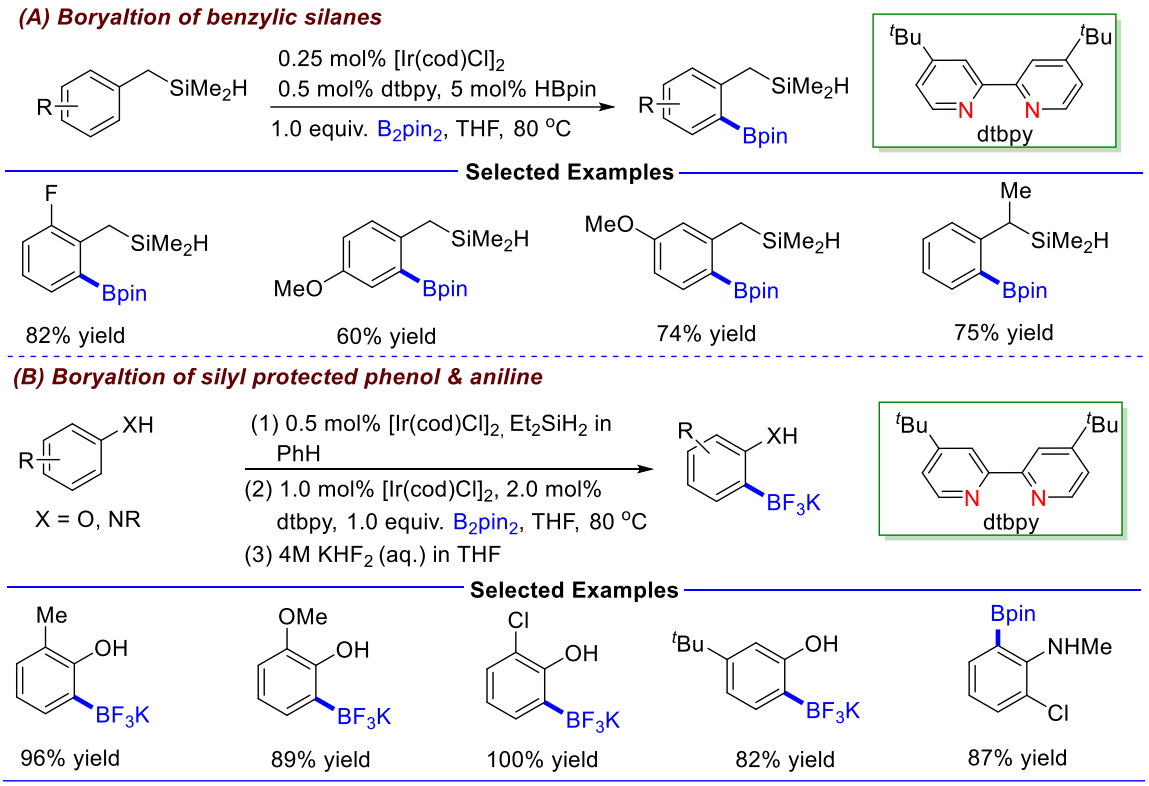
Scheme 1.22: Mechanism for Iridium-Catalyzed C-H Borylation of Arenes

The authors characterized the active catalyst intermediate [Ir(dtbpy)(coe)(Bpin)$_3$] by the NMR spectroscopy and X-ray crystallography. After several NMR experiments and kinetic data analysis, Hartwig group proposed a mechanism which is now widely used in the C-H borylation reaction. The mechanism is illustrated as follows: (i) reversible dissociation of labile cyclooctene from Ir-trisboryl complex (18 electron system), (ii) dissociation of cyclooctene that generates a vacant coordination site to produce 16-electron catalytic intermediate (iii) coordination of arene π-bond with 16 electron intermediate and subsequently oxidative addition gave Ir(V) intermediate (this step is the RDS), (iv) reductive elimination of Iridium(V) species produces Ir(III) intermediate, (v) finally, in presence of B_2pin_2 by oxidative addition Ir-trisboryl complex is generated after elimination of HBpin as well as catalytic cycle is completed. The entire mechanism is shown in **Scheme 1.22**.

1.5.3 Directed C-H Borylation of Arenes

Traditional directed *ortho* metalation (DOM) approach is a very well-known method to accomplish *ortho* selective C-H functionalization reaction. Although this strategy is very beneficial, there are many limitations which restrict its practical utility such as use of sensitive alkyl lithium reagents, cryogenic conditions and requirement of prefunctionalized substrate. Therefore, development of a new strategy to override those limitations is highly demandable. In recent years, regioselective Ir-catalyzed borylation reaction has emerged as an appropriate substitute of the conventional *ortho* metalation reaction. The regioselectivity of iridium based borylation reactions are mainly controlled by steric factors and the reaction mostly occurs at the less hindered aryl C-H bond. Therefore, the reaction

of 1,3-disubstituted substrate produced 1,3,5-trisubstited products and 1,4-disubstitued arenes afforded *ortho* substituted boronic acid.[6c] But, the major issue is that the monosubstituted arenes are unsuccessful for regioselective borylation. Therefore, such a process is essential which would overturn the sterically controlled regioselectivity issues. Keeping all these hitches in mind, several researchers have effectively started to develop complementary protocols such as directed C-H borylation reactions where regioselectivity is determined by the DG.[48]

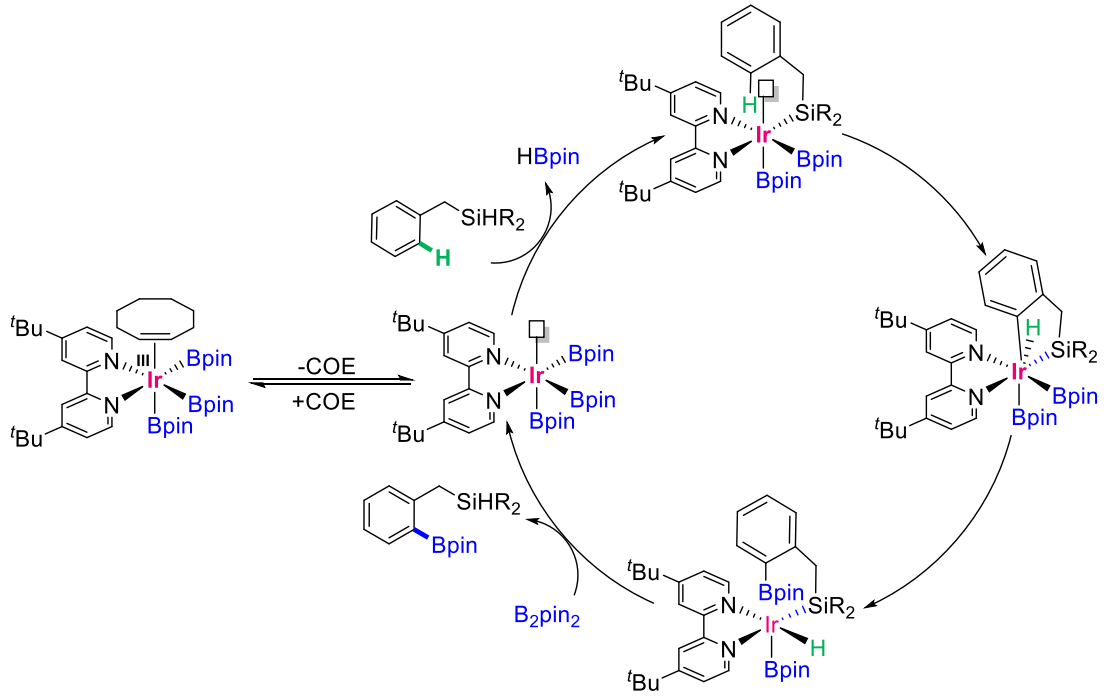


Scheme 1.23: Silyl-Directed *Ortho*-Borylation of Arenes

In 2008, for the first time, Boebel and Hartwig reported *ortho* brylation of aromatic system directed by hydrosilyl group (**Scheme 1.23**).[49] The substrate benzyldimethylsilane gave a mixture of mono to di (2.3:1) *ortho* borylated products in presence of $[Ir(cod)Cl]_2$, di-tert-butylbipyridine and B_2pin_2. However, no other borylated products (*meta* and *para*) were not observed in ^{1}H-NMR. The reaction of 2,3 and 4-substituted benzyldimethyl silane gave the desired *ortho* borylated product (**Scheme 1.23, A**). The purification of product was tough due to instability of borylated compounds. As a result, authors converted the corresponding borylated products to their stable trifluoroborate salts by treating the crude reaction mixture with excess amount of aqueous potassium hydrogen fluoride (KHF_2). This

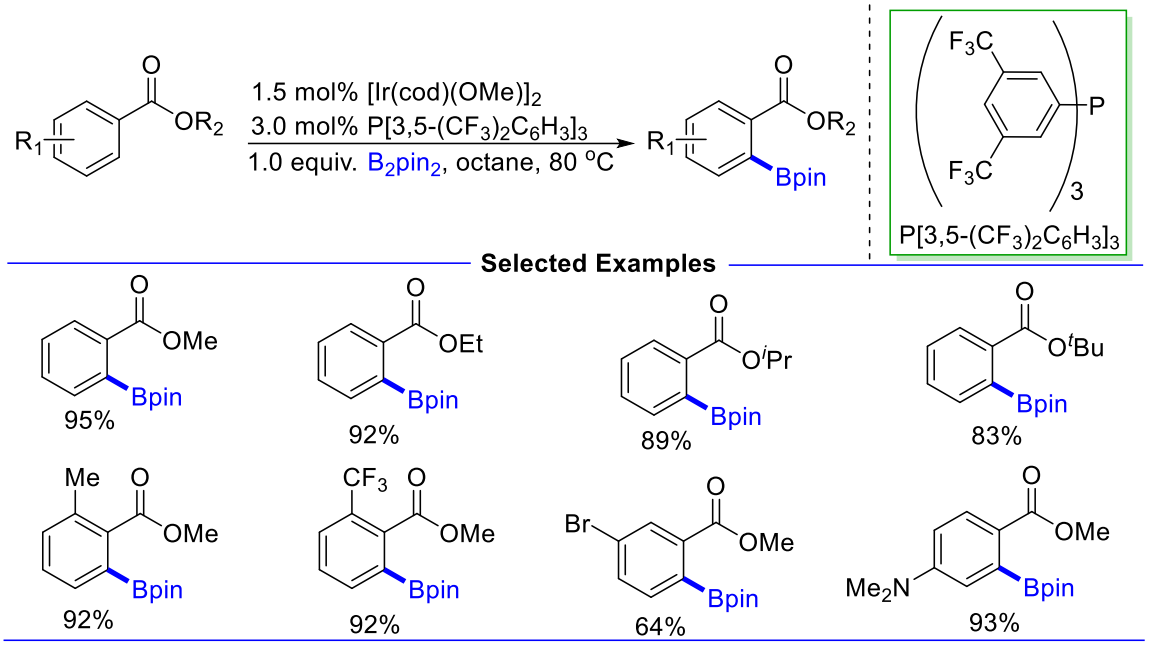
developed protocol has been successfully applied to the benzylic, phenols and anilines silanes, mentioned in **Scheme 1.23 B**.

The mechanism of this *ortho* borylation reaction is depicted in **Scheme 1.24**. In this mechanism, at first, iridium trisboryl complex is formed. Then, oxidative addition of Ir-trisboryl complex with Si-H bond of hydrosilyl group of the substrate occurs and generates diborylmonosilyl complex. After the formation of the diboryl monosilyl complex, an *ortho* carbon-hydrogen activation and functionalization gives hydride complex which subsequent addition of B_2pin_2 affords the desired *ortho* borylated product. Finally, Ir-trisboryl complex is regenerated.



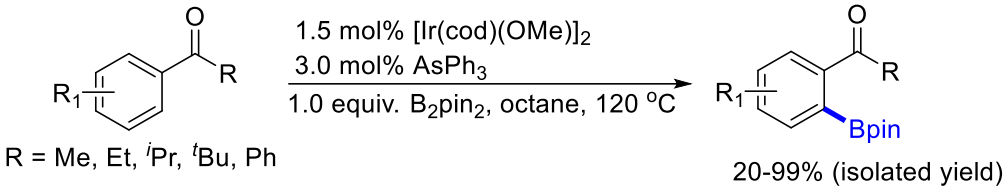
Scheme 1.24: Mechanism of Hydro Silyl Directed Borylation of Alkylarenes/Arenes

In 2010, a method for Ir-catalyzed directed *ortho* borylation for benzoate esters were reported by Ishiyama, Miyaura and co-workers.[50] Employment of electronically deficient and commercially available $[(3,5\text{-}(CF_3)_2C_6H_3)_3P]$ ligand in the presence of B_2pin_2 at 80 ^oC in octane solvent gave desired borylated product. A variety of substituted methyl benzoate show excellent regioselectivity toward the *ortho* borylation method (**Scheme 1.25**).



Scheme 1.25: Ir-Catalyzed *Ortho*-Selective C-H Borylation of Benzoate Esters

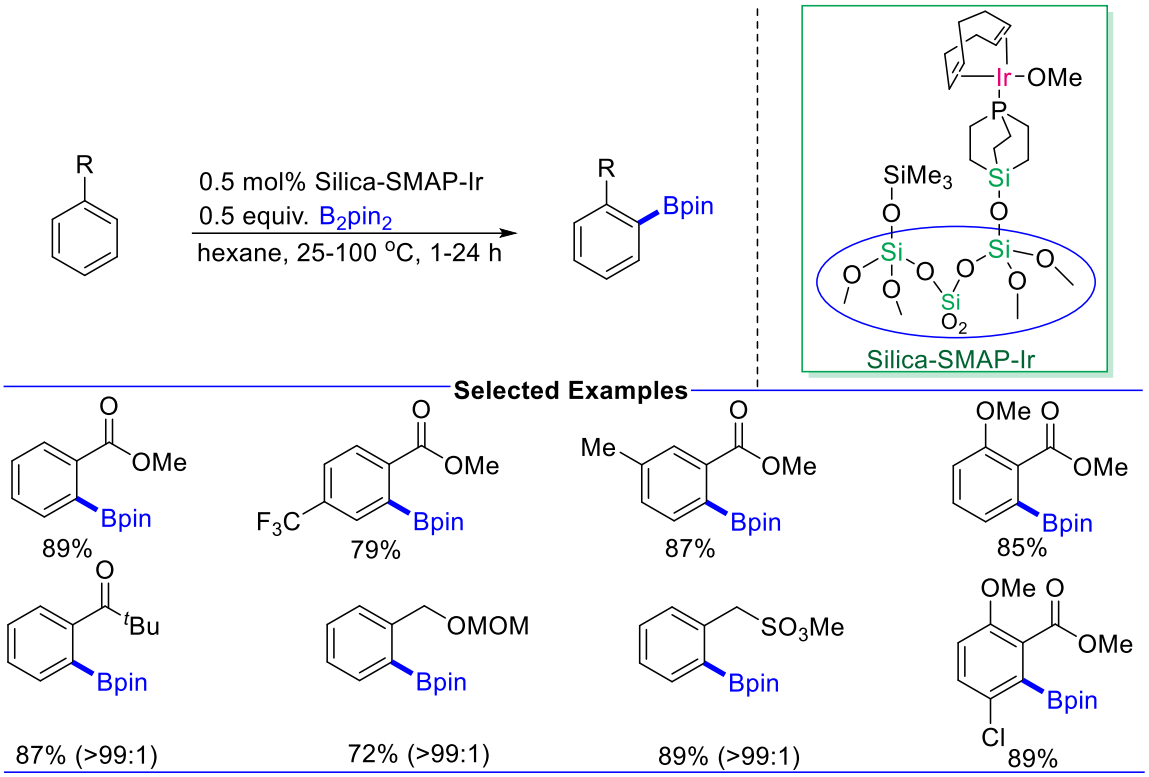
A strategy for Ir-catalyzed directed *ortho* borylation was next developed for aryl ketones by the same group. In this case, high reaction temperature was required for the directed borylation, which resulted in the decreased yield of the borylated products. Interestingly, the use of $AsPh_3$ ligand instead of the $[(3,5\text{-}(CF_3)_2C_6H_3)_3P]$ ligand showed the improvement in the catalytic activity (**Scheme 1.26**).[51] Later they reported the site-selective borylation of vinyl C-H bond of *α,β*-unsaturated esters by the use of same catalyst system.[52]



Scheme 1.26: Iridium-Catalyzed *Ortho*-C-H Borylation of Aryl Ketones

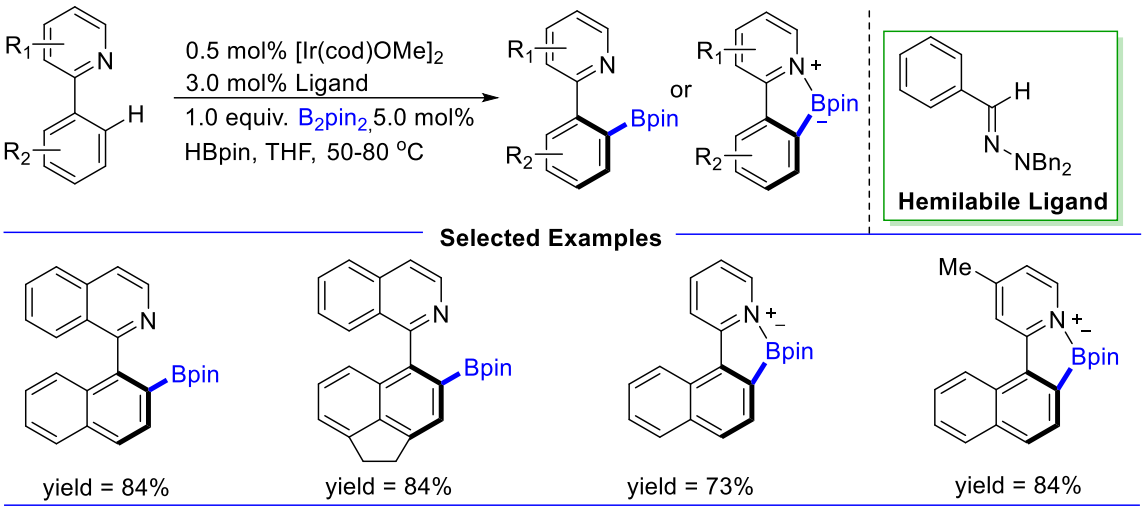
In 2009, Sawamura *et al.* reported *ortho* borylation of various arenes by the help of a silica-supported monophosphite Ir-system.[53] Silica-SMAP-Ir was synthesized in situ from $[Ir(cod)(OMe)]_2$ and silica-SMAP. This heterogeneous catalytic system exhibited good selectivity and reactivity for the *ortho* borylation of arenes in presence of B_2pin_2. Arenes bearing oxygenated functional groups like benzoate, benzamide, sulphonate, benzyl acetal and benzyl methoxymethylether are compatible under these Ir-based catalytic system and afforded *ortho* borylated products with high selectivity and yields (**Scheme 1.27**). Moreover, the reaction of chlorobenzene produced good amount of *ortho* selectivity [*o*/(*m*+*p*) = 92:8]. They found that immobilization of the silica-SMAP ligand is important

for the borylation reaction because when borylation was conducted under homogeneous conditions by using $[Ir(cod)(OMe)]_2$ and Ph-SMAP, it gave only minor amounts of *ortho*-borylated product at 25 °C. Use of other monodentate phosphine ligands like PPh_3, PMe_3, $PtBu_3$, PCy_3 resulted in no reaction under the developed reaction conditions. Authors anticipated that this silica-supported catalyst system facilitated the generation of the 14-electron catalytic intermediate which favoured the coordination of the directing group and triggered the C-H activation process.



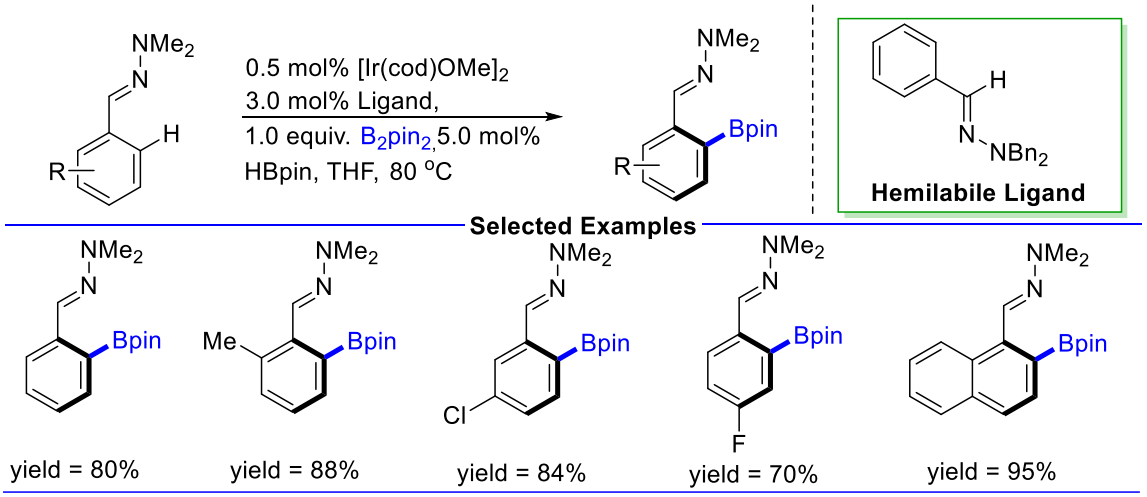
Scheme 1.27: *Ortho*-borylation of Arenes Catalyzed by Silica-SMAP-Ir-Complex

In 2011, Fernandez, Lassaletta and co-authors[54] discovered a *N*-directed *ortho* borylation of arenes with pyridine dibenzylhydrazone as a hemilabile ligand (**Scheme 1.28**). Employment of iridium catalyst, hemilabile ligand, B_2pin_2 and cat. amount of HBpin facilitate the borylation reaction. Substrates with 2-pyridyl and 2-isoquinolyl unit as the directing groups produced the corresponding borylated products in good yield, depicted in **Scheme 1.28**.



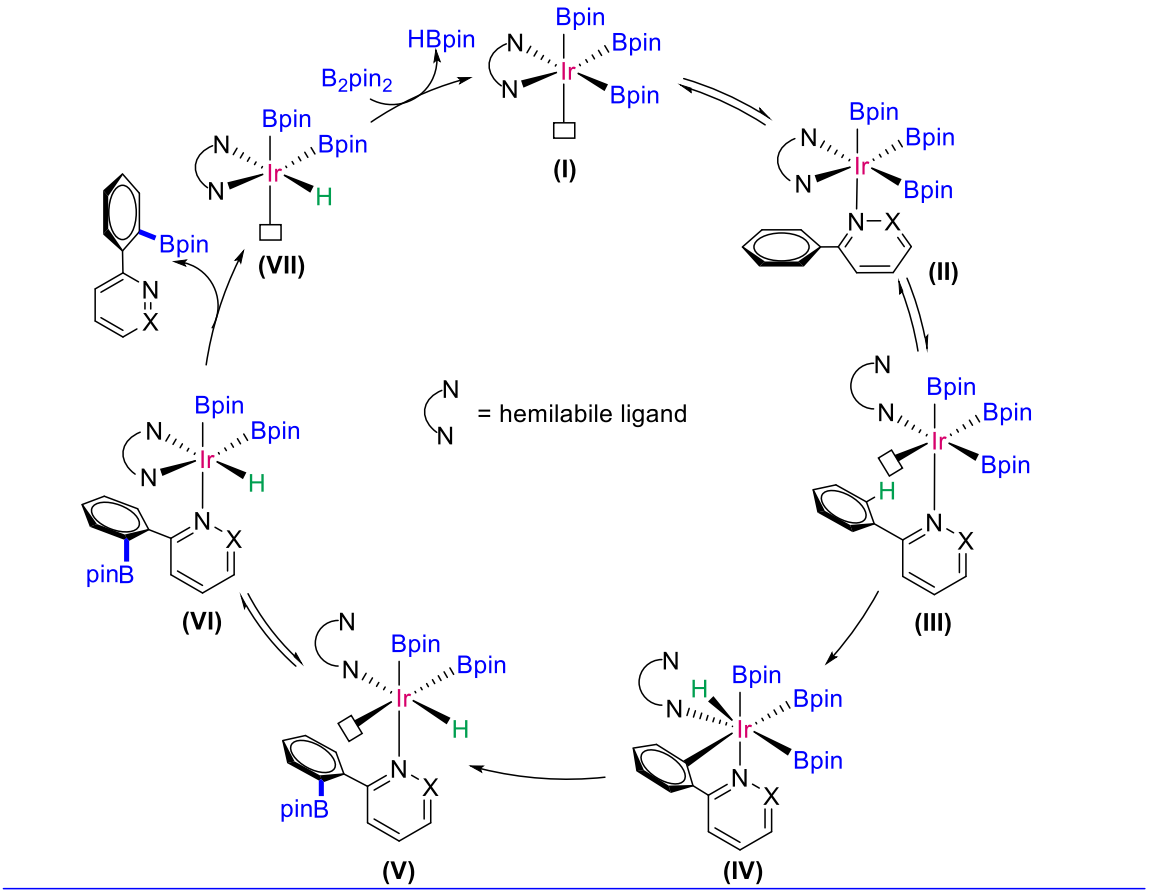
Scheme 1.28: Directed *Ortho* Borylations of 2-Aryl Pyridines

Benzaldehyde-derived imines were also tested as the substrates under developed conditions. Authors also extended their established borylation reaction conditions towards the borylation of *N*,*N*-dimethylhydrazones system. The results are summarized in **Scheme 1.29**.



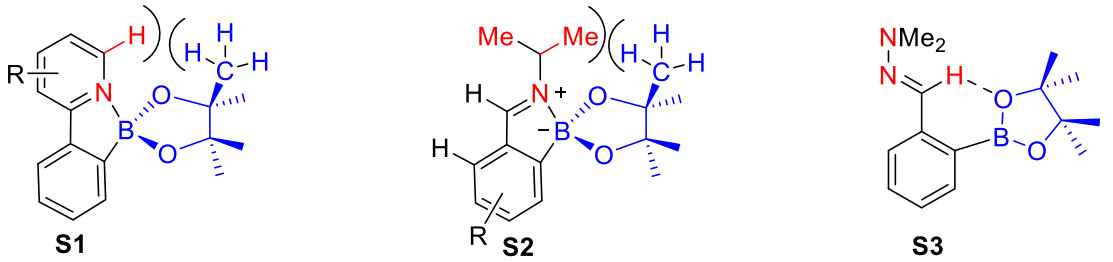
Scheme 1.29: Borylation of aromatic *N*,*N*-dimethylhydrazones

To explain the product formation of this *ortho* borylation reaction, they proposed a mechanism, shown in **Scheme 1.30.** In the mechanism, temporary dissociation of weaker nitrogen donor atom of hemilabile ligand generated vacant coordination site and then *ortho* C-H activation occurred. After that, reductive elimination of the corresponding *ortho* borylated product followed by subsequent re-coordination of ligand regenerated the catalytic cycle.



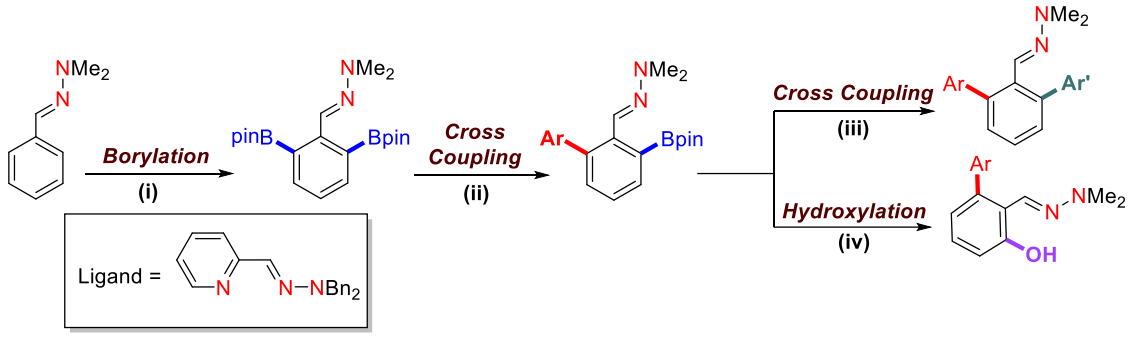
Scheme 1.30: Proposed Catalytic Cycle With *N,N*- Hemilabile Ligand

In 2012, the same group reported the diborylation of aromatic *N,N*-dimethylhydrazones employing a hemilabile ligand (pyridine-dibenzylhydrazone).[55] Based on the ^{1}H, ^{11}B NMR and crystallographic studies of the *ortho*-borylated product of the aryl pyridine suggested that it preferred **S1** conformation and stabilized by an intramolecular nitrogen-boron interaction and the nitrogen atom will not be accessible for the next borylation. However, in case of the *N,N*-dimethylhydrazones, no such B-N interaction was observed owing to the steric repulsion in between methyl groups of the substrate and pinacol (**S2**). However, it was proposed that there must be a possibility to have a hydrogen-bonding interaction in between the CH unit and OH group (CH··· OH) which was supported by the ^{1}H-NMR and crystallographic analysis (**S3**). As a result, sp^2 N-atom in mono-borylated *N,N*-dimethylhydrazone will be available for the subsequent directed *ortho* borylation reaction (**Scheme 1.31**).



Scheme 1.31: Preferred Conformers of *Ortho*-Borylated Aryl Pyridine and Aromatic *N,N*-Dimethylhydrazones

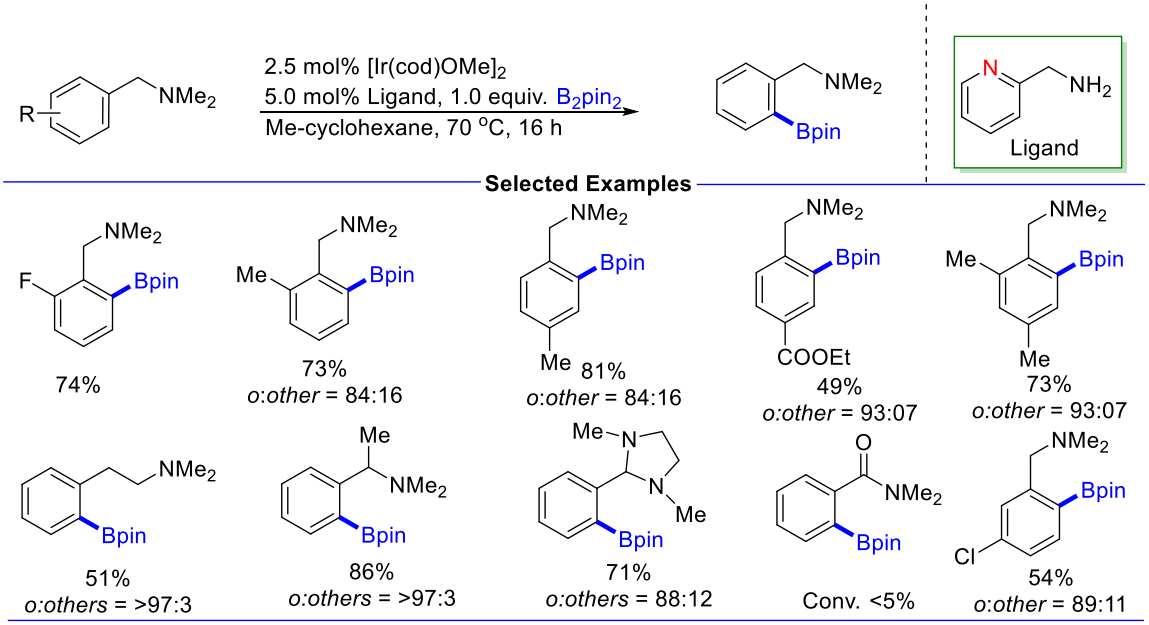
To display the synthetic usefulness of the stablished method, they performed the sequential unsymmetrical functionalization, shown in **Scheme 1.32.**



Conditions:(i)1.0 mol% $[Ir(cod)OMe]_2$, 2.0 mol% Ligand, 2.0 equiv. B_2pin_2, 5.0 mol% HBpin, THF, 80 °C. (ii) 3.0 mol% $[Pd(dppf)Cl_2$,1.05 equiv. **ArBr**,1.1 equiv. K_2PO_4, DMF, 40-60 °C. (iii) 2.0 equiv. **Ar'Br**, 2.0 equiv. K_3PO_4, 80-100 °C. (iv) NaOH/H_2O_2

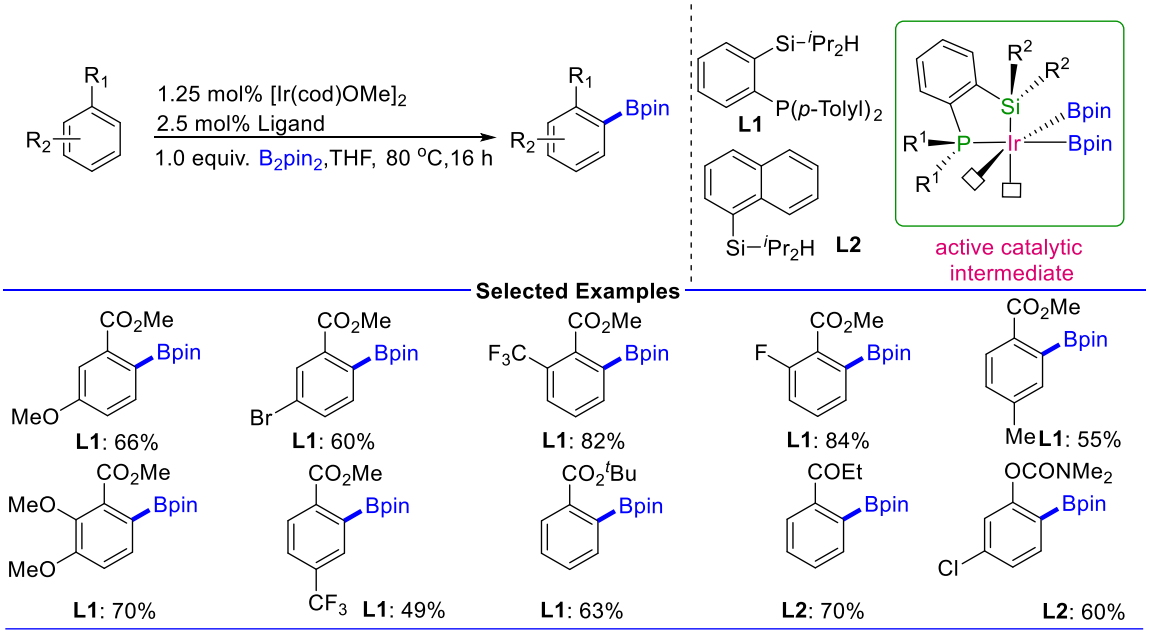
Scheme 1.32: Synthetic Highlight of Diborylation Reaction

In 2012, Clark group developed an iridium-catalyzed directed *ortho* borylation of *N,N*-dimethylbenzylamine utilizing picolylamine as a ligand.[56] The developed protocol exhibited good reactivity and selectivity and produced the *ortho* substituted borylated products in good yields (**Scheme 1.33**). Their mechanistic investigations suggested that the partial dissociation of one nitrogen atom of the picolylamine ligand is responsible for this directed *ortho* borylation reaction. The mechanism is similar to the previously reported mechanism[54] by Lassaletta and their co-workers.



Scheme 1.33: Directed C-H Borylation of Benzyl Amines

In 2014, Smith and co-workers discovered an elegant method for Ir-catalyzed *ortho* borylation of various aromatic molecules by designing a novel silyl tethered phosphorus and nitrogen donor ligands.[57]

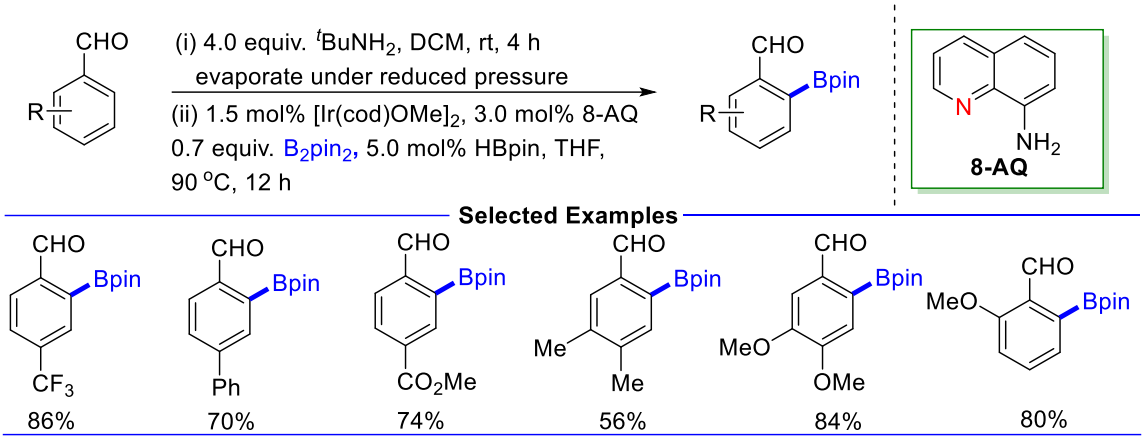


Scheme 1.34: Ir-catalyzed Borylation of Arenes Using Bidentate Si, P/N-Ligand

The author envisaged that if this Si-P ligand generates two vacant coordination sites in active iridium-catalytic intermediate, one empty coordination site would bind with the DG of the substrates and the other vacant coordination site will be accessible for the carbon-hydrogen bond breakage. Keeping this hypothesis in mind, the authors prepared a ligand that underwent

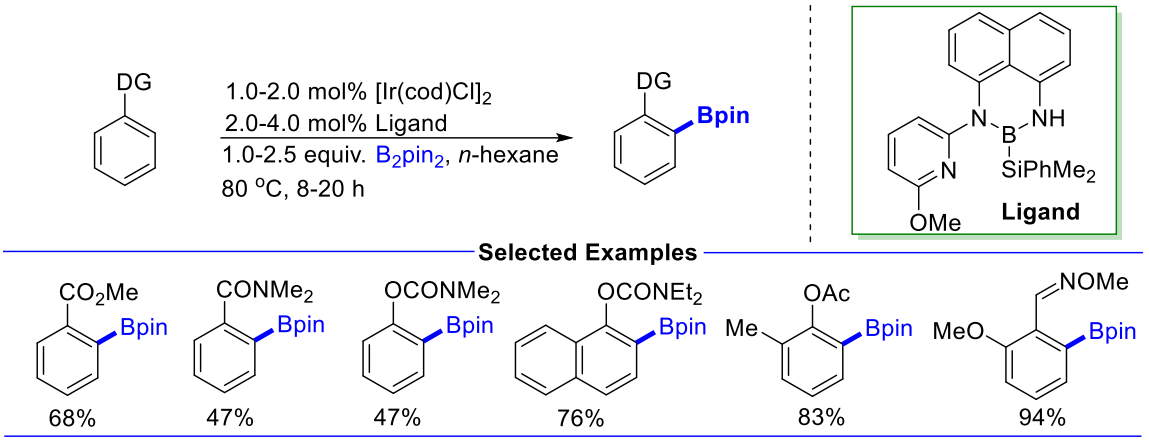
silane metathesis with the tris boryl complex and direct the P ligand towards the metal centre to make the active catalytic intermediate. The selected examples for the substrates are summarized in **Scheme 1.34**.

Motivated by the previously reported directed *ortho* borylation approaches,[54] in 2016, our group reported iridium-catalyzed *ortho* borylation of various aromatic aldehydes, where *tert*-butyl amine served as a traceless protecting and directing group. It was found that *tert*-butyl amine group along with hemilabile 8-aminoquinoline ligand and B_2pin_2 displayed excellent reactivity and selectivity towards the *ortho* borylation reactions. It was demonstrated that both the electronically rich and electronically deficient aromatic aldehydes yielded the desired *ortho* substituted borylated products under the developed C-H borylation conditions, shown in **Scheme 1.35**.[58]



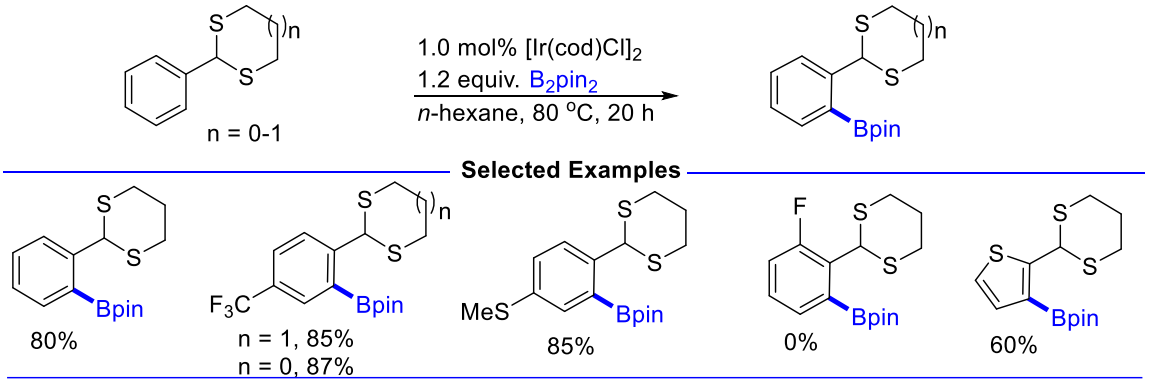
Scheme 1.35: Ir-Catalyzed *Ortho*-Borylation of Benzaldehydes via Hemilabile 8-AQ Ligand

In 2017, a newly designed *N*,B- bidentate ligand for the Ir-catalyzed directed *ortho* borylation was reported by Li group.[51] Motivated by the concept of the generation of two vacant coordination sites in electron rich Ir-intermediate, author hypothesized that silyl borane might be good precursor for this *N*,B-ligands. In case of silyl borane, silicon-boron bond may undergo oxidative addition process with transition metal and silyl group, which then easily participates in reductive elimination or ligand exchange process. Author evaluated a variety of substrates having distinct directing groups like aryl acetate, carbamates, *N*-containing directing group, oxime ether and hydrazones of aldehyde or ketones, which afforded the corresponding borylated compounds with moderate to high yields (**Scheme 1.36**).



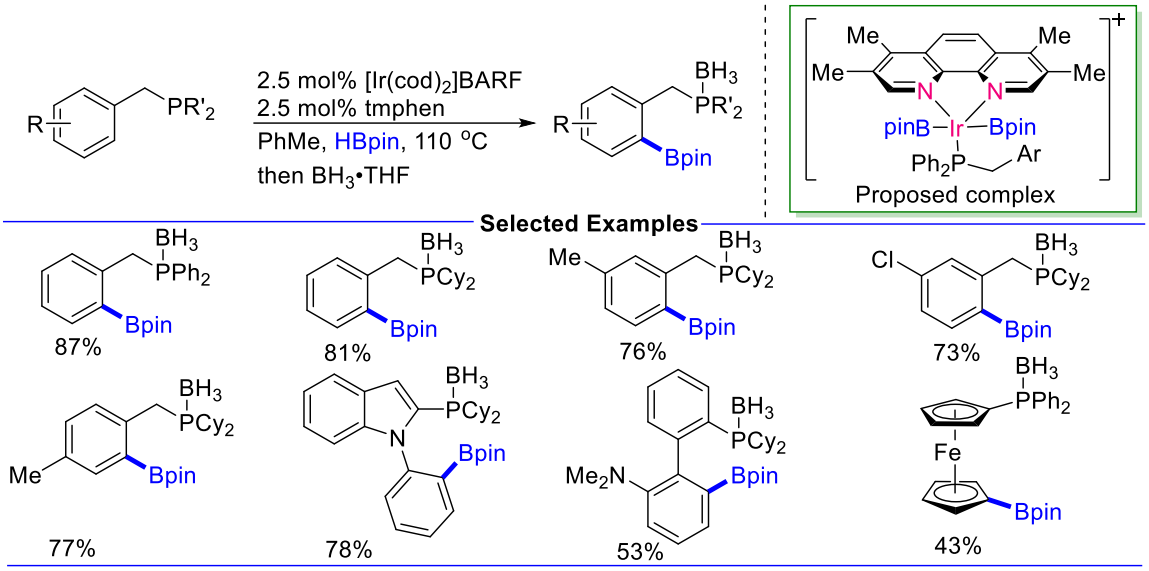
Scheme 1.36: Ir-Catalyzed Directed *Ortho* Borylation using *N*,B-bidentate Boryl Ligand

A cyclic dithioacetal directed *ortho* borylation of aromatic molecules was reported by Li group (**Scheme 1.37**).[60] Their proposed mechanism shows no need of external ligand and the reaction proceed via ligand free mechanism for Ir-catalyzed borylation reaction. In this work, the author explained the role of 1,3-dithiane or 1,3-dithiolane as directing group and as a supporting ligand for the *ortho* borylation. A variety of substituted substrates gave good to excellent yields under developed *ortho* borylation protocol.



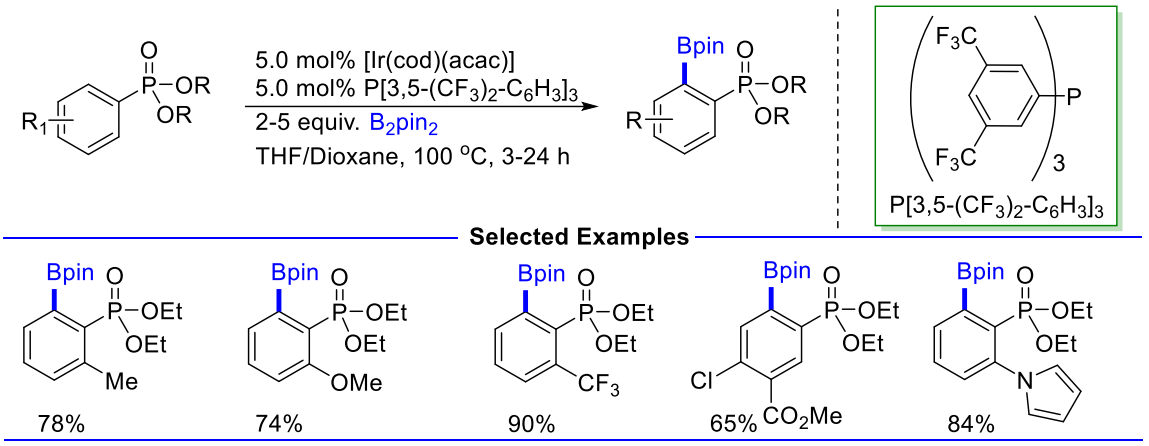
Scheme 1.37: Ir-catalyzed *Ortho* Borylation of Thiol Protected Aldehydes

In 2019, Clark *el al.*[61] discovered *ortho* borylation of phosphine derived arene systems via a unique cationic iridium complex (**Scheme 1.38**). They found that the electronically rich Me_4phen ligand produced a cationic metal complex with Ir pre-catalyst. The method exhibited excellent selectivity and reactivity for various arenes and heteroarenes phosphine substrates. The borylated products were isolated as the borane-protected phosphine and their deprotection gave the free amphiphilic phosphine boronates. In solid or solution state that these boronates do not show any distinguishable interactions in between the phosphorus and boron atoms.



Scheme 1.38: Cationic Ir-Catalyzed *Ortho* Borylation of Benzyl Phosphines

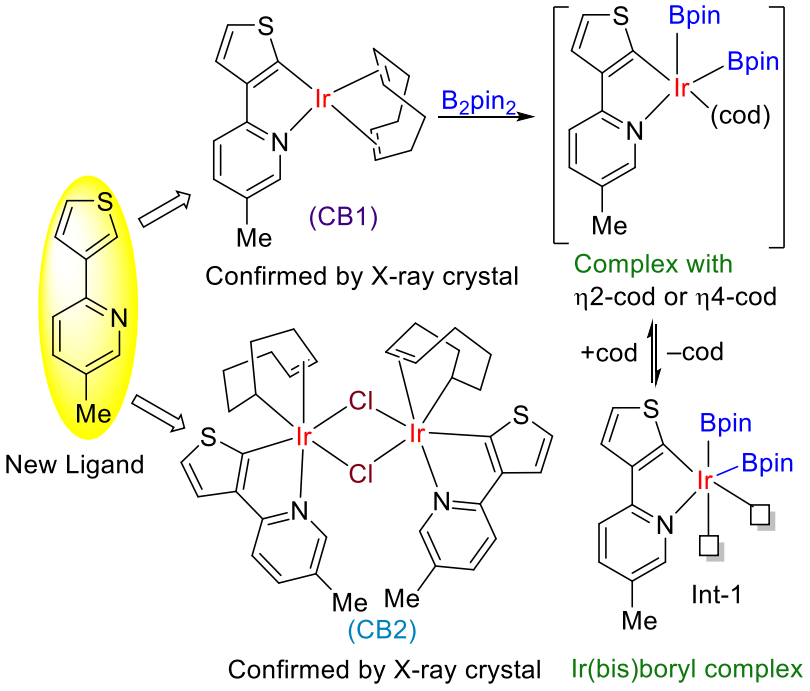
In 2020, Clark and Watson groups jointly reported the *ortho* borylation of phosphonate esters directed by the phosphonate group (**Scheme 1.39**).[62] They employed [Ir(cod)acac] catalyst and phosphine-based ligand (previously developed[50] by Ishiyama and Miyaura) for the *ortho* borylation. Their developed protocol furnished a direct method for the preparation of the *ortho*-phosphonate aryl boronic esters. The author performed a relative comparison of the directing group ability of phosphonate to esters. Under the standard reaction conditions, borylation preferred *ortho* to ester group but no mono borylated product obtained ortho to phosphonate group.



Scheme 1.39: Ir-Catalyzed *Ortho* Selective C-H Borylation of Phosphonate Esters

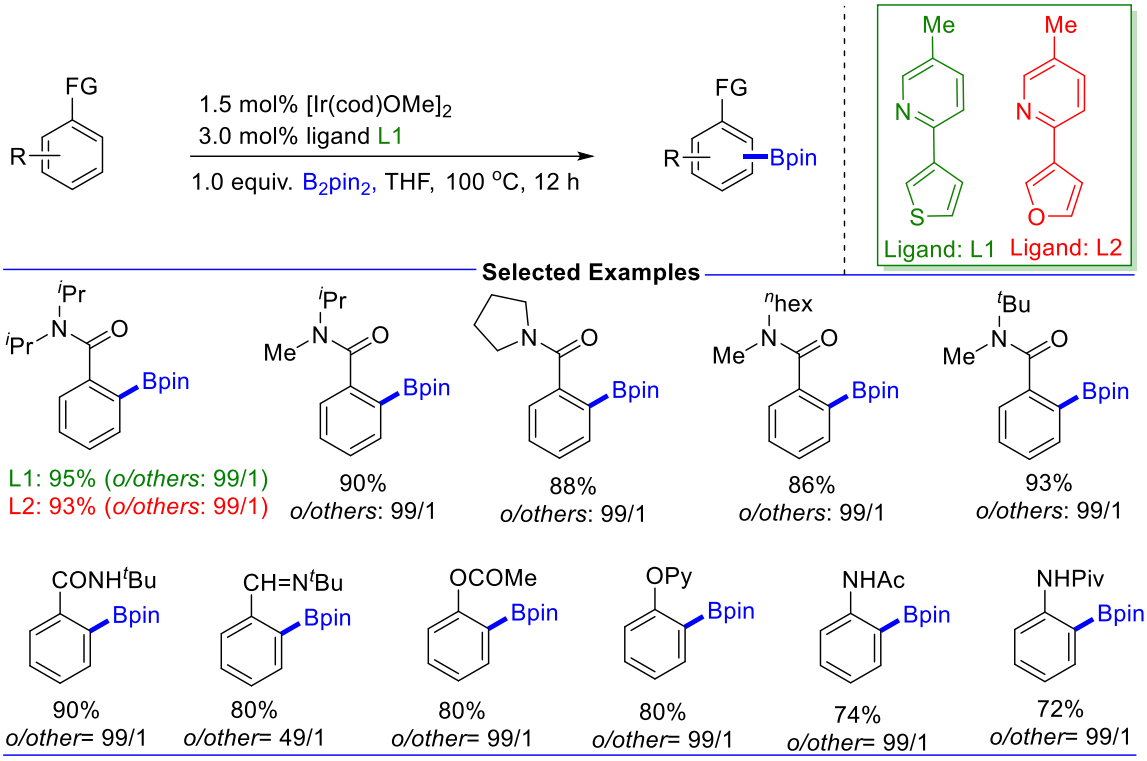
Recently, our group have developed[63] a unique catalyst i.e., **CB1** and **CB2** for the directed borylation of broad range of aromatic and aliphatic substrates (**Scheme 1.40**). Here, thienyl

or furyl based anionic ligands were utilized for the selective ortho borylation in place of the imine-containing neutral ligands which are well familiar in C-H borylation chemistry. During the screening of reaction, it was found that pyridyl thiophene ligand gave quantitative product conversion for the *N*,*N*- diisopropyl benzamide substrates. This is because of the higher reactivity of C-H bond of thiophene molecule, which formed a cyclic complex and facilitated the borylation reaction. Besides this pyridyl thiophene ligand, furan-based ligand framework gave similar results.



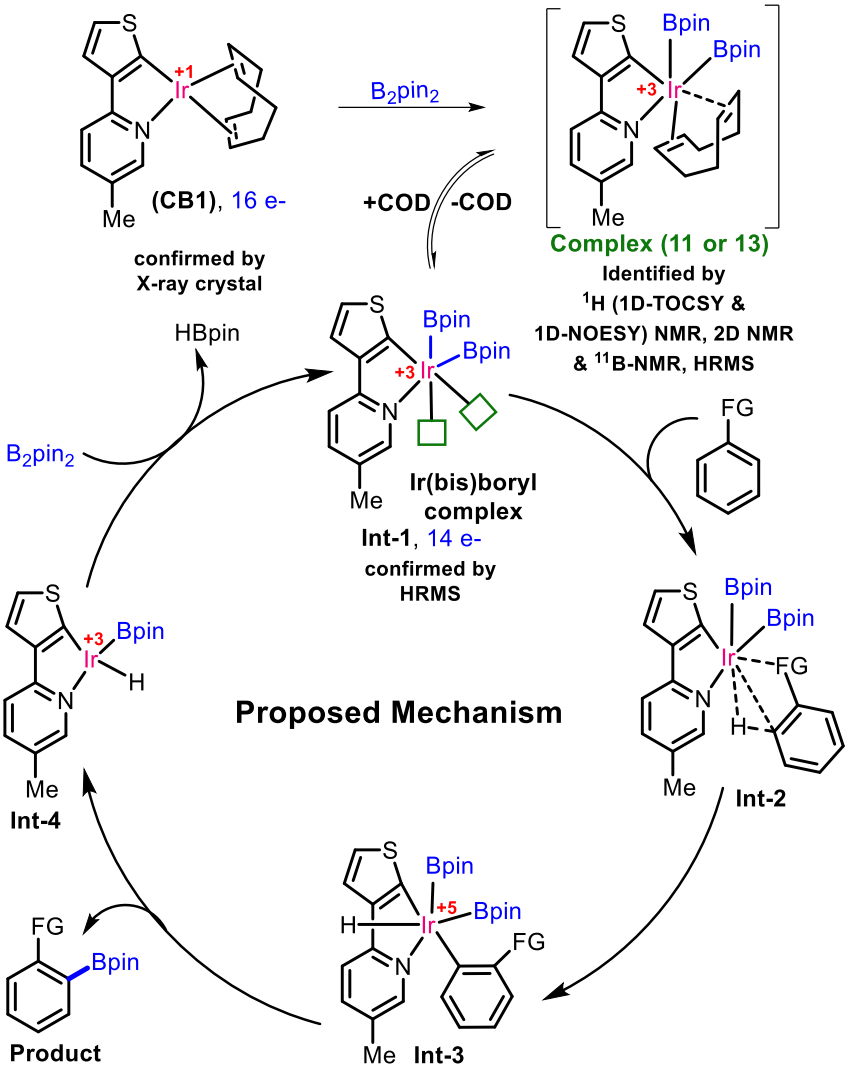
Scheme 1.40: Representation and Characterization of CB1 and CB2 Catalyst

The developed method showed excellent outcome towards the broad substrate classes. It was found that the arenes having amide, aldimine, acetate, carbamoyl, phenoxy pyridine, anilido pyridine, benzyl pyridine, NHAc, NHPiv, NHMe, OMe-benzyl, MOM-benzyl, MOM, benzyl NHAc, enthylamine, ketones, ester, Opiv, carbonate, hydrosilyl, carbamate, NHBoc, methylthiol, acetal etc. undergo borylation reaction and showed excellent reactivity and selectivity as well as produced high yields of the products (**Scheme 1.41**). Interestingly, it was found that this method was found to be effective for the non-directed benzene borylation and gave mono-borylated product.



Scheme 1.41: *Ortho* Borylation of Diverse Classes of Substrates Using a New Class Catalyst

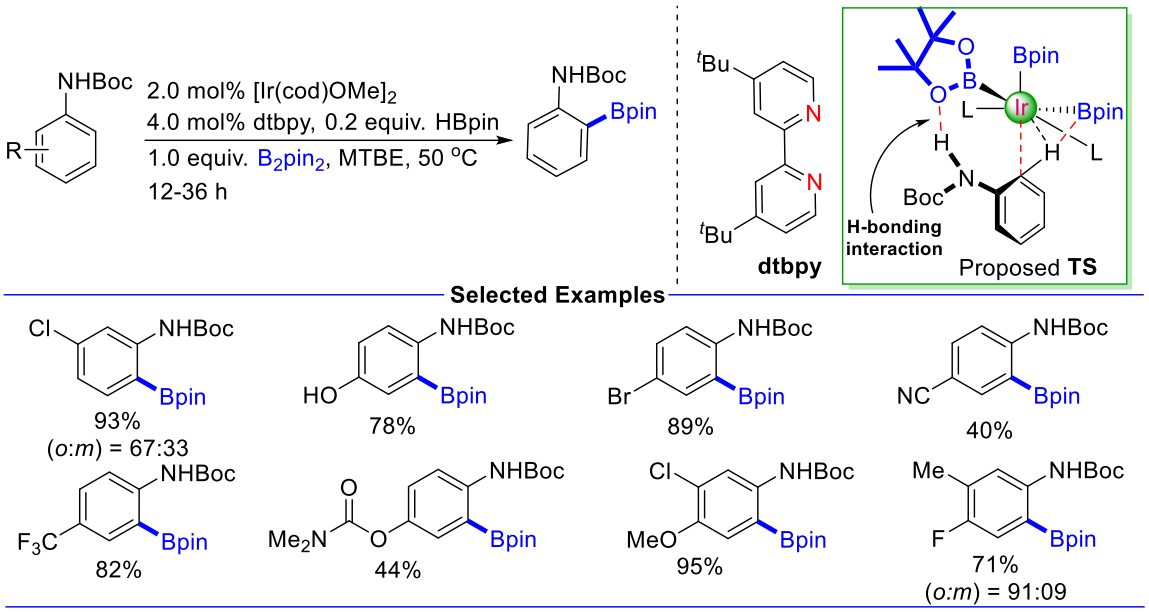
Gratifyingly, it was observed that in open air, the second-generation air stable catalyst (**CB2**) demonstrated excellent outcomes for aliphatic and aromatic molecules. The proposed mechanism for the C-H borylation is represented in **Scheme 1.42**. First, the **CB1** catalyst undergoes oxidative addition of B_2pin_2 to form the cod ligated bis(boryl)(Ir)complex (either A: η^2 or B: η^4), which may undergo a reversible dissociation of cyclooctadiene to form the bis(boryl)(Ir) complex. Next, in the catalytic cycle, functional group of the substrate get coordinated and C-H bond activation occur. Finally, reductive elimination process produced the desired borylated compound and activation of the B_2pin_2 regenerates the catalytic cycle.



Scheme 1.42: Proposed Mechanism for the Borylation Using CB1 Catalyst

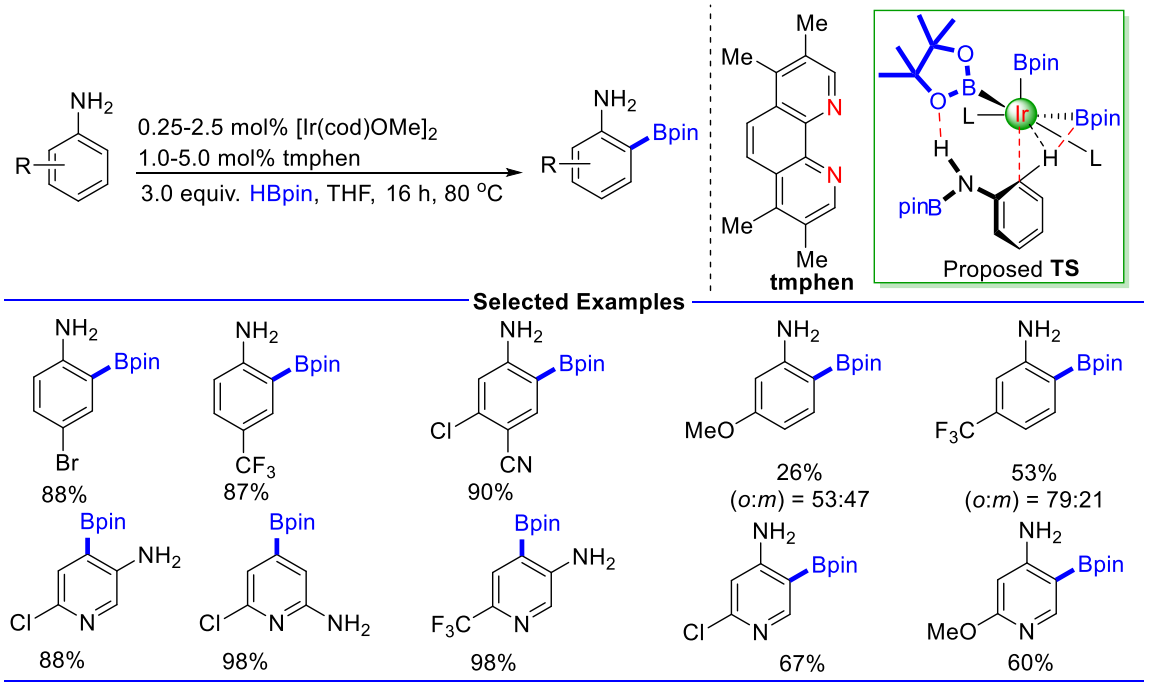
1.5.4 Role of Noncovalent Interaction in *Ortho* C-H Borylation

The pioneering report of *ortho* borylation using noncovalent interaction was disclosed by Smith, Maleczka and Singleton in 2012 (**Scheme 1.43**).[64] In this study, they mentioned that C-H borylation of unprotected aniline substrate resulted in poor selectivity, but when one hydrogen atom of aniline is protected by one Boc group, it showed different results. With the help of experimental and computational studies, they proposed a H-bonding interaction between the hydrogen atom of the NHBoc group and O atom of the boryl ligand. Notably, only 4-substituted Boc-protected aniline gave excellent *ortho* selectivity. The selectivity of other monosubstituted substrates were not good.



Scheme 1.43: *Ortho* Borylation of Boc-Protected Aniline

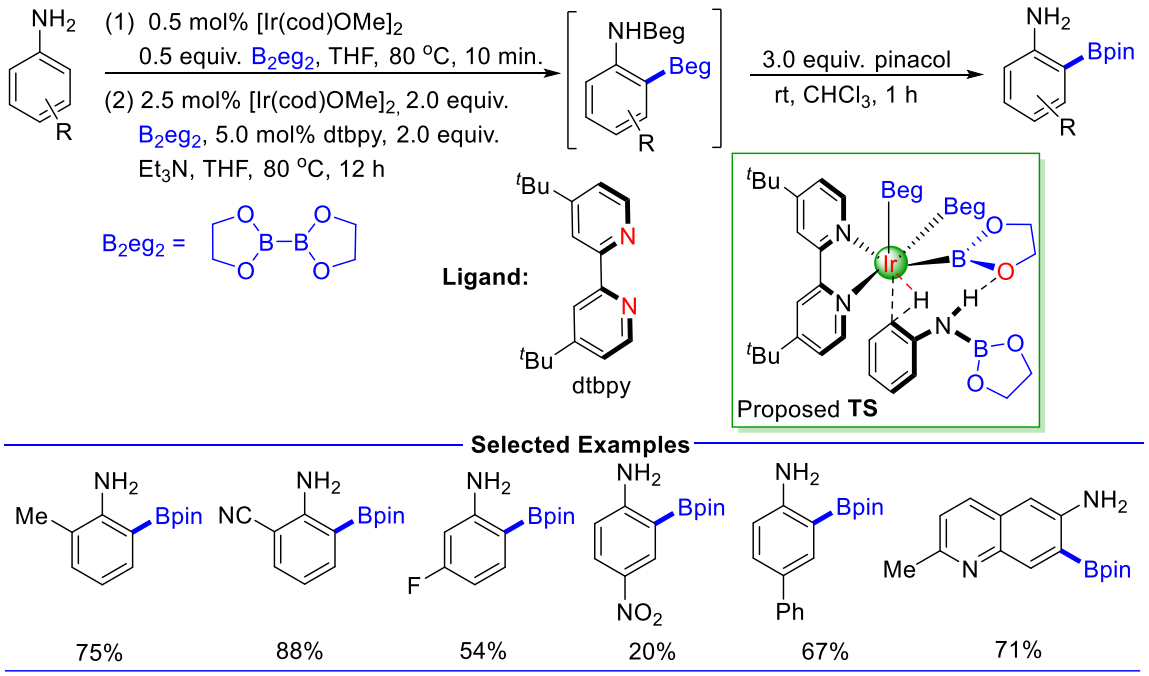
Same group, in 2013, revisited their aniline *ortho* borylation strategy and overcame the shortcomings of their previous method[64] by using Bpin group instead of the Boc group, as the traceless protecting and directing group. It was reported that the previously developed method requires an additional step for the protection and deprotection of Boc group in case of the heterocyclic substrates.



Scheme 1.44: *Ortho* borylation of Bpin-protected aniline

It was envisioned that the Bpin group may be the substitute for the Boc group. Catalytic turnover number and conversion of the borylated reaction were improved by the modification of the ligand from dtbpy to Me_4phen with catalytic amount of HBpin. Only *p*- substituted and *m*, *p*-disubstituted substrates are compatible under these developed borylation conditions. Moreover, *ortho* borylation strategy is also applicable for some aminopyridine substrates (**Scheme 1.44**).[65]

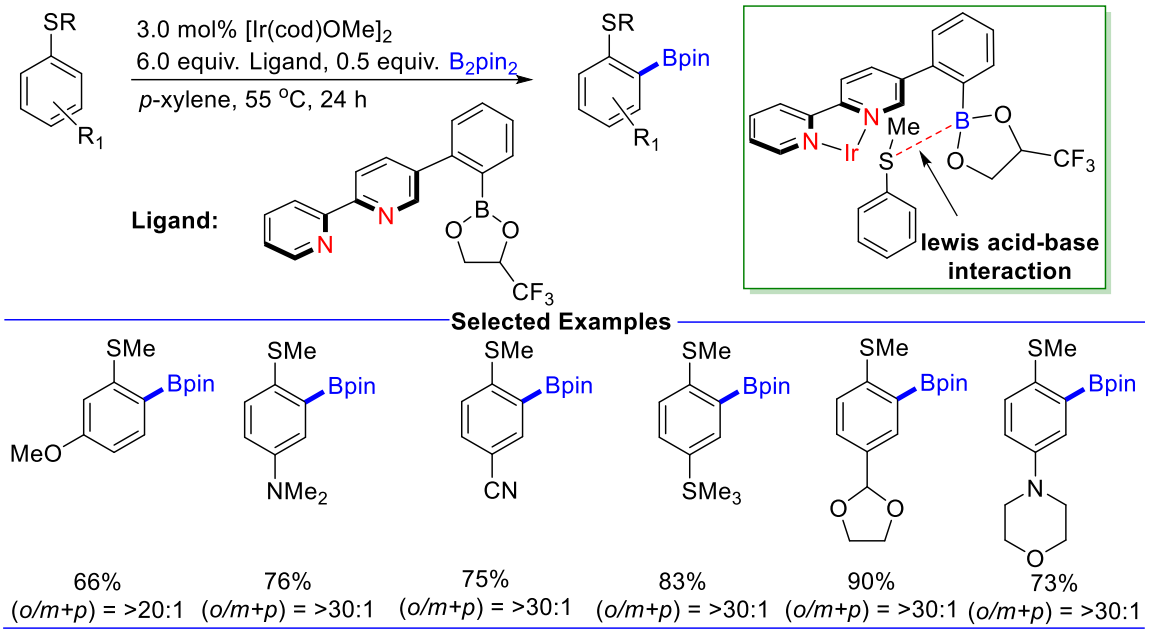
To overcome the restrictions of formerly reported methods, in 2018, Chattopadhyay group in collaboration with Smith and Maleczka, discovered a modified borylating agent i.e., B_2eg_2 (eg = ethylene glycolate) which showed the high *ortho* selectivity of various anilines.[66] Here, Beg group behave as a traceless protecting and directing group. DFT analysis revealed that H-bonding interaction between the H atom of PhN(H)Beg molecule and oxygen atoms in Beg ligands governed the *ortho* selectivity. Their ^{1}H NMR experiment suggests that PhN(H)Beg is formed before the C-H borylation. Their developed protocol is applicable for *ortho* borylation of 2,3 and 4-substituted anilines like 2-methyl, 2-cyano, 3-fluoro, 4-phenyl aniline etc (**Scheme 1.45**).



Scheme 1.45: *Ortho* borylation of Beg-protected aniline

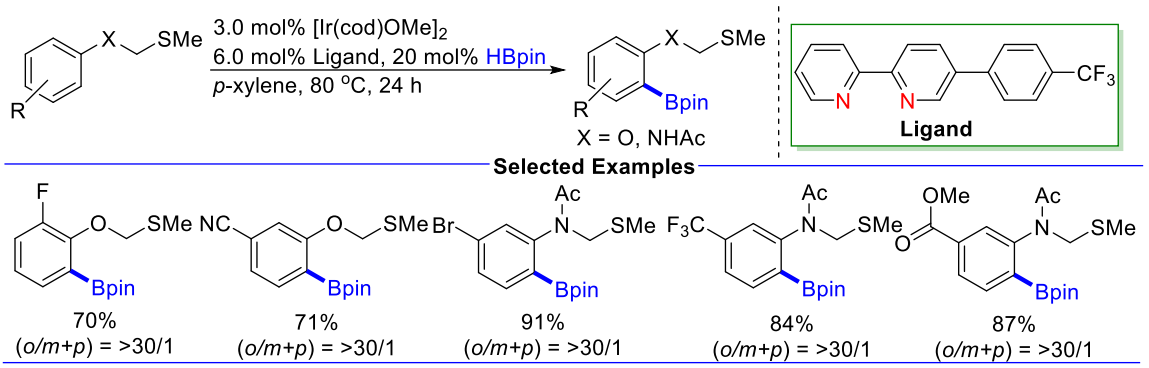
In 2017, Kanai and Kuninobu first demonstrated a Lewis acid-base interaction approach for the *ortho* borylation reaction (**Scheme 1.46**).[67] In this study, the authors achieved iridium-catalyzed *ortho* borylation of sulfide containing aromatic molecules using a LA-LB interaction between the Lewis acidic boryl group of the designed ligand with Lewis

basic sulphur atom of the substrate. Most of the *para* substituted substrates like OMe, Me, Br, Ph, etc. as well as *meta* substituted substrate like ester, amide NMe_2, Cl, CN etc. were well endured under the developed conditions. However, their optimized protocol was not successful with some heterocyclic substrate like 3-(methylthio)- pyridine, furan, and pyrrole. During the control experiments, they found that (*o*/*m* + *p*) selectivity increased in non-polar solvent and at low reaction temperature. It was noticed that *ortho* selectivity of aryl sulphide dropped when a bulky substituent used on sulphur atom. Moreover, they showed that *ortho* selectivity also depends upon the Lewis acidity of the boryl group present on the ligand.



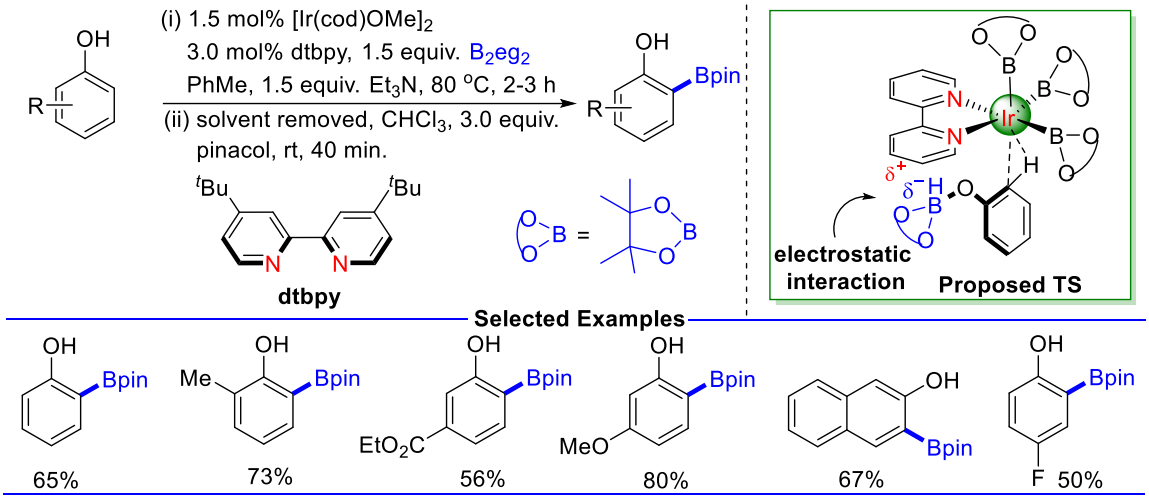
Scheme 1.46: *Ortho* Borylation of Aryl Sulphide Directed by Lewis Acid-Base Interaction

Later, the same group reported the *ortho* borylation of phenol and aniline derived substrates using a modified bipyridine ligand (**Scheme 1.47**).[68] While Ir/bpy-catalyzed borylation reaction produced *meta* and *para*-borylated products, introducing one CF_3 unit in bipyridine type system the regioselectivity completely changed for thiomethyl derived phenol and aniline substrates. A variety of functional groups were suitable under the reaction conditions that gave high selectivity. Markedly, their developed protocol also suitable for the synthesis of calcium receptor modulator.



Scheme 1.47: *Ortho* Borylation of Thiomethyl Derived Phenol and Aniline

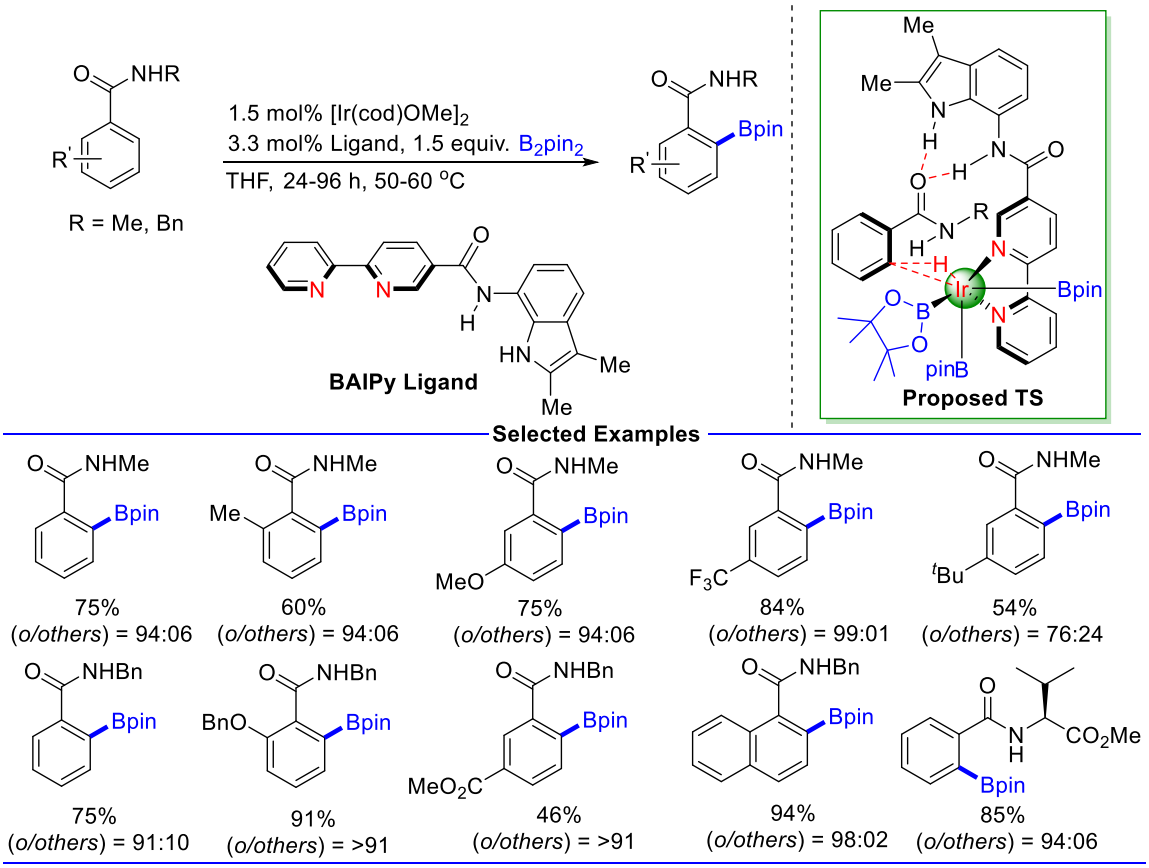
The concept of traceless protecting and directing group was modified by Chattopadhyay, Maleczka, Smith and co-workers in 2017.[69] They reported *ortho* an selective borylation of phenol with the combination of Ir / dtbpy and B_2eg_2 borylating agent which behave as a traceless protecting and directing moiety (**Scheme 1.48**). Authors proposed a unique electrostatic interaction between the partially positively charged bpy ligand and partially negatively charged OBpin group of substrates. The proposed electrostatic interaction was confirmed by both the experimental and theoretical studies. From further computational study, they found that Beg group significantly improved the *ortho* selectivity over Bpin group because methyl unit of OBpin group destabilized the transition state. Authors also noticed that the electron poor bipyridine ligand afforded high *ortho* selectivity and lower the reactivity which correlate with their computational study.



Scheme 1.48: *Ortho* Borylation of Phenol

Recently, Reek and co-workers reported an Ir-catalyzed *ortho* selective borylation of secondary amides (**Scheme 1.49**).[70] They designed a BAIPy ligand in which an indole amide moiety is attached with the bipyridine unit. They found that three hydrogen bonds

are responsible for the high *ortho* selectivity. Along with two probable hydrogen bonds between the both the NH group of the deigned ligand and the C=O group of the substrate, the third H-bonding was possible in between the NH group of the substrate and the O atom of boryl group, which was confirmed by the computational studies. It was found that substrate *N*,*N*-dimethylbenzamide and methylbenzoate afforded poor *ortho* selectivity due to lack of hydrogen bonding interaction. They evaluated the scope of these borylation reactions and found that various *meta* and *para* substituted *N*-methyl benzamides and *N*-benzyl benzamides are well tolerated under these established reaction conditions.

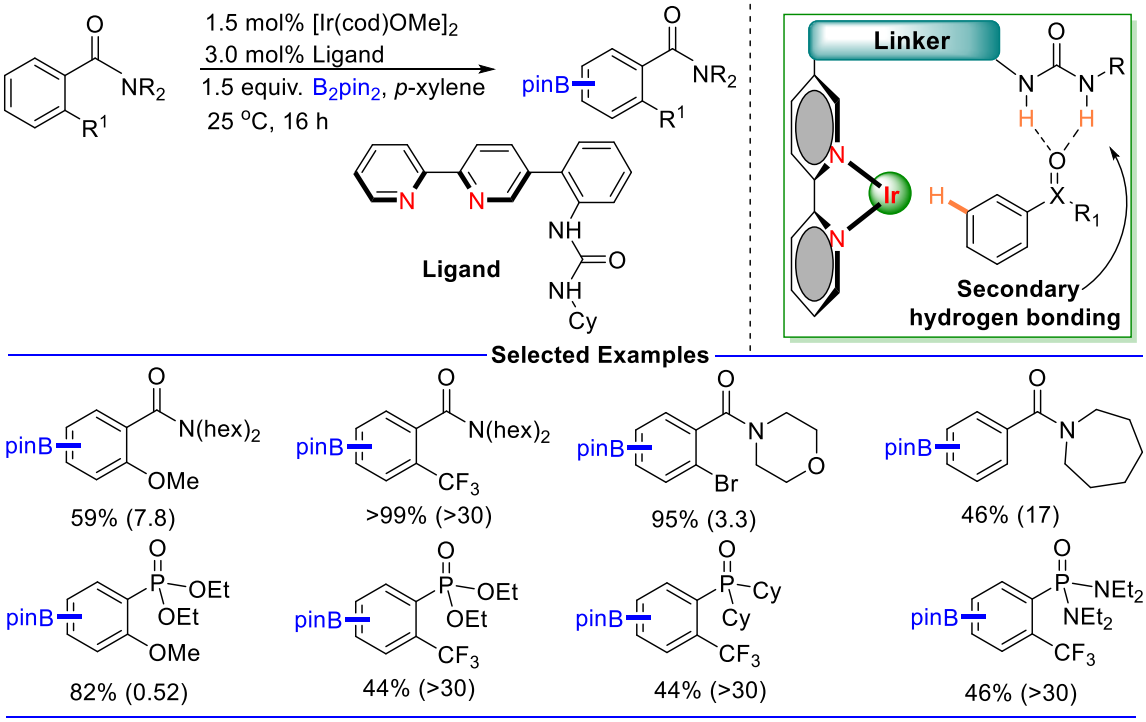


Scheme 1.49: Ir-Catalyzed *Ortho* Borylation of Amide

1.5.5 Iridium-Catalyzed *meta*-Borylation of Arenes

In 2002, the remote *meta*-C–H borylation was reported autonomously by the groups of scientists.[71,72] They have illustrated that 1,3-disubstituted aromatic substrates gave selective *meta* borylated product. Besides this *meta* borylation report, which was controlled by steric factor, there was no general methods for the remote *meta*-C-H borylation reactions found in literature. After a decade, the field of *meta*- borylation have been explored. In this section, report of iridium-catalyzed *meta*- borylation reactions using noncovalent interaction will be discussed.

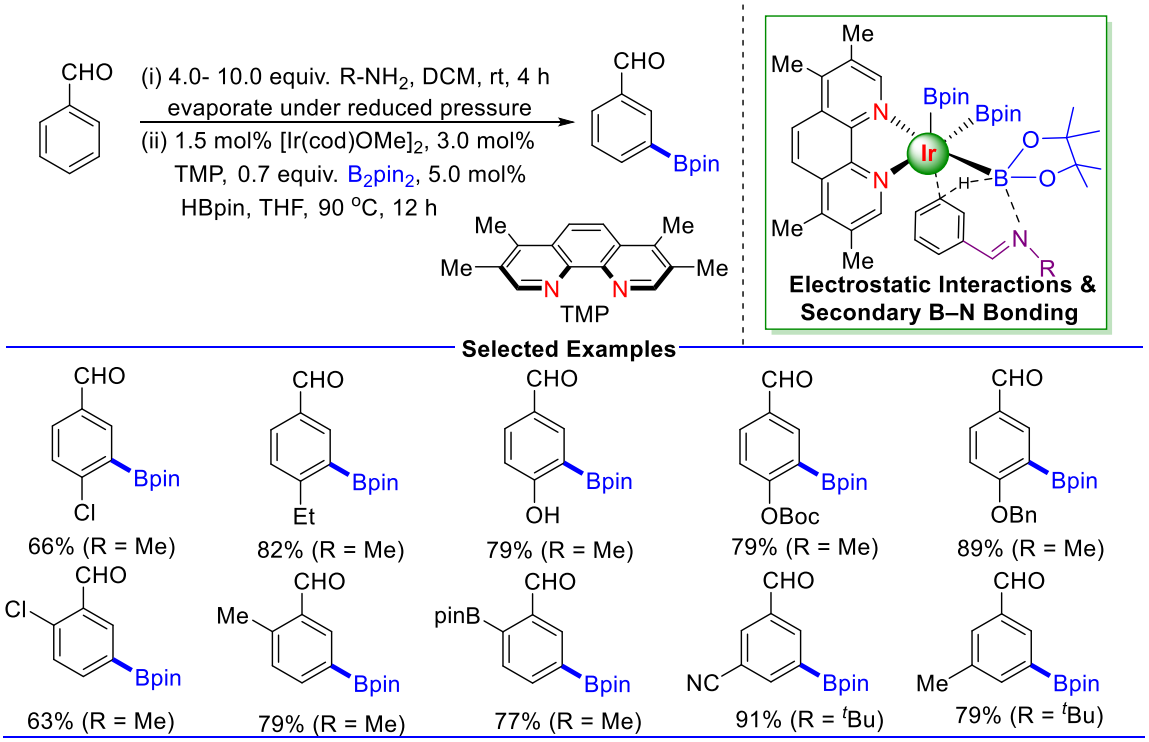
The pioneering report for Ir-catalyzed *meta*-borylation of aromatic molecules was reported by Kanai and Kuninobu group in 2015, depicted in **Scheme 1.50**.[73] The substrates included in this borylation was aromatic amides, esters and many phosphorus containing subtrates. In this report, authors showed that the origin of this *meta* selectivity can be controlled by the hydrogen bonding. They discovered a newly designed ligand system which contains a bipyridine unit with a urea moiety, through which a secondary interaction is possible between the free H atom of urea molecule and the O atom of the substrate. This hydrogen bonding interaction helps the Ir- metal to come in close vicinity of the *meta* carbon-hydrogen bond and governed the selectivity of this *meta* borylation reaction.



Scheme 1.50: *Meta*-C–H Borylation Controlled by Hydrogen Bonding

To understand the concept of this H-bonding between the O atom of aromatic substrates and the NH group of the designed ligand framework, author performed several controlled experiments. Author performed ^{1}H NMR experiment which show lower field shifts of the NH protons of the designed ligand in the presence of substrate, supported their H-bonding interaction concept. Next, they executed a borylation reaction with a ligand in which the NH protons of the designed ligand was replaced by Me group. The outcome showed that selectivity of *meta/para* ratios was drastically dropped. The result of ^{1}H NMR experiment indicated that no significant change in the chemical shift of protons of NH group of the protected methyl ligand. These experiments showed the importance of the bipyridine pendent urea moiety for hydrogen bonding interaction.

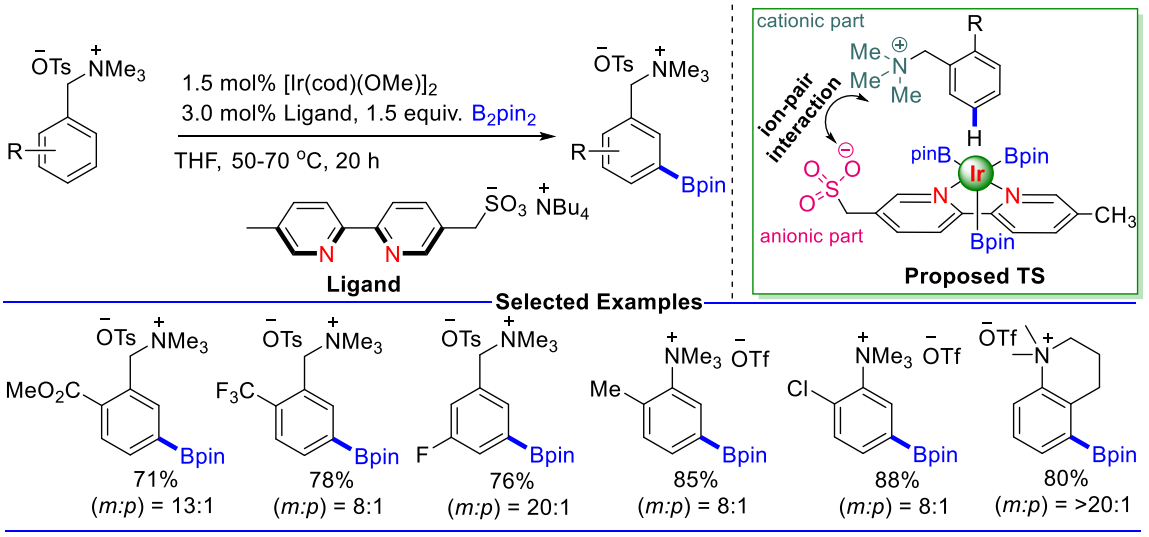
In 2015, our group developed the *o*-and *m*-borylation of aromatic aldehydes using 8-aminoquinoline and tetramethyl phenanthroline ligand respectively.[58] For *meta* borylation, there were two important factors. First one was an electrostatic interaction originating due to the encapsulation between the iridium trisboryl complex ligated with electronically rich tetramethyl phenanthroline ligand and the imine substrate and the second factor was the nitrogen atom of the imine group and B atom of boryl group of the catalyst show secondary interaction.



Scheme 1.51: Ir-Catalyzed *Meta*-Borylation of Aromatic Aldehydes

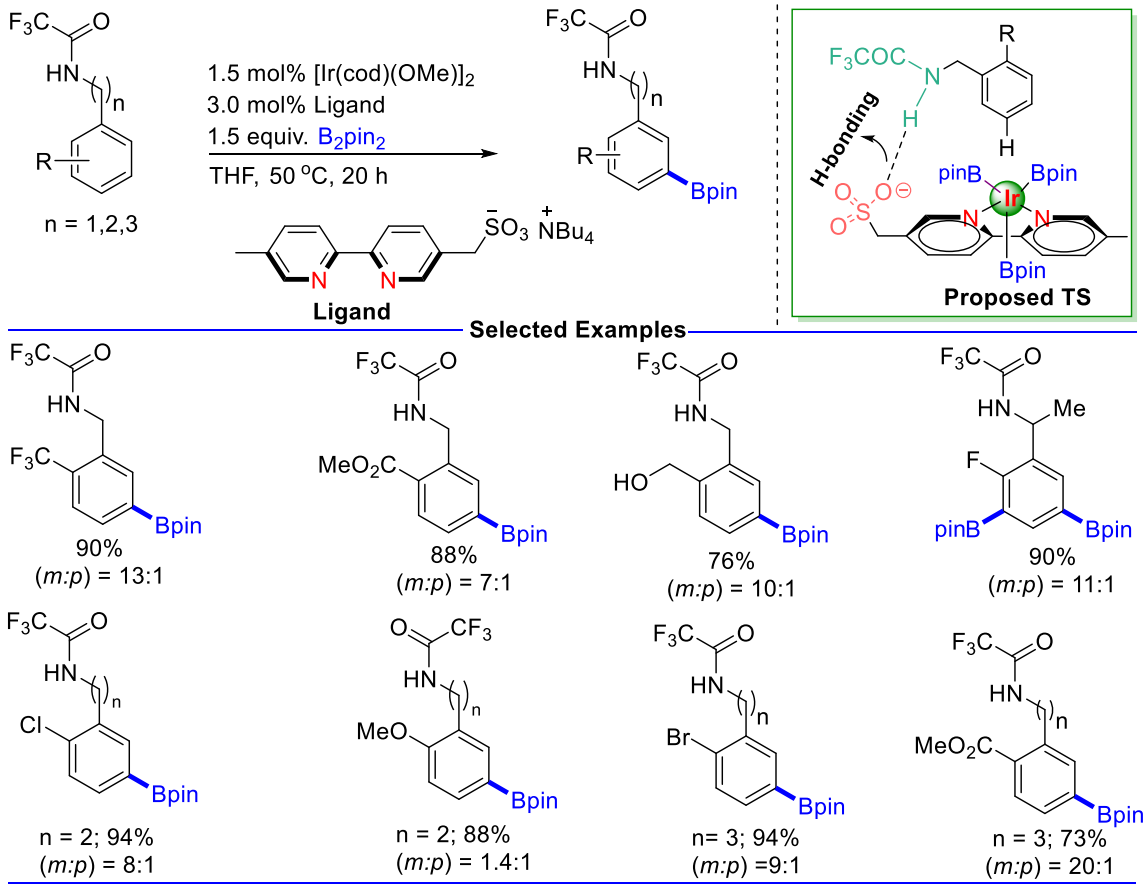
The high *meta* selectivity was observed when the substituent on imine nitrogen was less bulky, which supported the B-N interaction more effectively. A variety of *ortho* substituted aldehyde substrates and also the *para* substituted substrates like CN, OMe, Cl, F furnished *meta* borylated products with excellent regioselectivity (**Scheme 1.51**).

In 2016, Phipps *et al*. demonstrated a novel method for the Ir-catalyzed *m*-borylation of the aromatic substrates having quaternary ammonium salts using ion-pair interaction, shown in **Scheme 1.52**.[74] They observed that noncovalent interaction between the positively charged quaternary ammonium salts and the negatively charged sulfonate bearing bipyridyl ligand preferred the *meta*-C-H bond borylation reaction. They investigated various cationic arene substrates. First, they tested chlorobenzyl amine substrate which gave 10:1 *meta* selectivity while dtbpy gave poor selectivity 1:2 (slightly preferred *para* selectivity). A number of *ortho* substituted substrates were highly suitable under the established protocol. Substrate like *m*-F where the possibility of *para* borylated product is more, gave high *meta* selective product in presence of their designed ligand. They also explored aniline-derived quaternary ammonium salts having EWG, EDGs and observed the corresponding *meta* borylated products with good selectivities, albeit less in compared to one carbon unit more quaternary ammonium salts. Heteroaromatic substrates like 2-substituted pyridines with dtbpy gave mixture of isomer. When pyridyl substrate was converted into the ammonium salts, it gave non-selective outcome like 5- and 4,6-diborylation with dtbpy ligand. However, using anionic ligand 4,6-diborylated product was obtained which meant the anionic ligand favoured borylation at 4-position over 5-position.



Scheme 1.52: Ir-Catalyzed *meta* Borylation of Quaternary Ammonium Salt

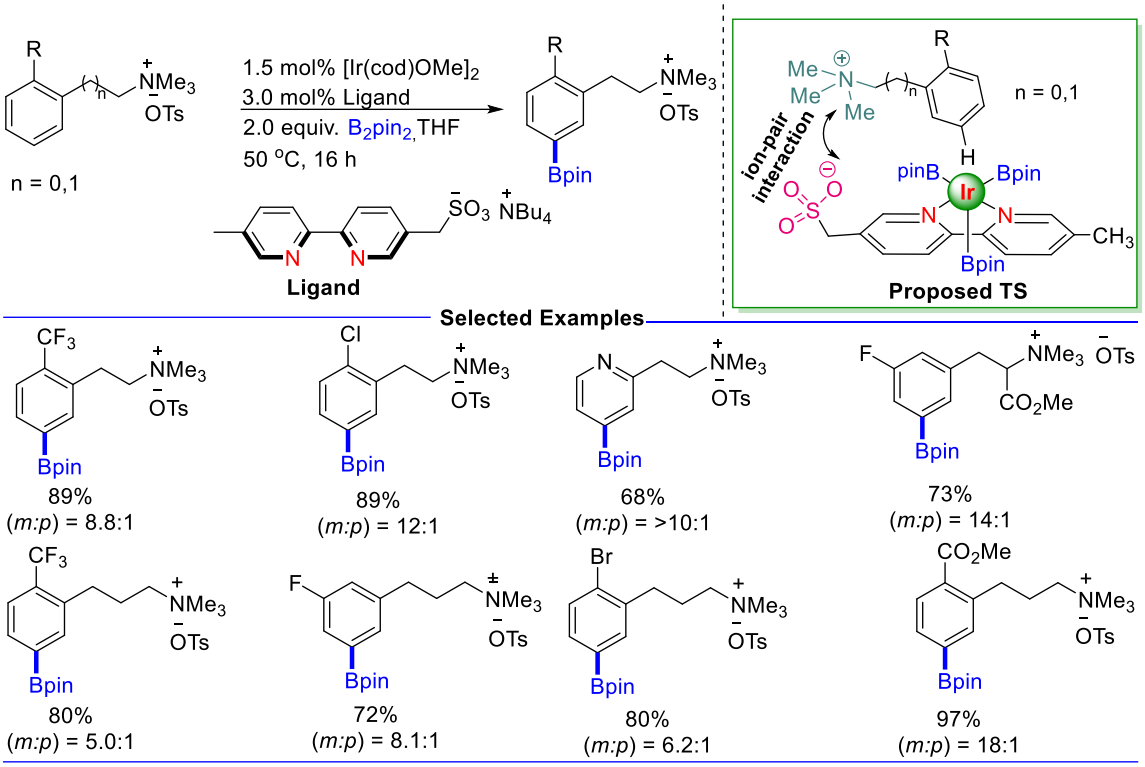
In 2017, same group developed the concept of hydrogen bonding interaction for the *m*-borylation of arenes having amine group using the same anionic ligand.[75] High *m*-selectivity was accomplished by the interaction of anionic ligand with the substrate having hydrogen bond donor atom. Here, the authors reported a regioselective *meta* borylation of benzylamine, phenethyl-amine and phenylpropylamine- derived amides, summarized in **Scheme 1.53**.



Scheme 1.53: Ir-Catalyzed *Meta* Borylation via Hydrogen-Bonding Interaction

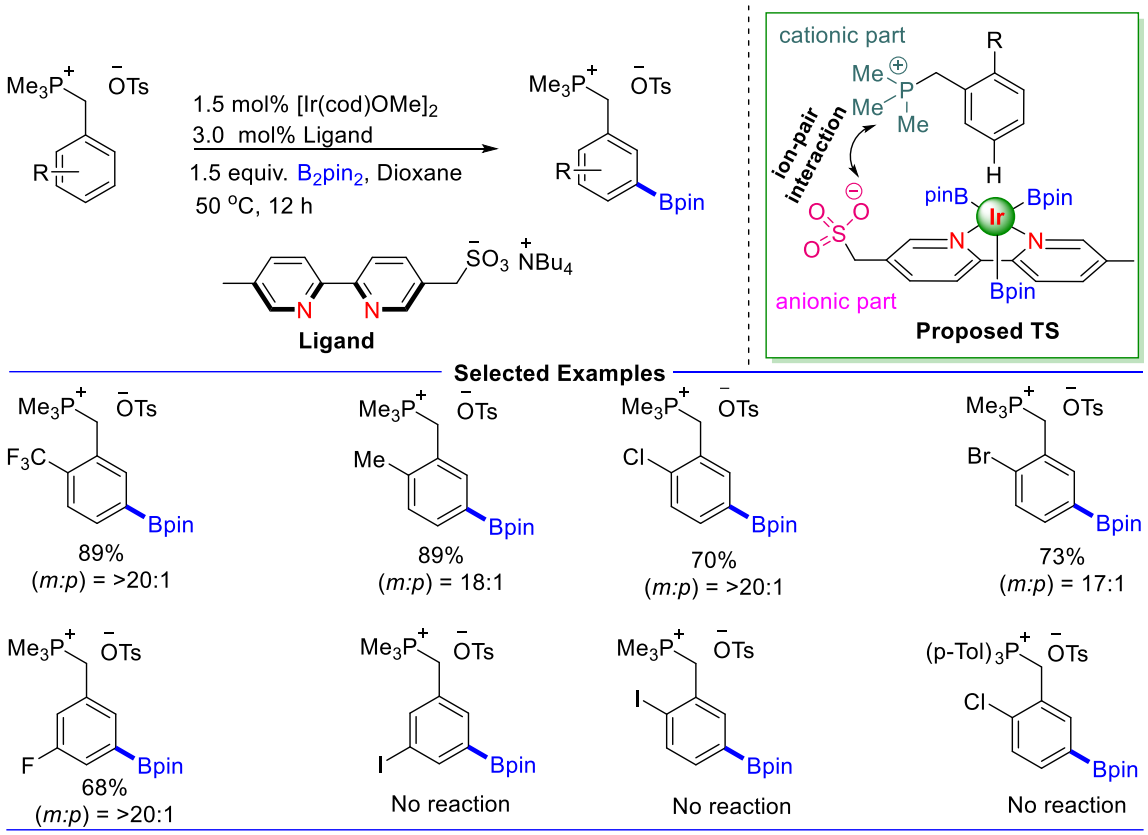
To check the generality of the ion pair approach, Phipps group selected conformationally more flexible substrates such as phenylethylamine and phenylpropyl amine for the *meta*-*C*-H borylation.[76] Their optimal ligand for the borylation consist a sulfonate group, attached to 5-position of the bipyridine with the help of a methylene unit. A variety of substrates were well tolerated under their developed conditions but unsubstituted substrates and electron donating groups found to be inactive towards borylation reaction because the distance of ammonium cation increases from the arene ring decreases its inductive effect. Next, they attempted reaction with the substrate having four carbon chain, but

regioselectivity decreased in comparison to two or three carbon chain containing substrates (**Scheme 1.54**).



Scheme 1.54: Ir-Catalyzed *Meta* Borylation via Electrostatic Interaction

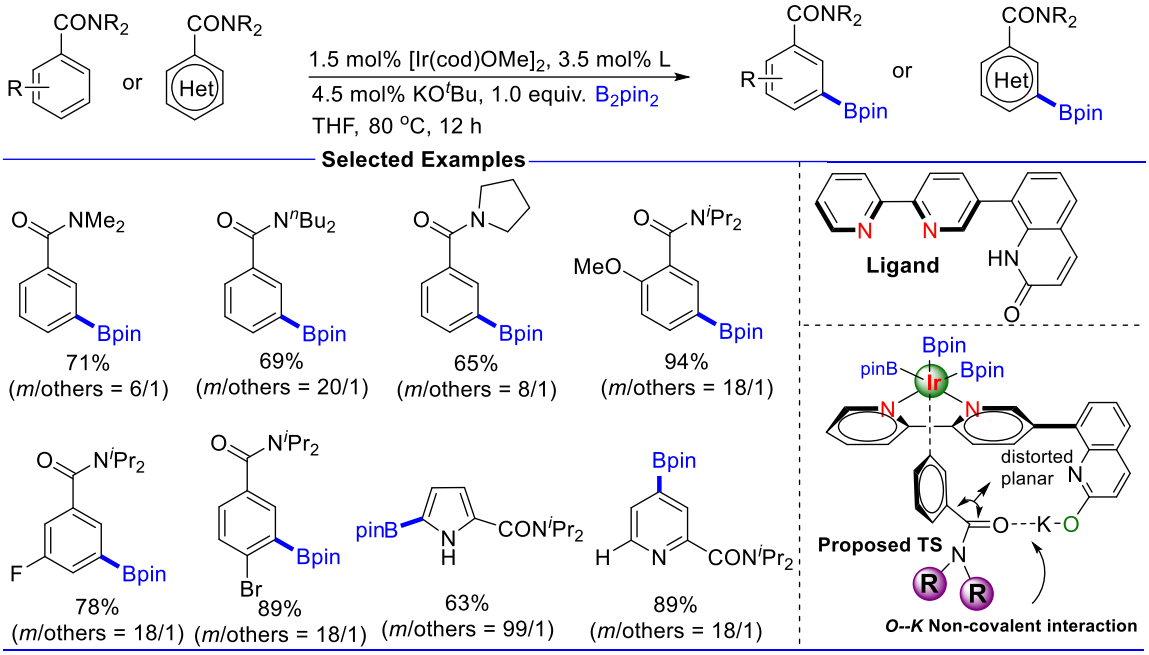
After exploring the Ir-catalyzed *meta* borylation on different ammonium salts, Phipps group extended their chemistry on aromatic phosphonium salts by applying the concept of ion-pair interaction (**Scheme 1.55**).[77] They tested different commercially available ligands like dtbpy, tmphen but found that their optimized sulfonate group containing bipyridine ligand gave the best result in dioxane solvent. A variety of two and three substituted substrate like -CF_3, -Cl, -Br, -Me etc. are well tolerated under the employed reaction conditions except the iodo group at two positions. Borylation of pyridine molecule acquired phosphonium salt was quite challenging due to the second borylation, however, the borylation reaction occurred at the fourth position of pyridine molecule and the ratio of C4/C5 borylation was 10:1. Finally, they concluded that the electrostatic interaction in between the phosphonium salt and the sulfonate ligand, play an important role for the high *meta* selectivity in aromatic phosphonium salt.



Scheme 1.55: Ir-Catalyzed *Meta* Borylation of Aromatic Phosphonium Salt

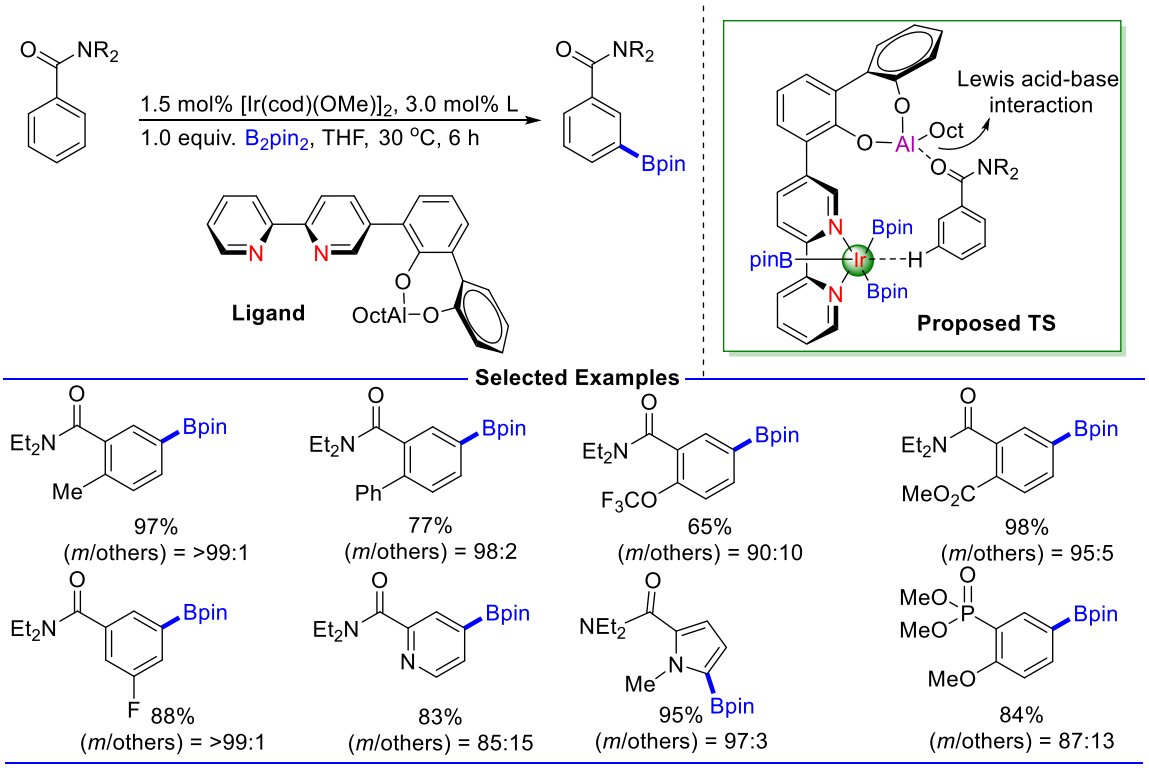
In 2017, our group designed a unique L-shaped bifunctional ligand consisting of a simple bipyridine unit which is connected to the quinolone moiety (**Scheme 1.56**). This quinolone group undergoes tautomerization and converted into the more stable OH group which generated the O-M (M = metal) bond in presence of metal. At first, it was reported that high level of *para* selective borylation of ester can be obtained in which the carbonyl oxygen interacts with quinolone oxygen through O-K---O=C noncovalent interaction.[78] In contrast, borylation of amides with the designed L-shape ligand gave different results. Aromatic amides gave high *meta* selectivity with the same L-shape bifunctional ligand by participating in *O--K* noncovalent interaction with the carbonyl O atom of the substrate.[79] The *N,N*- diisopropyl amide was selected as a model substrate due to higher product conversion in comparison to the *N,N*- dibutyl amide. It was reported that *ortho*-monosubstituted substrates, challenging *meta*- substituted substrates as well as *para*-substituted substrates furnished high *meta* selectivity. Heterocyclic amides like furan, thiophene, pyrroles and indoles also gave excellent *meta* selectivity, while reaction with dtbpy ligand gave poor *meta* selectivity or mixture of isomer in almost all cases. Next, to showcase the utility of the borylation reaction some useful synthetic transformations have

been performed like hydroxylation, chlorination, bromination, iodination, deuteration, arylation, amination, and methoxylation. The authors stated that the *O---K* noncovalent interaction (supported by several experimental evidences) is strongly responsible for *meta* borylation of amides. However, there is a possibility of a cation π- interaction. Usually, two important factors direct cation π- interaction such as (i) substrate electronics (EWG deteriorates the interaction and EDG fortifies the cation π- interaction (ii) polarity of solvent (with increasing solvent polarity, interaction increases). In order to verify the above two important considerations, authors conducted various experiments which discarded the probability of the cation π- interaction.



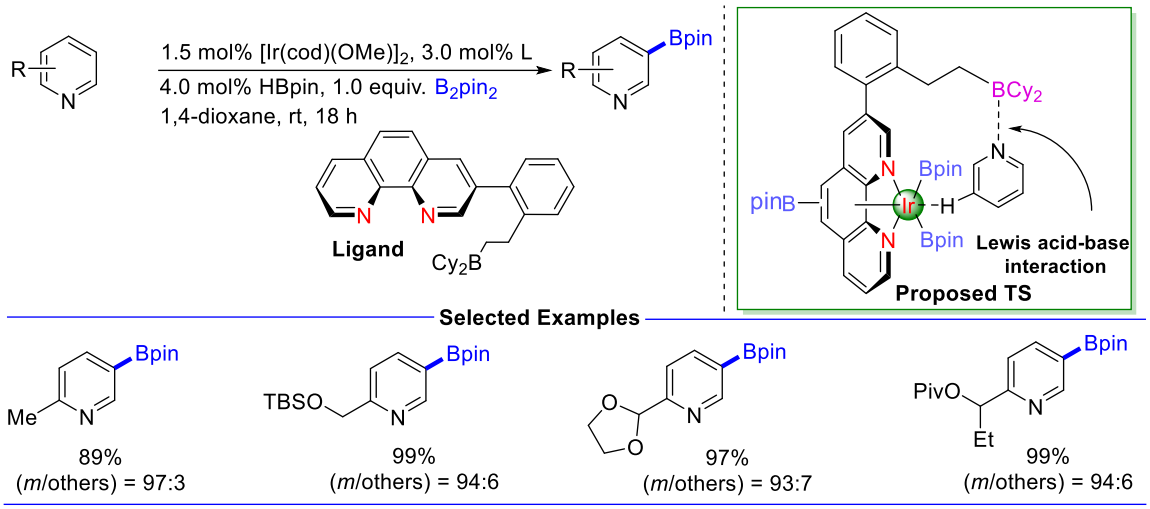
Scheme 1.56: Ir-Catalyzed *Meta* Borylation of Amides Using L-Shape Ligand

In 2019, Nakao group developed a unique protocol for the *meta* borylation of benzamide and pyridine substrates using Lewis acid-base interaction.[80] A bpy based ligand having Lewis acidic alkylaluminium group interacts with the carbonyl oxygen of amide. They explored variety of *ortho* substituted substrates like 2-methyl benzamide, methoxy, phenyl, CF_3, OCF_3 and halogenated substrates which gave good to excellent selectivity as well as yields in hexane solvent (**Scheme 1.57**). After successful borylation of benzamides, they next moved for pyridine borylation (**Scheme 1.58**). Generally, borylation of pyridine at 2- and 4-position is more favourable but borylation at three position is quite difficult. At first, they tried a reaction of 2-methyl pyridine with commercially available ligand like dtbpy, TMP, which gave a mixture of borylated products at four and five position.



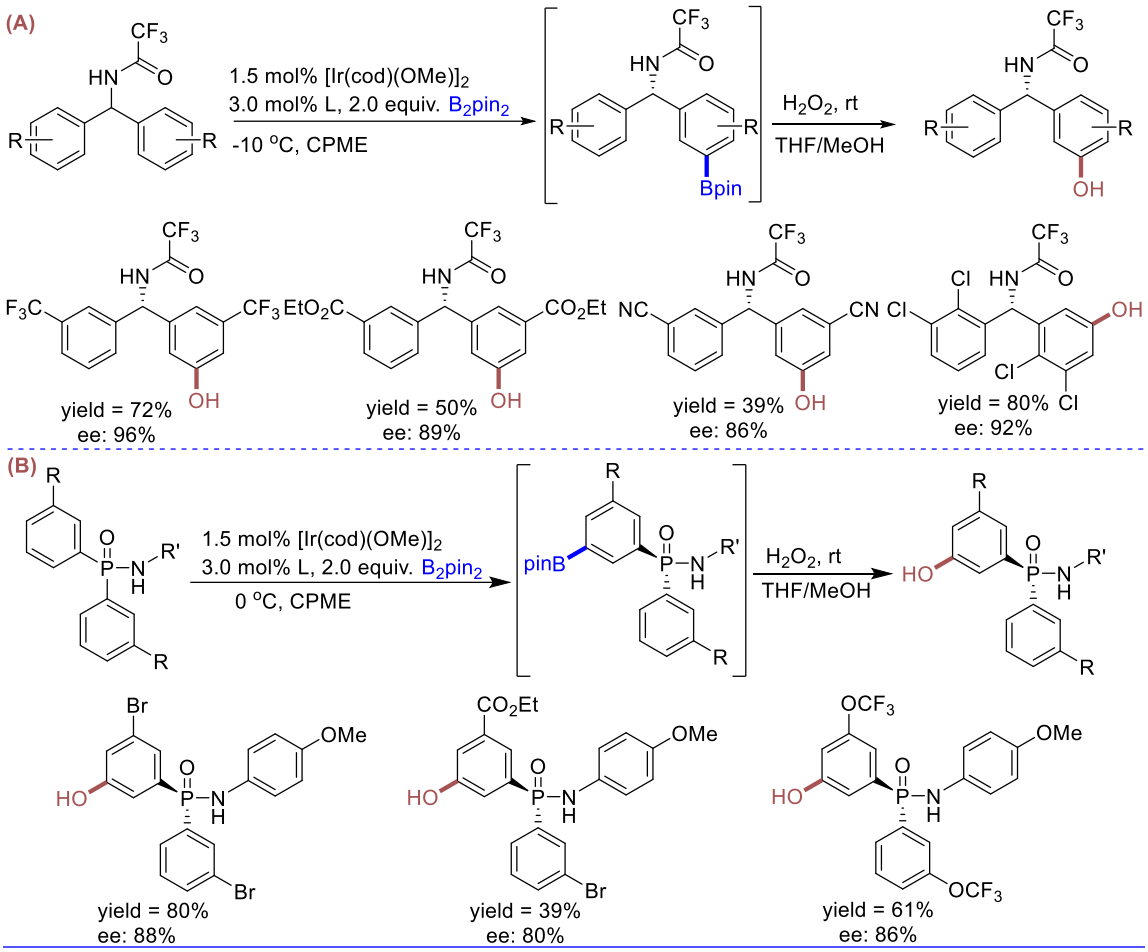
Scheme 1.57: Ir-Catalyzed *Meta* Borylation of Amide via Lewis Acid-Base Interaction

Next, a borylation reaction with ligand which have bipyridine unit attached with alkylaluminium group (used for benzamide borylation) was conducted but it resulted in non-selective borylation with poor yield. A phenanthroline ligand (instead of bipyridine) attached with alkylaluminium moiety gave better conversion. Authors thought that weak Lewis acidity of the aluminium group attached to phenanthroline ligand was responsible for the non-selective reaction, hence a boron-based Lewis acidic framework was attached with phenanthroline ligand and used for borylation of 2-Me pyridine. After screening of boron-based ligand, they found that using BCy_2 substituted 2-ethylphenyl side chain attached with phenanthroline ligand gave maximum C-5 selectivity as well as yield. Although, various nitrogen and oxygen containing 2-substituted pyridines, ether, amines, 2-ethyl pyridine were tolerated under the established reaction conditions, selective borylation of 2-methoxy, 2-halogenated pyridines were unsuccessful. In this way, the authors presented a powerful method for remote borylation using Lewis acid- base noncovalent interaction.



Scheme 1.58: Ir-catalyzed *meta* borylation of pyridines via Lewis acid-base interaction

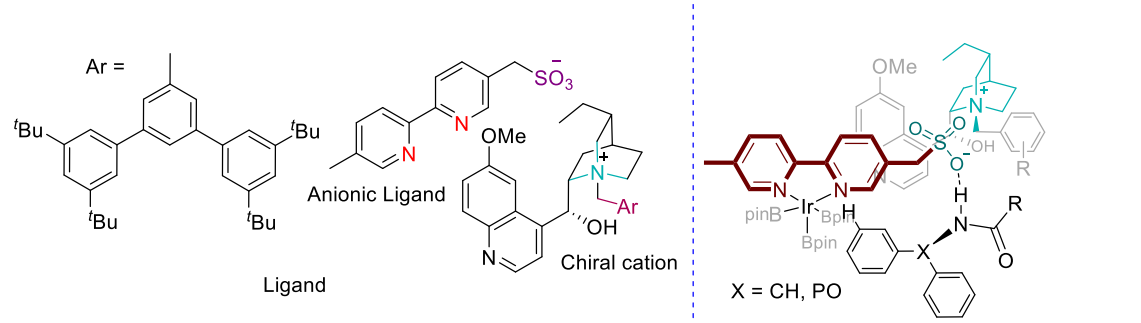
Recently, in 2020, Phipps groups developed an iridium-catalyzed enantioselective remote borylation reaction.[81] The hypothesis behind the enantioselective borylation is that the interchange of the achiral tetrabutylammonium ion of the ligand for a chiral cation might favour enantioselective, desymmetrizing carbon hydrogen activation in a prochiral substrate. They initiated their work with symmetrical benzhydrylamide and tested a number of ion-paired ligands with a number of chiral cations, which could be obtained through counterion exchange. After screening a variety of conditions, they found that their optimized sulfonate bearing bipyidine ligand with *tert*-butyl substituted cation preferred high enantioselectivity at -10 ^{o}C in cyclopentyl methyl ether (CPME) solvent without affecting the reactivity of reaction (**Scheme 1.59**). To isolate the desired stable product, after borylation, they transformed Bpin to hydroxy group. Next, they explored the variety of substituents on the substrate aryl rings, like halogens are well tolerated in optimized conditions. Moreover, substituents at three position like CF_3, ester, and nitrile were well tolerated. Next, they found that the vicinally dechlorinated and difluorinated substrates worked effectively. On the other hand, substituents having electron releasing property like 3-Me and 3-OMe showed lower reactivity under this methodology.



Scheme 1.59: Ir-Catalyzed Enantioselective *Meta* C-H Borylation

The developed method works successfully for symmetrical phosphinamide bearing a paramethoxy phenyl group on the phosphinamide nitrogen, which gave excellent enantioselectivity and show excellent reactivity as well. To prove the concept of the H-bonding interaction between the aromatic substrate and designed ligand, they performed some control experiments. At first, they conducted a reaction with the *N*-methylated substrate using the developed conditions, which resulted in no borylated product at −10°C. But, when the temperature of the reaction was shifted to 10°C, it produced borylated product with only 8% ee. This outcome clearly showed the utility of the hydrogen-bond donor in the substrate for both reactivity and enantioselectivity. Next, the authors used neutral 5,5′-dimethylbipyridine ligand together with the optimal chiral cation as a bromide salt instead of the ion-paired ligand and found the formation the racemic product. This reaction further proves the utility of ligand and chiral cation to be associated to achieve high enantioselectivity. The use of ligand having achiral tetrabutylammonium as the cation, was used in conjunction with bromo counter anion of chiral cation, which showed lower

amount of enantioselectivity of the product, accordant with some degree of counterion exchange occurring between the two, leading to average enantioinduction. In this study, the authors reported the incorporation of chiral cations into the conventional transition metal catalysis and showed the utility in asymmetric synthesis (**Scheme 1.60**).



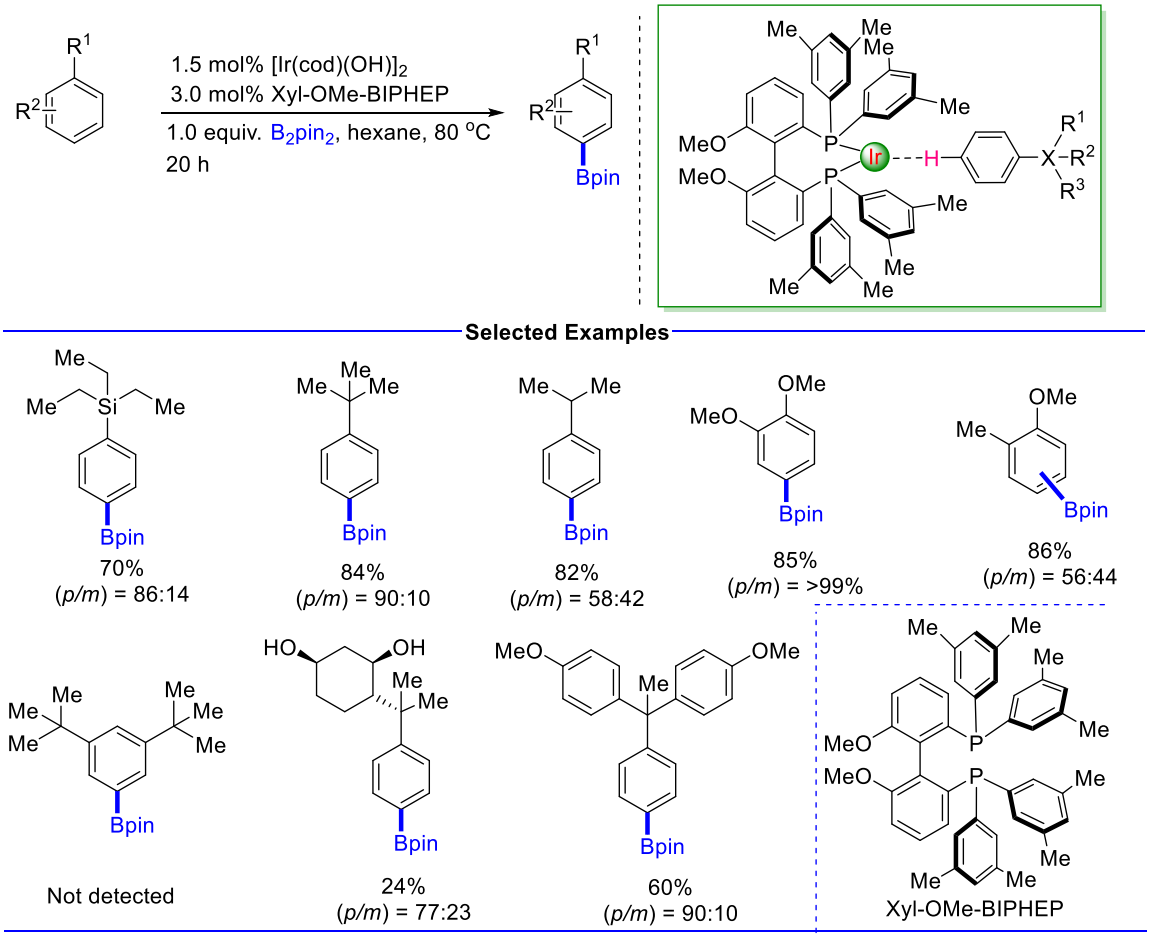
Scheme 1.60: Representation of Chiral cation and Ligand Interaction with Substrate H-Atom

1.5.6 Iridium-Catalyzed *Para*-C-H Borylation of Arenes

The activation and functionalization of remote *para*-C-H bond in arenes are very important due to their utility in synthetic organic chemistry. The most common method for *para* functionalization is electrophilic aromatic substitution reaction. In this case, when a strongly electron-releasing group presents on the benzene rings, it produced a mixture of *o*- and *p*- products. Therefore, to get the desired *p*- functionalized product, it is necessary to block the *ortho* position. The field of C-H borylation chemistry provide an important route for specific functionalization of *p*- C-H bond in arenes. Selective *p*- C-H bond borylation is challenging but extremely desirable. Smith and co-worker[82] developed an illustration of *para* selective borylation, in which Bpin group showed *p*- directing effect at room temperature and gave 64% *p*- borylated product. This result was further reanalyzed by Marder and Steel,[83] they increased the selectivity up to 68% by changing the boryl group of the same reaction. After that, Shinokubo and Osuka reported[84] sterically controlled *para* borylation of octaethylporphyrinyl benzene. Considering the importance of *para* selective borylation reaction, in this section, I will discuss some important examples of Ir-catalyzed *para* borylation.

In 2015, Itami group reported the very first general method for the *p*- selective borylation using a bulky diphosphine ligand.[85] The high selectivity as well as reactivity of the reaction was achieved by the combination of $[Ir(cod)OH]_2$ catalyst and Xyl-MeO-BIPHEP ligand in *n*-hexane solvent (**Scheme 1.61**). The authors explored various mono substituted arenes

like triethylphenylsilane, *tert*-butylbenzene and *tert*-amylbenzene which furnished high *para* selectivity. They found that the *para* selectivity decreases as the steric bulk of the substituent decreases, which concluded that the substituent on the aromatic molecule show steric repulsion with the ligand, which is playing a crucial role for the high *para*-selectivity. When borylation reaction was performed with disubstituted arenes, it resulted in high yields and almost independent of their electronic property. A useful synthetic application of this strategy was reported by the authors as they transformed a drug molecule (Caramiphen, which is utilized in the therapy of Parkinson's disease as an anticholinergic drug) into their 5- derivatives.



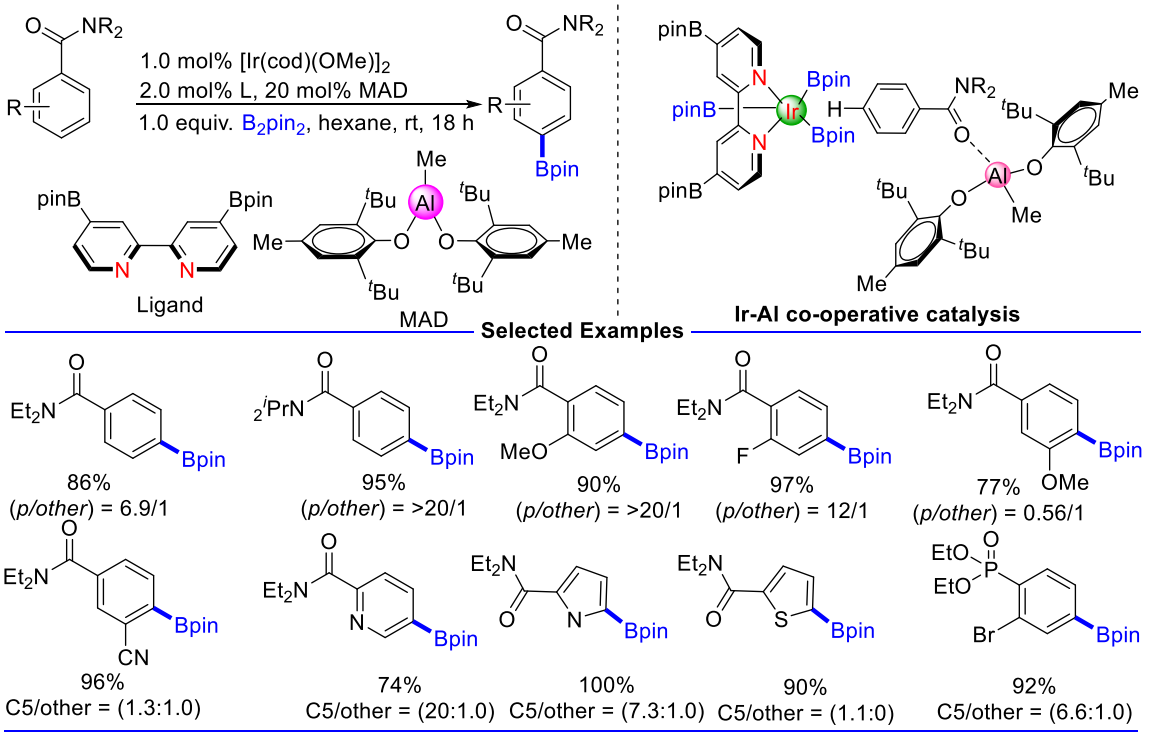
Scheme 1.61: Ir-Catalyzed *Para*-C-H Borylation with Bulky Phosphine Ligand

In 2016, Itami and Musaev studied DFT calculation to find out the mechanism of this iridium-catalyzed *p*- selective borylation involving the bulky diphosphine ligand.[86] They reasoned that the origin of the high *para* selectivity depends on several factors such as : (i) the aromatic substrate and ligand show combined effect of the attractive and repulsive interactions, (ii) entropic penalties across the high-energy C-H activation and (iii) TS of

the C-B bond formation occurs in the reaction pocket. The authors distinguished that as the size of substituent on the aromatic ring increased, *para*-selectivity of the product increased (i.e., SiH_3 < $SiMe_3$ < $Si(^tBu)_3$), which showed corelation with the experimentally observed result. The bulkier 3,5-disubstituents on the phenyl rings of ligand increases the steric bulk and decreases the *para*-selectivity. According to the computational study and experimental examination, the authors revel that high *p*-selectivity achieved through the combined effect of steric and electronic factors.

In 2017, Lan *et al.* studied the mechanism of the Ir-catalyzed *p*- borylation reaction by Density functional theory method.[87] Here, the authors reported that the mechanism of the Ir/Xyl−MeO−BIPHEP-catalyzed *p*-selective borylation reaction is completely different. This *para*-C-H borylation reaction does not follow the previously reported[86] Ir(III)/Ir(V) catalytic cycle, actually it proceeds via an Ir(I)/Ir(III)-based catalytic cycle.

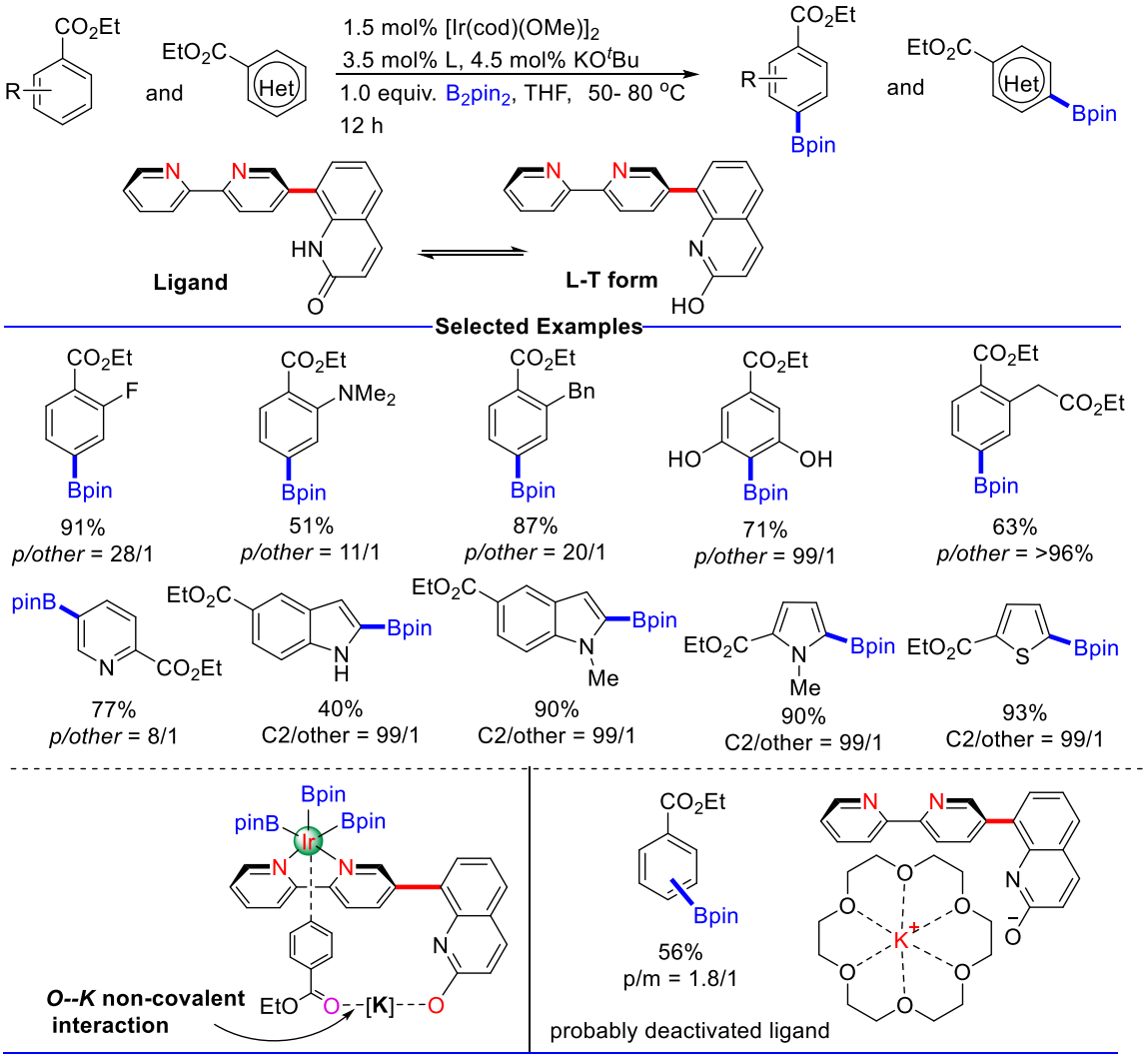
In 2017, Nakao group demonstrated a *p*-selective borylation of benzamides and pyridine derivatives with the help of a cooperative Ir/Al catalysis, mentioned in **Scheme 1.62**.[88]



Scheme 1.62: Ir-Catalyzed *Para*-C-H Borylation via Lewis Acid-Base Interaction

The concept for iridium-aluminium catalysis was based on some important factors. First one was that the interaction a Lewis basic substrate with a ligand having a Lewis acid group, it resulted in charge transfer, which make the substrate molecule highly reactive and electronically deficient. Second one was that the ligand on the Ir-catalyst show the steric

repulsion with bulky Lewis acid core in the active catalytic intermediate would restrict both the *o*- and *m*-carbon-hydrogen bonds of substrate and only the *para* carbon-hydrogen bond would be available for borylation. Based on these two important considerations, they devised an elegant method for this *para* borylation reaction. Applying the developed method, a series of different *N*-substituted benzamide gave high *para* selective borylation reaction. Although pyridine derivatives produce non-selective reaction, their developed method controls the borylation of pyridine with C-4 selectivity but failed to borylate the C-3 substituted pyridines.



Scheme 1.63: Ir-Catalyzed *Para* Borylation via *O--K* Noncovalent Interaction

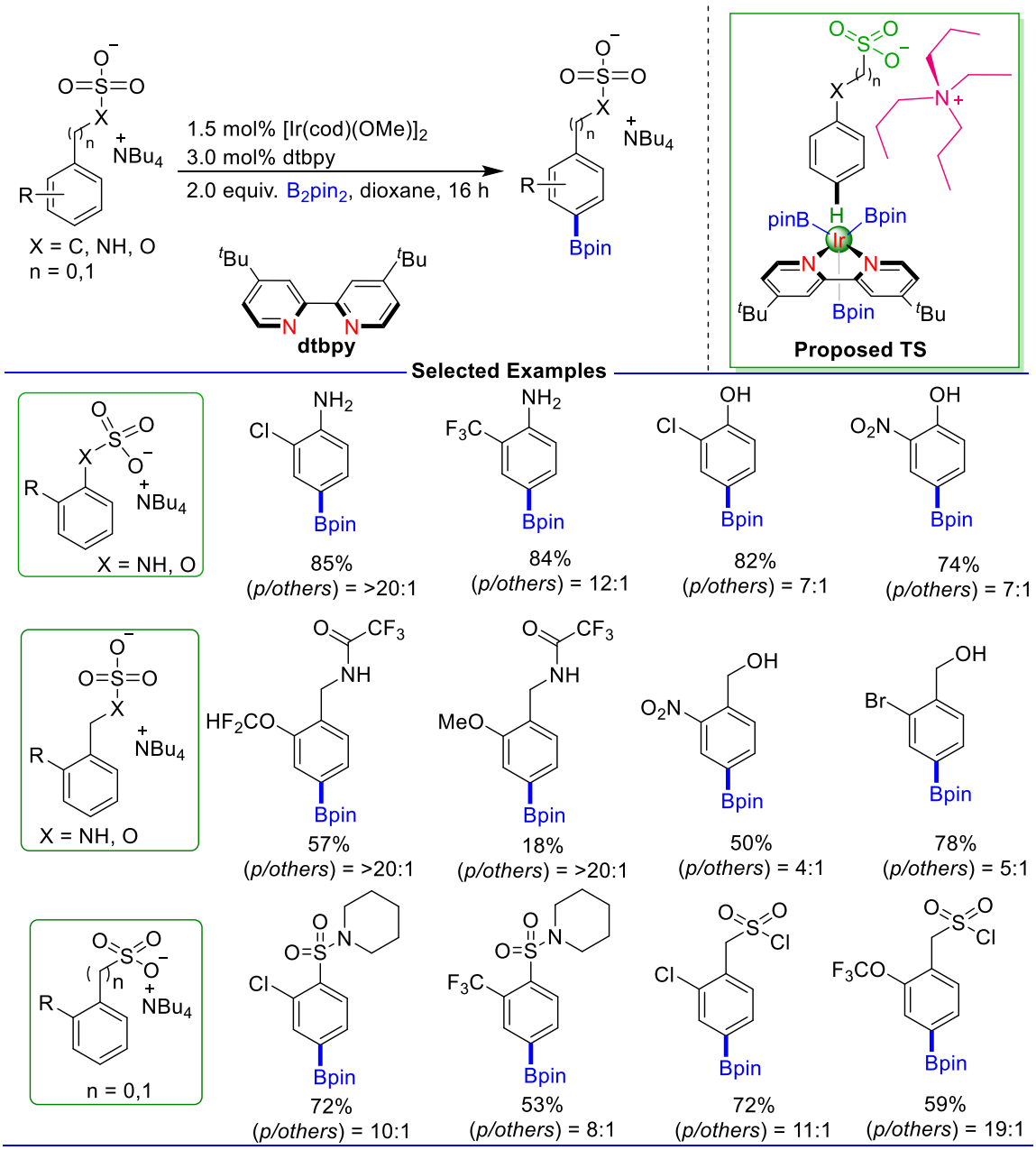
A unique strategy for iridium-catalyzed *p*-selective borylation of aromatic esters using noncovalent interaction was demonstrated by our group in 2017,[78] shown in **Scheme 1.63**. A newly designed L-shaped ligand showed the noncovalent interaction to control the selectivity. L-shape ligand contains two basic units- one is the bpy unit and another is a

quinolone molecule, which likely present in stable L-T form via tautomerization. The origin of *para* selectivity of aromatic esters could be explained by considering the non-covalent interaction between the hydroxy group of ligand or the oxygen-metal (M i.e., Li, Na, K) bond (in situ generated) of ligand and O atom of C=O of the aromatic ester.

The developed borylation strategy can borylate a series of substituted aromatic ester for example alkyl, alkoxy, amine, halogens as well as a variety of heteroarenes are well suited. Surprisingly, when borylation performed in the presence of 18-Crown-6, selectivity of *para* borylation drastically decreased from 33/1 to 1.8/1.0 due to the strong binding affinity of the 18-Crown-6 with K^+ ion and it forms a deactivated complex which diminished the selectivity of borylation reaction and also supported the concept of *O--K* noncovalent interaction.

Utilizing the previously developed ion-pair interaction concept for the *meta* borylation of arenes, Phipps group developed[89] an Ir-catalyzed *para* selective borylation of most common arenes like anilines, benzylamines, phenol and benzylamine using commercially available catalyst and ligand (**Scheme 1.64**). They thought that using similar approach (that was used previously[89] for *meta* borylation) for borylation at *para*-C-H bond would be very difficult due to the long distance between ligand and substrate. They envisioned an alternative path for this ion pair strategy where counterion of the arene is bulky and not functionalized, stand-in as a "steric shield" to restrict borylation at the *m*- position. As a result, this counterion will act as a "off-the-shelf" borylation catalysts to borylate at *para* position. They started their investigation by converting the substrates to the corresponding tetra butyl ammonium sulfamate salt and subsequently exchange of cation with Bu_4NHSO_4. Pleasingly, when borylation was performed with the modified substrates using Ir-catalyst and dtbpy ligand, it gave *para* borylated product. To get back the parent structure of corresponding borylated product, they treated the crude reaction mixture with HCl in methanol.

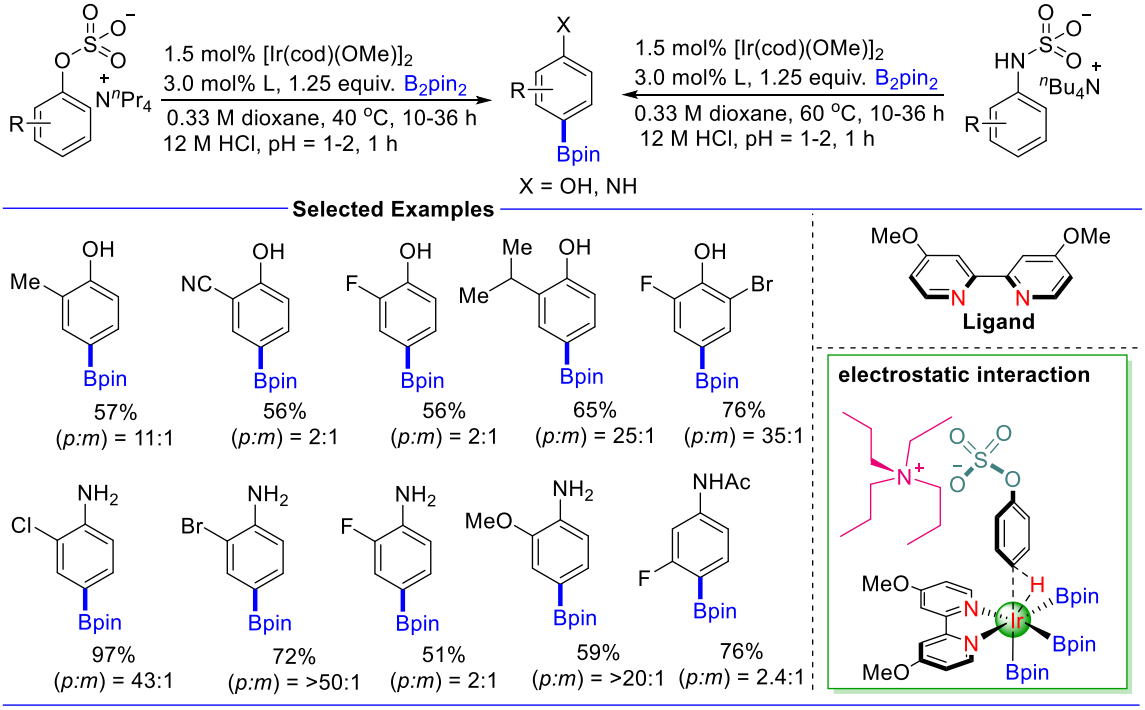
Numerous substituted anilines were also explored. Benzylamine derived sulfamates and different 2-substitued benzylamine like trifluoromethoxy, trifluoromethyl, difluoro methoxy and halogens were highly suitable under the developed borylation protocol and afforded good selectivity. Inspired by the outcome of nitrogen containing arenes, they next tested most common oxygen containing substrates like phenols and benzyl alcohols.



Scheme 1.64: Ir-Catalyzed *Para*-C-H Borylation via Ion-Pairing with a Bulky Counteraction

Interestingly, different 2-substituted phenol derived sulphate salts produced selectively *para* borylated products. The authors next explored benzyl alcohol derived sulphate substrates and found that benzyl alcohol derived substrates were also suitable for the borylation reaction. To prove the concept of the bulky counter ion interaction, they performed reaction with small tetraethylammonium cation and found that three out of four different classes of ammonium cation showed low amount of *para* selectivity. It may be

stated that employing the remarkable concept of bulky counterion interaction, the authors reported high *para* selective borylation of most common and important class of arenes.



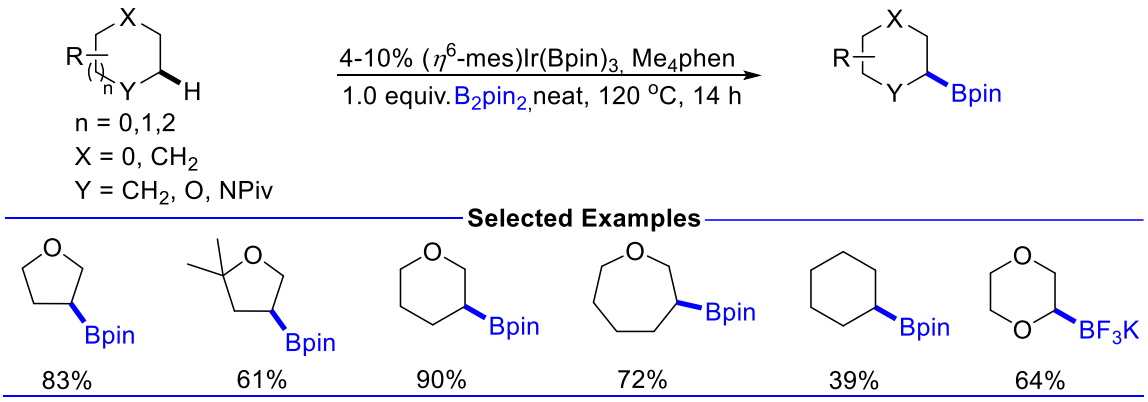
Scheme 1.65: Ir-Catalyzed *Para*- C-H Borylation via Electrostatic Interaction

Simultaneously, Smith and Maleczka independently discovered[90] *p*-C-H borylation of tetra alkylammonium sulfates and sulfamates utilizing the bipyridine ligand and Ir-catalyst. The authors found that the alkyl chain length of tetra alkylammonium cations and the group present on the bipyridine ligands control the selectivity of borylation reaction. Their screening started with easily available substituted bpy and phenanthroline ligand framework and found that electronically rich ligands produced more reactive system as compared to the electronically poor ligands. The best *para* selectivity was obtained with dimethoxy-2,2′-bipyridine ligand which gave 100% conversion of borylated product in dioxane solvent. Authors mentioned that the selectivity of borylation reaction was affected by alkyl chain length of the counter ion. Shortening the alkyl chain length drops the *para* selectivity. The authors found appreciable results with the phenol and aniline derived sulfates having *n*-Pr_4N^+ and *n*-Bu_4N^+ as the counterion respectively. Next, they explored the class of benzyl alcohol derived sulfates which gave slightly decreased *para* selectivity in comparison with phenol and anilines, summarized in **Scheme 1.65**.

1.5.7 Iridium-Catalyzed C(sp^3)-H Borylation

The activation of unreactive alkyl carbon-hydrogen bond and successive functionalization is a major challenge in synthetic organic chemistry[91] due to the high BDE of C(sp^3)-H bond (104 kcal/mol). Among several similar sorts of carbon-hydrogen bonds, activation of a particular carbon-hydrogen bond with excellent selectivity remains a big challenge. In recent years, activation of inert aliphatic C(sp^3)-H bonds using transition metal-catalyst[92] emerged as a valuable and competent method to access highly beneficial intermediate alkylboronates.[6a,93,94]In the literature, methods reported for selective functionalization of aliphatic carbon-hydrogen bonds require either with the employment of a group that chelates to a metal centre and guides the carbon-hydrogen bond functionalization reaction[95] or the use of reactive carbon-hydrogen bonds due to the electronic effects. Several pioneering works have been reported by the Hartwig group. They have shown that metals like Re,[92a] Rh[92b-d,f] and Ru[92e] form metal-boryl catalysts activate the alkane primary carbon-hydrogen bonds at terminal sites and facilities the formation of primary alkyl borylated products.

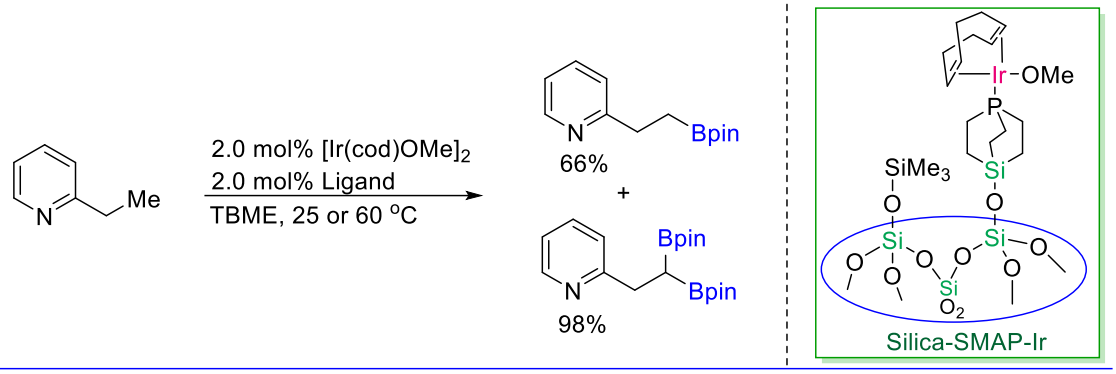
In 2012, an aliphatic borylation reaction of cyclic ethers was reported by Hartwig group[96]. In this study, they have used tetramethylphenanthroline (TMP) ligand in presence of Ir-catalyst to borylate 2° carbon-hydrogen bonds of cyclic ethers (**Scheme 1.66**). The β carbon-hydrogen bond is preferentially borylated under the established reaction conditions. From the experimental studies, they concluded that before isomerization β carbon-hydrogen bond cleaved at faster rate than α carbon-hydrogen bond.



Scheme 1.66: Ir-Catalyzed Borylation of Secondary C-H Bonds in Cyclic Ethers

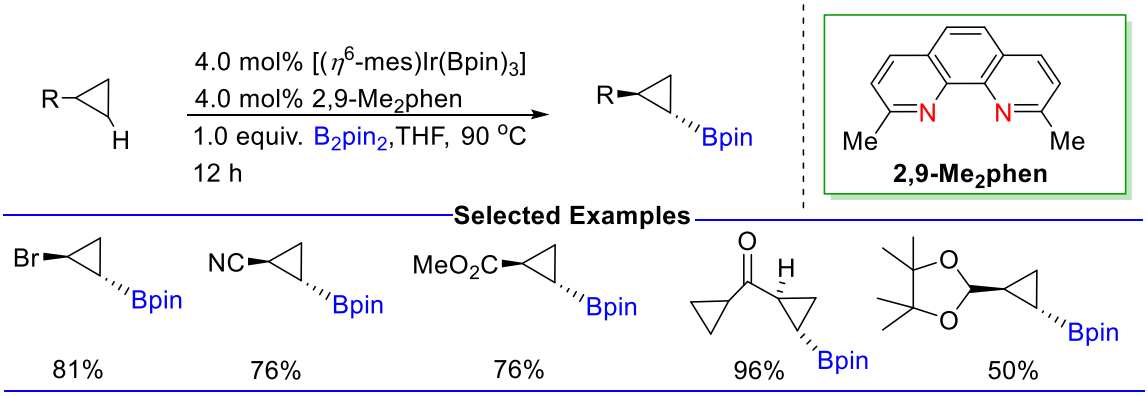
Same year, Sawamura group reported Rh-catalyzed borylation of α-carbon-hydrogen bond of amide,[97] urea and 2-amino-alkane substrates employing silica TRIP ligand. Next year, same group demonstrated aliphatic carbon-hydrogen bond activation and borylation of 2-

alkylpyridines.[98] A mixture of $[Ir(cod)OMe]_2$ and silica-supported monophosphite produced heterogeneous catalyst system, which preferentially borylate the γ-carbon-hydrogen bond of pyridine *N*-atom (**Scheme 1.67**). High site-selectivity of borylation reaction was achieved through carbon-hydrogen activation aided through proximity effect because of nitrogen to-iridium coordination.



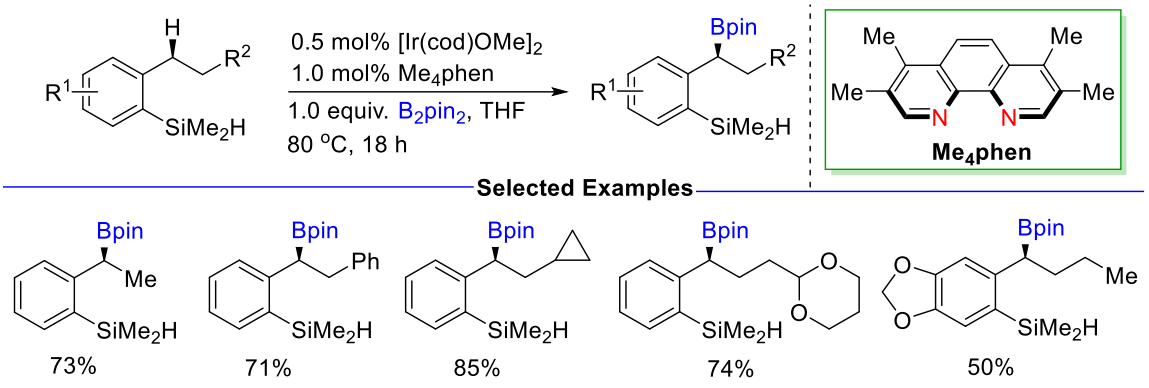
Scheme 1.67: Silica-SMAP−Ir-Catalyzed C(sp^3)-H Borylation of Alkylpyridine

In 2013, borylation of the methylene carbon-hydrogen bonds of cyclopropanes were reported by Hartwig group.[99] The ligand 2,9-Me_2phen in presence of [(η^6-mes) $Ir(Bpin)_3$] or $[Ir(cod)OMe]_2$ catalyst gave cyclopropyl boronate ester (**Scheme 1.68**). The differently substituted cyclopropane gave decent yield and excellent diastereoselectivity. The cyclopropyl boronate esters act as a synthetic intermediate for variety of transformations.



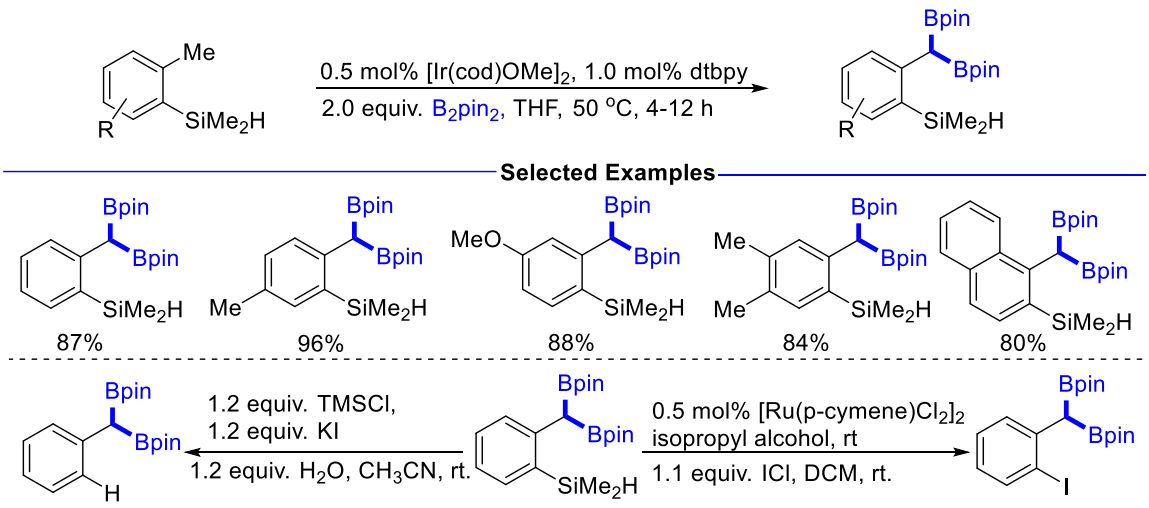
Scheme 1.68: Iridium-Catalyzed C-H Borylation of Cyclopropanes

As reported earlier,[96] Ir precursor and phenanthroline frameworks are suitable for C(sp^3)-H borylation. In 2013, Hartwig group reported Iridium-catalyzed borylation of 2° benzylic carbon-hydrgen bond in presence of tetramethyl phenanthroline ligand.[100] This benzylic borylation was achieved by a hydro silyl directing group and after borylation this hydrosilyl group was transformed into a variety of functional group and gave various secondary benzyl boronate esters (**Scheme 1.69**).



Scheme 1.69: Hydrosilyl Directed Ir-catalyzed Borylation of Secondary Benzylic C-H Bonds

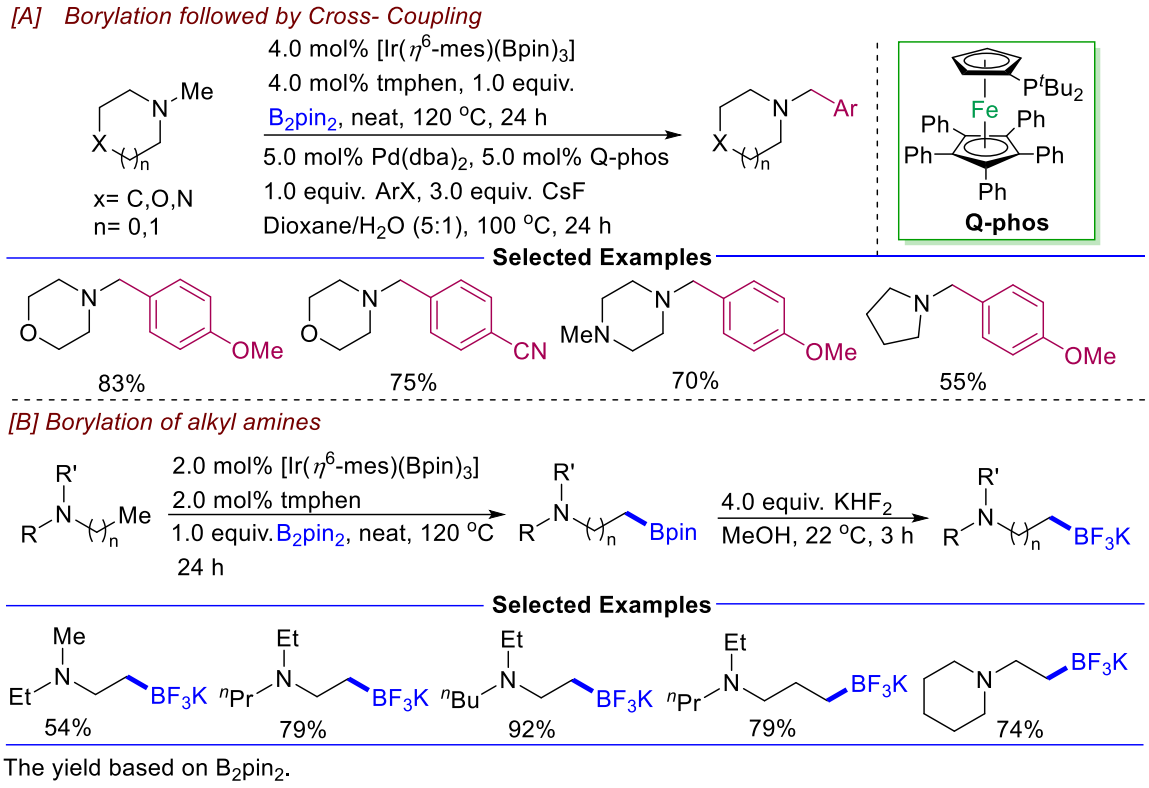
Utilizing the hydrosilyl directed borylation idea, same group discovered a diborylation reaction[101] of benzylic carbon-hydrogen bonds. In this study, along with $[Ir(cod)OMe]_2$ catalyst, they have used di tertbutyl bipyridine as a ligand. In this case, a series of 1,1-benzyldiboronate esters have been prepared and silyl group further converted to other useful FGs without affecting the 1,1-benzyldiboronate esters (**Scheme 1.70**).



Scheme 1.70: Hydrosilyl Directed Diborylation of Benzylic C-H Bond

In 2014, borylation of alkylamine and alkyl ethers in presence of $[(\eta^6\text{-mes})Ir(Bpin)_3]$ and Me_4phen ligand[102] was disclosed by Hartwig *et al.*,depicted in **Scheme 1.71.** This borylation preferred at terminal β-carbon-hydrogen bond to O and N atoms in comparison to other terminal carbon-hydrogen bonds. The alkyl boronate products can be used directly for Suzuki-Miyaura cross-coupling reaction or isolated as potassium trifluoro borate salt. The high reactivity of terminal carbon-hydrogen bond borylation reaction of ethylamine and ethers is due to the combined striking LA and LB interaction and H-bonding interaction

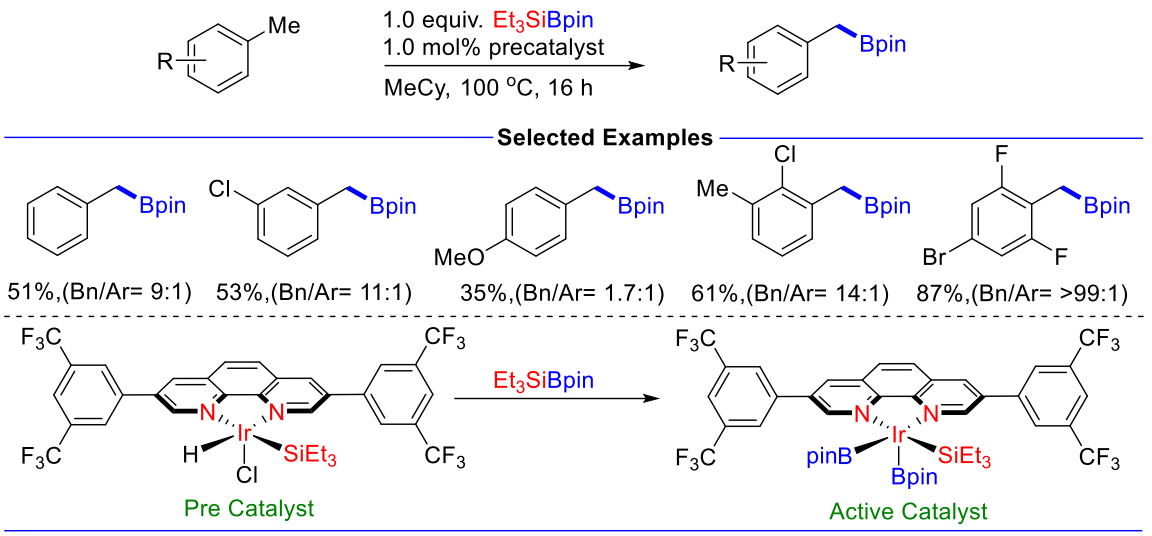
together with repulsive interaction in TS. The breakage of carbon-hydrogen bond is the rds for the borylation reaction which was confirmed by computational and experimental studied.



The yield based on B_2pin_2.

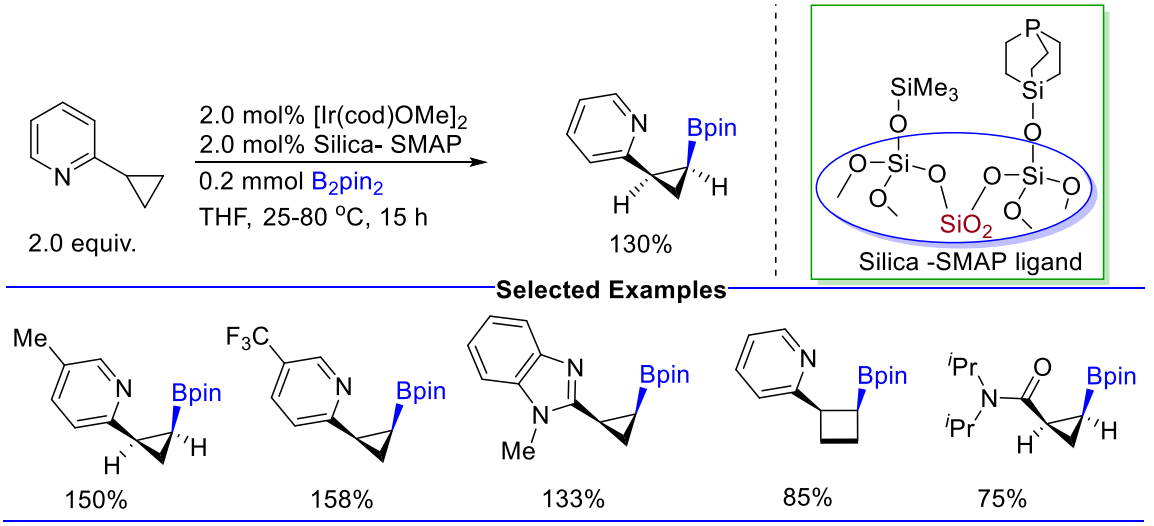
Scheme 1.71: Regioselective Aliphatic Borylation of Alkyl Ethers and Alkyl Amines

In 2015, the same group reported a protocol for the benzylic C(sp^3)-H bond borylation of methylarenes without the use of any directing groups.[103] Borylation reactions were performed using catalytic amount of iridium-catalyst, electron poor Phen ligand and borylating agent. $Et_3SiBpin$. Various functional groups were well tolerated and gave the benzylic borylated products with high selectivity and good yield (**Scheme 1.72**). To realize the pathway, the authors conducted many mechanistic experiments as well as computational calculations. The iridium diborylmonosilyl complex was used as an active catalyst for this borylation reactions which is more electron poor than the commonly employed Ir-trisboryl complex for the borylation. As the electron density at the metal centre decreases benzylic borylation increases. The new reactivity towards C-H borylation reaction was achieved by replacing one boryl ligand with silyl ligand and an electron-donating ligand is replaced by a weakly coordinating dative ligand from the standard iridium trisboryl complex in the active catalytic system.



Scheme 1.72: Iridium-Catalyzed Benzylic C(sp^3)-H Bond Borylation

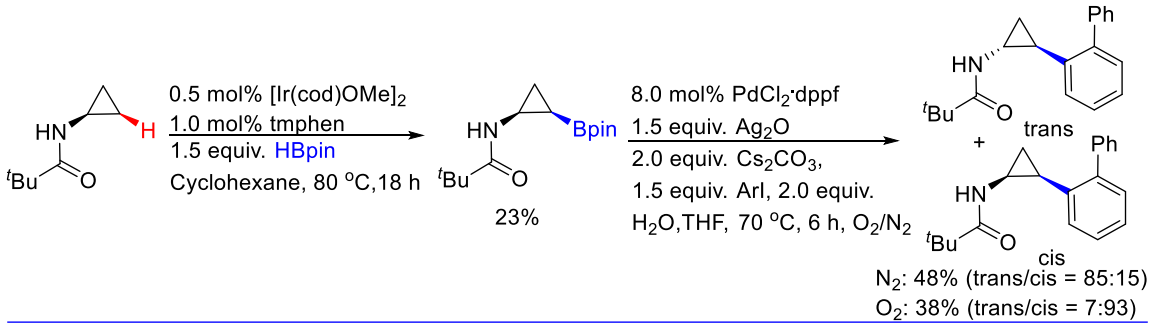
The modification of silica-supported TRIP ligand (reported earlier) to a silica-supported tripod triaryl phosphine ligand, Sawamura *et al.* established a unique directed aliphatic C-H borylation[104] of a various amide and 2-alkyl pyridine derivatives in presence of iridium and rhodium catalyst.



Scheme 1.73: Silica-Supported SMAP ligand Catalyzed Aliphatic Borylation

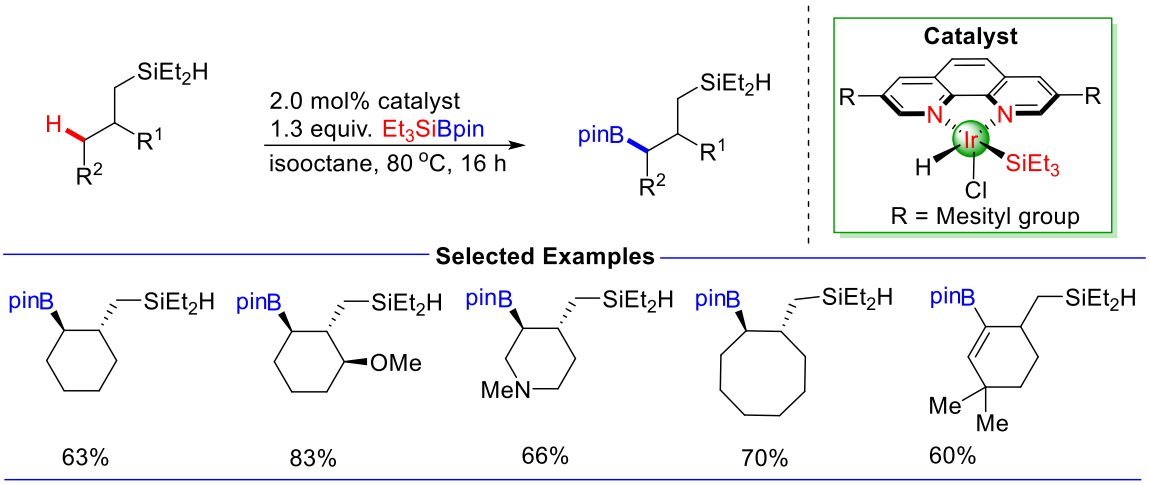
In 2014, the same group reported[105] a heteroatom-directed C-H borylation of cyclopropane and cyclobutene employing silica-supported monophosphate iridium catalysts (**Scheme 1.73**). Borylation reaction preferred at the γ carbon-hydrogen bond of nitrogen or oxygen directing group with exceptional *cis* stereoselectivity. A B-N coordination found in between the nitrogen atom of the pyridine directing group and the boron functionality of the borylated product. The developed borylation protocol showed remarkable selectivity for various substrates and also useful for steric congested substituted cyclopropane.

An iridium-catalyzed aliphatic C-H borylation and subsequent Suzuki–Miyaura coupling sequence reaction of aryl substituted cyclopropylamines was reported[106] by Yamaguchi and Itami in the year of 2015 (**Scheme 1.74**). This stereodivergent borylation strategy is also step-economical. The borylation of *N*-cyclopropylpivalamide proceeds with *cis* selectivity and followed by Suzuki-Miyaura coupling using [$PdCl_2$(dppf)]/Ag_2O-catalyst underwent with retaining of configuration at the carbon centre attaching with the boron functionality. The authors observed that epimerization at the carbon atoms attached with N-atom. However, atmospheric O_2 quashed the epimerization process. The major advantages of this developed method are that it not only reduced significantly reaction step but also this method is capable to produce selectively one isomer (*cis* or *trans)* by the amendment of the atmosphere (nitrogen or oxygen) in the coupling step.



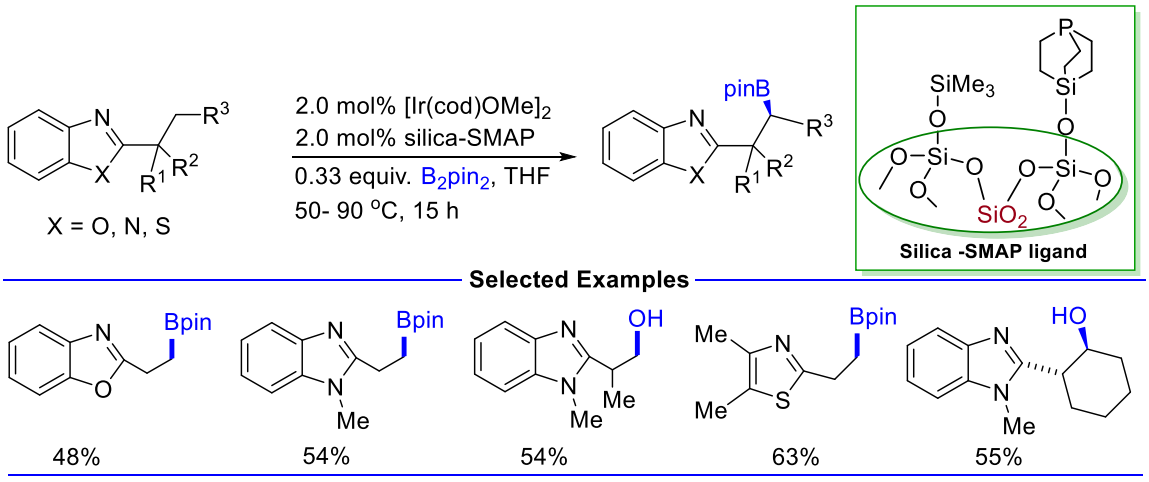
Scheme 1.74: Synthesis of 2-Arylcyclopropylamines (ACPAs) via a Sequential C(sp^3)-H Borylation followed by Suzuki–Miyaura Coupling Reactions

The hydrosilyl directed borylation of 1° and 2° aliphatic carbon-hydrogen bonds in presence of iridium catalyst was reported[107] by Hartwig group in 2016 (**Scheme 1.75**). The borylation reactions preferred at 1° γ carbon-hydrogen bond to the hydrosilyl group and selectively form 1° alkyl diboronate esters. While 1° C-H bonds are unavailable, the borylation reaction preferred at a 2° γ carbon-hydrogen bonds with high diastereoselectivity. These alkyl boronate esters having hydrosilyl group can be transformed into variety of functional group (amination, oxidation and arylation) with respect to the C-B or C-Si bonds.



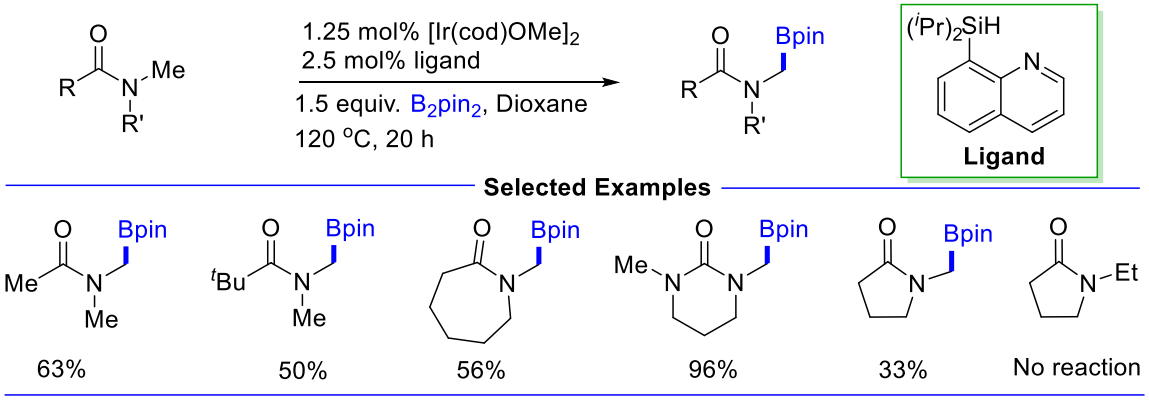
Scheme 1.75: Hydrosilyl-Directed Borylation of the Primary and Secondary Alkyl C-H Bonds

In 2016, Sawamura group reported[108] a nitrogen-directed C(sp^3)-H bond borylation of side chain of the 1,3-azole ring by silica-supported phosphine ligand (developed earlier). Borylation preferred at the γ aliphatic carbon-hydrogen bond of 1,3-azole compounds and high site-selectivity was achieved through the coordination of substrate nitrogen atom with metal center. The borylation favors both terminal and internal carbon-hydrogen bonds of the 1,3-azole. Many substrates were well tolerated under developed conditions. To display the synthetic efficacy of the established method, alkyl boronates were transformed to different functional groups that formed an important azole framework. However, few borylated products further transformed to their corresponding alcohols (**Scheme 1.76**).



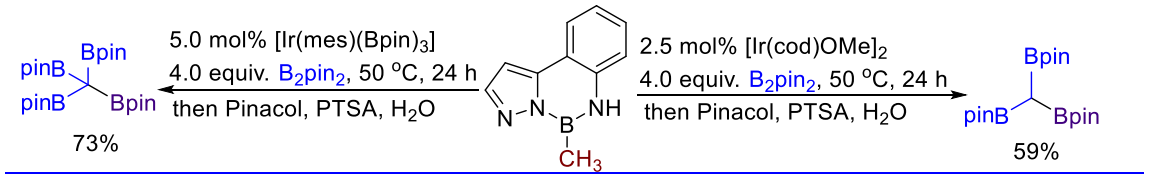
Scheme 1.76: Borylation of Inactivated or *N*-adjacent γ-C(sp^3)-H Bond of Side Chain of 1,3-Azole Ring

In 2019, Clark *et al.* reported[109] iridium-catalyzed aliphatic carbon-hydrogen borylation of a variety of amide substrates with *N*-Si monoanionic bidentate ligand (earlier developed by Smith and co-workers). They demonstrated that the 5-membered cyclic amide substrate with *N*-methyl group showed 33% product conversion, while the 5-membered cyclic amide with *N*-ethyl group failed to undergo the borylation reaction (**Scheme 1.77**).



Scheme 1.77: Ir-Catalyzed α-Borylation of Amides by Clark

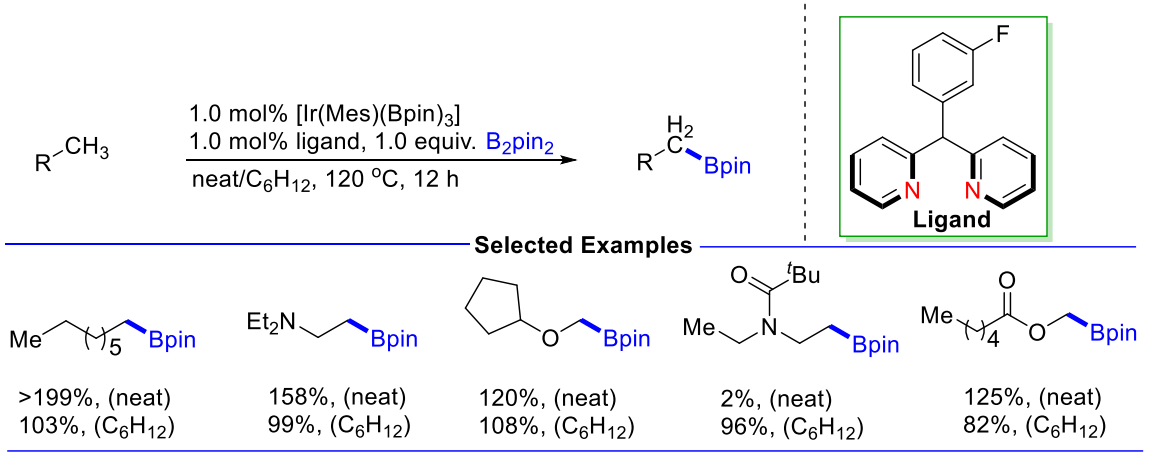
In 2019, Suginome *et al.* reported[110] a method for iridium-catalyzed aliphatic borylation of alkylboronic acids having PZA (pyrazolylaniline) unit as a temporarily directing group on the boron atom. The directed C(sp^3)-H borylation preferred at the α-, β-, and γ-C-H bonds of the substrate and gave polyborylated products. The structure of alkyl group plays an important role for selectivity of borylation reaction. In comparison to α-, β-, and γ-C-H borylation, reaction preferred at the α-C-H bond of primary alkylboronic acid derivatives, whereas β- or γ-borylation reactions also occurred if β- or γ-C-H bonds were present on the methyl group. Here, authors developed a useful method for the synthesis of polyborylated compounds from the unfunctionalized starting materials (**Scheme 1.78**).



Scheme 1.78: Ir-Catalyzed Pyrazolylaniline Directed C(sp^3)-H Borylation

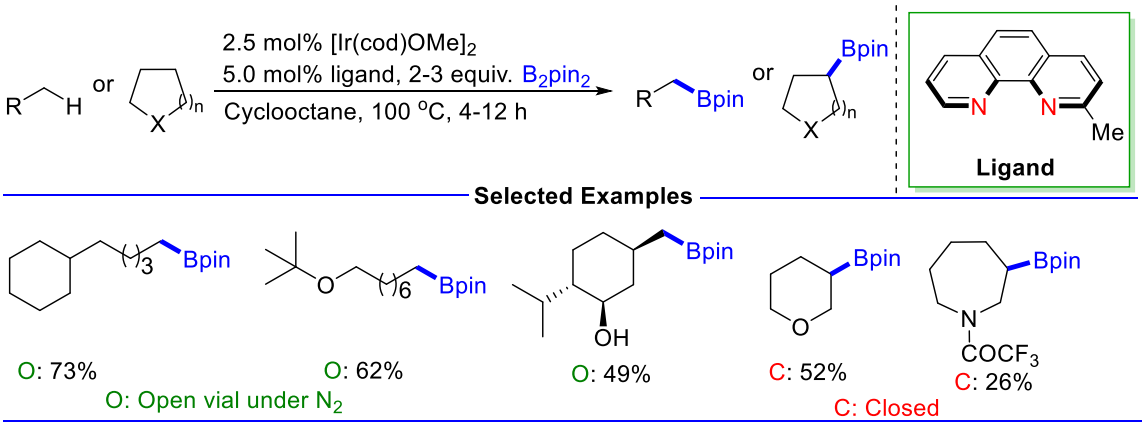
In 2020, Schley group established an elegant borylation method[111] for various alkanes by a newly designed dipyridylarylmethane ligand (**Scheme 1.79**). This newly designed ligand with Ir-catalyst showed remarkable reactivity and selectivity for the borylation reactions with improved efficiency. At low catalyst loading, they showed complete utilization of the diboron reagent and gave two molar equivalents of borylated product. The borylation of

the inert alkanes preferred in hydrocarbon solvent with a less amount of the starting material and variety of FG tolerance. This borylation protocol also useful for challenging substrates having polar functional group like esters, ethers and tertiary amines that are commonly unreactive to the C(sp^3)–H borylation under neat conditions. They proposed that the newly designed ligand structure gave κ^3 binding by cyclometalation with the Ir-catalyst.



Scheme 1.79: Ir-Catalyzed Alkane C-H Borylation with Dipyridylarylmethane Ligand

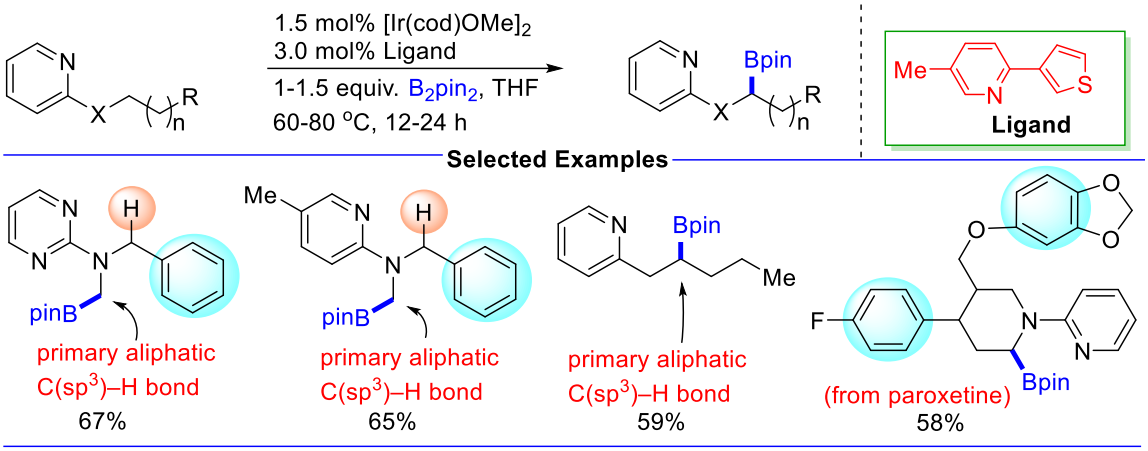
In 2020, Hartwig group reported[112] Ir-catalyzed undirected borylation of the primary alkyl C(sp^3)-H bonds of several organic molecules and β C-H bond borylation of saturated heterocycles (**Scheme 1.80**).



Scheme 1.80: Ir-Catalyzed alkane C-H Borylation with 2-mphen Ligand

A mixture of [Ir(cod)OMe]$_2$, 2-mphen and B_2pin_2 afforded desired boronate esters using cyclooctane as solvent. Numerous functional groups like ether, silyl ether, imide, carbamate, amine, ketal, and acetal well tolerated under the developed conditions and borylation preferred selectively at the 1° carbon-hydrogen bonds of the substrate. Notably,

borylation happens at the 2° carbon-hydrogen bonds in the absence of the primary carbon-hydrogen bond. A foremost restriction of this borylation protocol is the requirement of continuous flow of the inert gases for complete borylation as well as isolation of the products.



Scheme 1.81: Ir-Catalyzed C(sp^3)-H Borylation

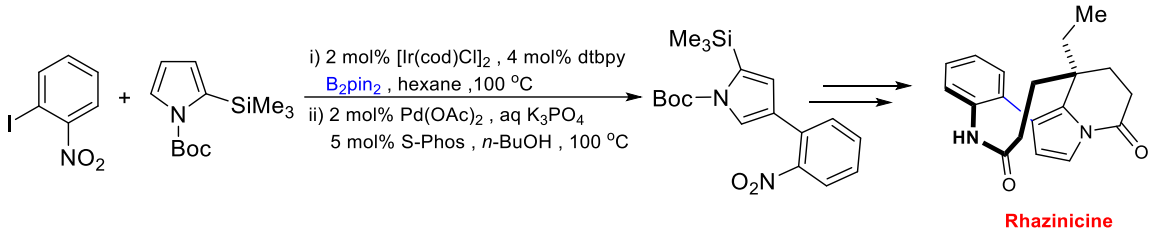
A variety of alcohols underwent borylation and produce the alkyl boronate esters. Recently, our group have reported[63] C(sp^3)-H borylation by a new class of iridium-catalysts system. The newly designed ligand shows remarkable selectivity for diverse classes of substrates for the aromatic and heteroaromatic molecules. A series of aliphatic substrates gave desired boronate esters in good to excellent yields. This aliphatic borylation reaction proceeds through a nitrogen-directed manner. Importantly, it was found that the borylations selectively preferred C(sp^3)-H bond before more reactive aromatic C-H bonds (**Scheme 1.81**).

1.5.8 Application of C-H Borylation

It has been well documented in literature[23] that organoboron compounds could be used as a vital synthon in many synthetic transformations. It deserves mentioning that form last couple of years C-H borylation strategy using iridium catalyst has emerged as cornerstone due to this wide applicability in natural product synthesis, drug discovery as well as in pharmaceuticals.[18-21] In this segment, I will discuss some important methods to highlight the usefulness of carbon-hydrogen borylation reaction used as key step to synthesize many high value-added molecules.

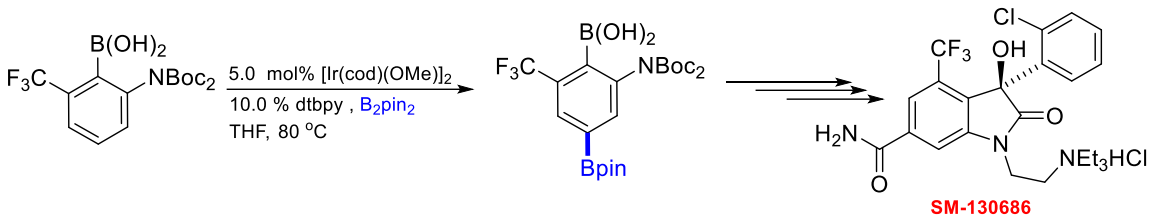
(i) Synthesis of Rhazinicine: Gaunt group disclosed the first total synthesis of rhazinicine[113] from the readily accessible materials in 11 synthetic steps, shown in **Scheme 1.82**. In this study, they have mentioned that iridium-based carbon-hydrogen borylation

strategy could be utilized as a one of the crucial steps to synthesize one of the important intermediates.



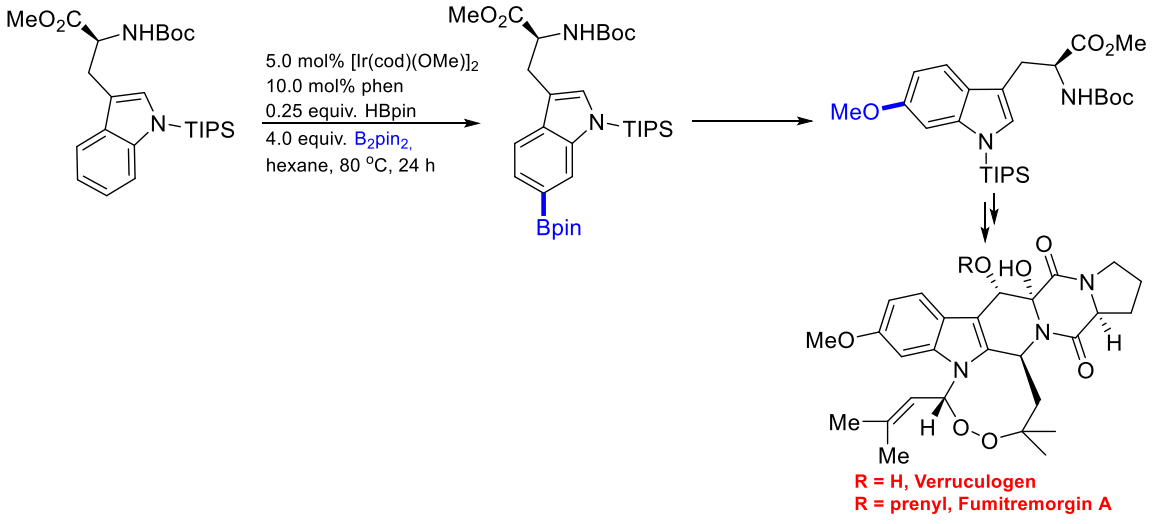
Scheme 1.82: Synthesis of Rhazinicine

(ii) Synthesis of SM-130686: Shibasaki *et al.* exploited the concept of iridium-catalyzed carbon-hydrogen borylation strategy for the synthesis SM-130686 (acts as a growth hormone secretagogue).[114] They conducted *meta* borylation of diboc protected aniline, shown in **Scheme 1.83**.



Scheme 1.83: Synthesis of SM-130686

(iii) Synthesis of Verruculogen and Fumitremorgin A: Using readily accessible tryptophan derivatives, Baran *et.al* reported total synthesis of Verruculogen and Fumitremorgin A[115].



Scheme 1.84: Total Synthesis of Verruculogen and Fumitremorgin A

In this total synthesis, one of the vital synthetic steps (**Scheme 1.84**) is carbon-hydrogen borylation reaction. They have achieved this total synthesis in 11-12 steps.

1.6 Conclusion

Certainly, the evolution of innovative strategies to construct high-valued carbon-boron bonds utilizing carbon-hydrogen bond activation and subsequent functionalization is of eminent interest for scientists. In comparison to other C-H functionalization methods, borylation of aryl C-H bond happens at lenient conditions and many functionalities are compatible. To achieve high selectivity of arene carbon-hydrogen borylation reactions (proximal and distal), steric is not only the main factor for regioselectivity, however non covalent interaction, traceless directing group, designing of substrates also play important roles. In this introductory chapter, particular emphasis is given to the recent advancements of C-H borylation reaction. Compared to arene C(sp^2)-H borylation, borylation of inert aliphatic carbon-hydrogen bonds are highly challenging and they are useful feedstocks in organic synthesis. Several research groups contributed significantly to develop valuable strategy for the undirected and directed aliphatic carbon-hydrogen bond borylation. Non-directed aliphatic C-H borylation provides a straight forward route for the installation of broad range of functional groups. Carbon-hydrogen bond activation/borylation chemistry showed broad application in the area of organic synthesis, pharmaceuticals, material chemistry, and so on.

1.7 References:

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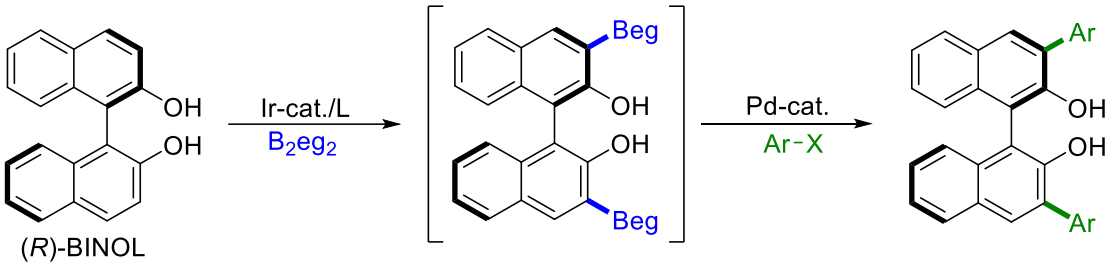
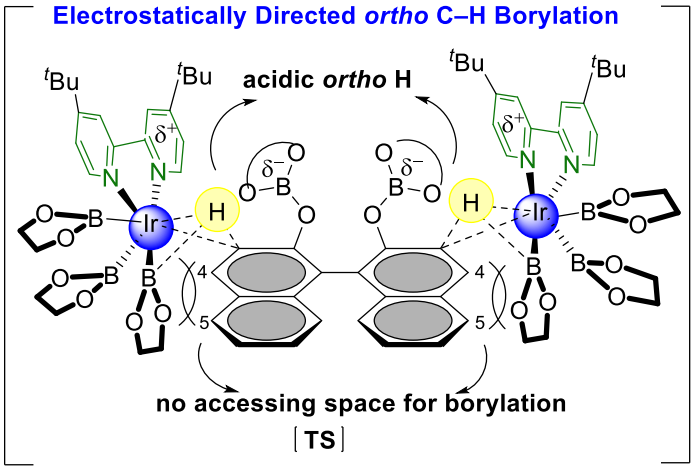
CHAPTER 2

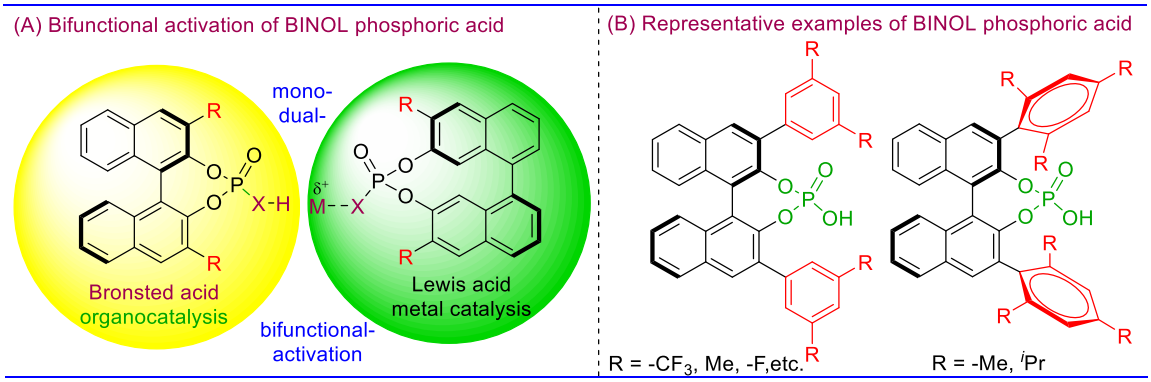
Double-Fold Ortho C–H Bond Activation/Borylation of BINOL: A Unified Strategy for Arylation of BINOL





2.1 Introduction

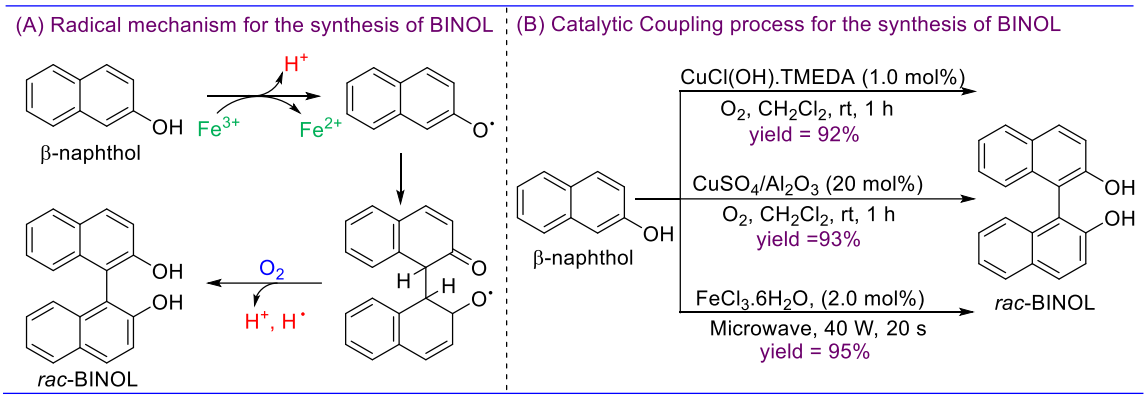
Over the past few decades, enantioselective catalysis using various chiral ligands have gained a tremendous amount of consideration in the area of asymmetric synthesis. The main goal of enantioselective reaction is to make a chiral product (specially a single enantiomer) from an achiral substrate by the use of chiral reagents. Among many chiral ligands, 1,1′- binaphthyl-2,2′-diol i.e. BINOL and its derivatives have achieved particular interest due to its broad application in many asymmetric reactions (stoichiometric as well as catalytic) as a ligand. BINOL is an axially chiral molecule with two enantiomerically pure forms i.e. (*R*)-BINOL and (*S*)-BINOL. Due to the high thermal stability of two atropisomers of BINOL, it can participate in many asymmetric transformations under several experimental conditions.[1] Moreover, BINOLs are well known for bifunctional activation in organic synthesis **(Scheme 2.1)**. It has been found that phosphoric acids of *ortho,ortho′*-disubstituted BINOLs used as catalyst in many enantioselective transformations (mostly in organocatalysis) under simple and mild reaction conditions. The main aspect that has permitted the BINOL-derived phosphoric acid to be used in a huge number of research projects is that they are unbelievably versatile.[2]



Scheme 2.1: Application of BINOL Skeleton

BINOL was first synthesized as a racemate by von Richter in 1873.[3] Since this report, many strategies have been discovered for the preparation of racemic BINOLs. Among them, one of the commonly used method is $FeCl_3$-catalyzed oxidative coupling of β-naphthol.[4] However, other coupling reagents such as $Mn(acac)_3$,[5] $K_3Fe(CN)_6$,[6] copper-amine complexes[7] also produced the racemic BINOLs in reasonable yield. Mechanistically, the oxidative coupling of β-naphthol proceeds via radical mechanism pathway as shown in **Scheme 2.2A**.[4a,8,9] At first, one electron oxidation of β-naphthol in presence of Fe^{3+} gave the radical species, which after coupling with another neutral β-naphthol produced a

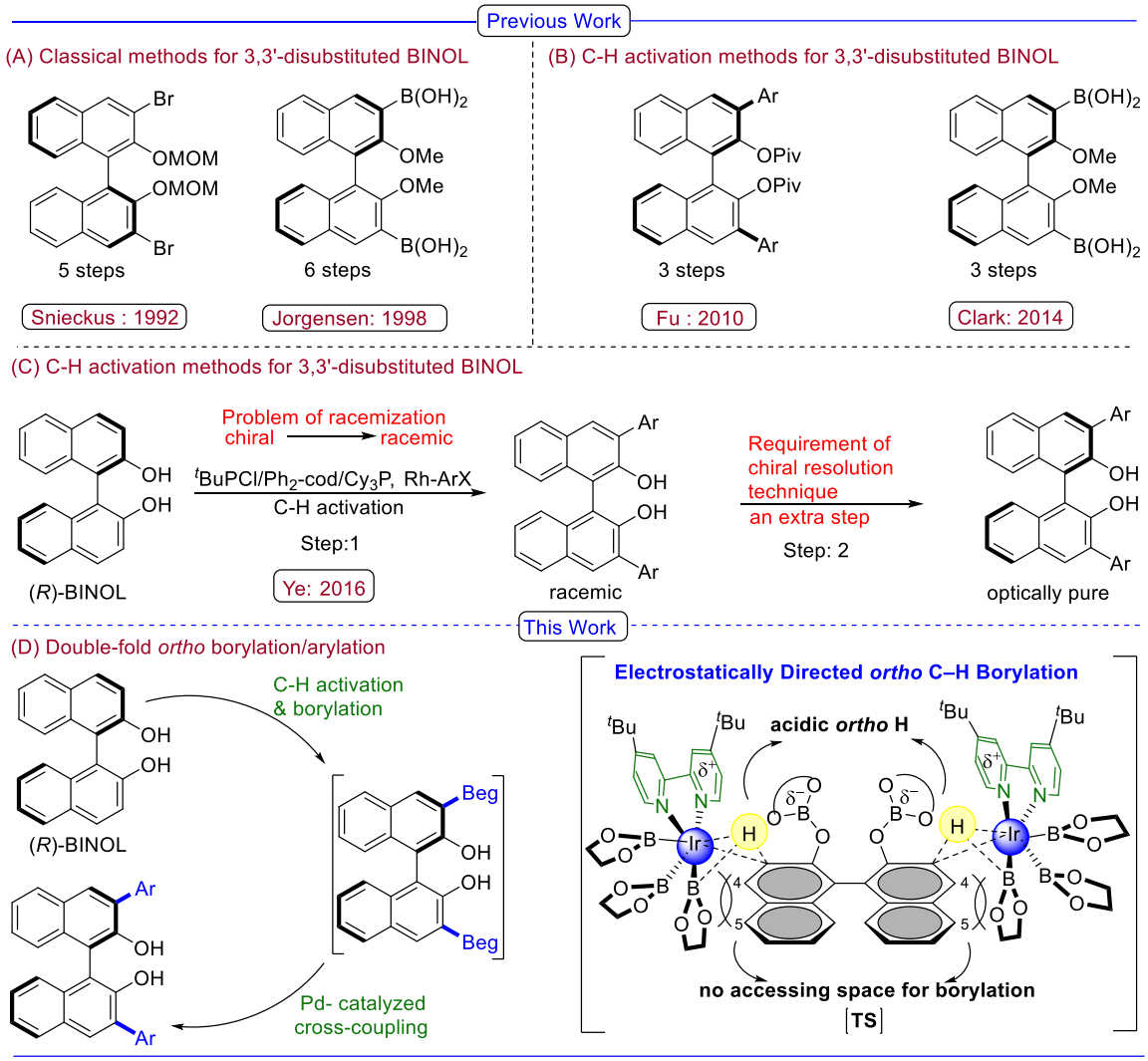
carbinyl radical. Finally, carbinyl radical eliminates hydrogen radical and then further oxidized in presence of O_2 to liberate H^+ species to produce the desired product. The major limitation of the coupling process is that it is not a catalytic process i.e., it required excess amount of metal salts. Some literature reports are present for catalytic coupling process, for example, the ultrasonic radiation of β-naphthol by the use of $FeCl_3.6H_2O$ (2 mol%),[4c,10,11] $FeCl_3/Al_2O_3$,[12] Cu-amine complex (1 mol%)[7c,13-15] and so on **(Scheme 2.2B)**.



Scheme 2.2: Synthesis of BINOL Skeleton

From last few decades, it has been well documented in the literature that 3,3'-diaryl BINOLs have established themselves as the most important framework for chiral ligands in asymmetric catalysis.[16,17] According to the literature report, 3,3'-diaryl BINOLs could be synthesized by four methods. First one is Snieckus's directed ortho metalation (DOM) protocol,[18] developed in 1992 **(Scheme 2.3 A)**. By this method, one can prepare differently 3,3'-disubstitued derivatives of BINOLs from easily accessible biphenol having carbamate and methoxymethyl directing groups. However, for the preparation of 3,3'-disubstituted aryl BINOL, Suzuki cross-coupling followed by deprotection of directing group is necessary. Second one is the Jorgensen method (1998)[19] to synthesize 3,3′-diaryl BINOL. The 3,3′-diaryl BINOL is prepared from 3,3'-diboronic acid and readily available aryl bromide by a Suzuki coupling reaction followed by demethylation **(Scheme 2.3 A)**. Although these two classical methods are the pioneering reports for the synthesis of 3,3'-diaryl BINOLs, there are many limitations which restrict their practical utility such as, the use of delicate R-Li reagent, requirement of more steps, and prolonged reaction time. The third method was developed by Fu group.[20] In 2010, they reported pivalate directed C-H activation and arylation of BINOL to prepare *ortho* 3,3'-diaryl BINOL using Pd-catalyst. Last method was reported by Clark group in 2014.[21] In this work, they reported a silyl

directed *ortho* carbon hydrogen bond borylation and subsequent Suzuki-Miyaura coupling sequences for the preparation of 3,3'-diaryl BINOLs.



Scheme 2.3: Previous and Current Work

However, necessity of extra steps for installation and exclusion of the DG as well as production of the stoichiometric amount of wastes limits the practical utility of these two carbon-hydrogen bond activation methods **(Scheme 2.3B)**. In this context, it is worth mentioning about Yu work in which authors developed[22] a one-step synthetic route to synthesize 3,3'-diaryl BINOLs using Rhodium catalyst in combination with newly designed ligands $^{t}Bu_2PCl$, Ph_2cod and $Cy_3P.HBF_4$ **(Scheme 2.3 C)**. While this method afforded a variety of 3,3'-diaryl BINOLs in desirable yields, the major drawback of this method was the racemization of final diarylated product under the established reaction conditions. As a result, additional chiral resolution step is required to get the optically pure

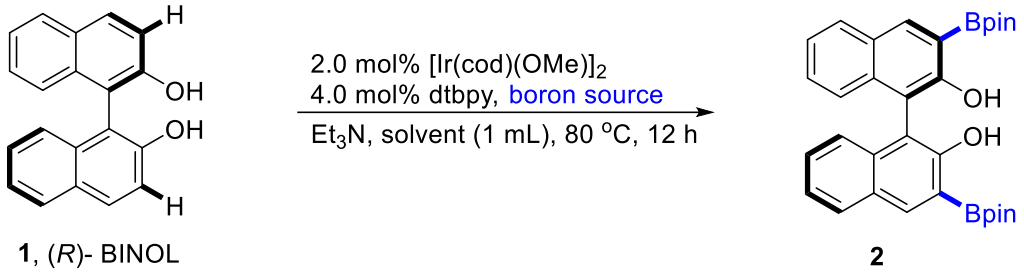
isomer. From the aforesaid reports, it is now clear that there is no general method for the synthesis of optically pure 3,3'-diaryl BINOLs.

Furthermore, carbon hydrogen bond activation and borylation has gained significant importance in organic synthesis due to their wide applicability in numerous synthetic transformations.[23,24] In carbon hydrogen bond borylation reaction of aromatic systems, one of the key challenges is the controlling site selectivity[25] among several identical type of carbon hydrogen bonds. The most common strategies for the *ortho* borylation of arenes are i) directed metalation[26] and ii) functional group directed[27] borylation. But all these methods are highly reliant on nature of the substituent present on the substrate. Keeping all these considerations in mind, we discovered an elegant Ir-catalyzed double-fold *ortho* C-H borylation and subsequent arylation method by means of chiral BINOL as a substrate in one pot **(Scheme 2.3D)**. In 2017, Smith *et al.* reported[28] an electrostatically directed *ortho* borylation of phenol substrates. The *ortho* selectivity is controlled by an unprecedented electrostatic interaction. This interaction operates between a OBeg group (having a partially negative charge on B atom) and partially positive charge ligand. Inspired by their study, we anticipated that in our cases also there is a strong possibility of electrostatic interaction between OBeg group (having a partially negative charge on B atom) and partially positive charge ligand. If so, this interaction will make two *ortho* hydrogens of BINOL more acidic and facilitate borylation selectively at ortho position **(Scheme 2.3D, TS)**, albeit there are many C-H bonds in BINOL in contrast to small phenol substate.

2.2 Results and Discussion

For this double-fold *ortho* borylation strategy, we took (*R*)- BINOL as a model substrate. At first, we applied previously reported[28] phenol's *ortho* borylation conditions, but solvent borylated product was observed **(Table 1; entry 1)**. To suppress the solvent borylation, we changed the solvent from toluene to cyclohexane and *para*-xylene; but in both solvents, we observed no product formation **(Table 1; entry 2 & 3)**. Delightfully, when we run the borylation reaction in THF solvent, we observed reasonable amount of desired diborylated product by analyzing crude NMR.

Table 1: ***Optimization of the Double-Fold Ortho Borylation***[a]



1, (*R*)- BINOL

2

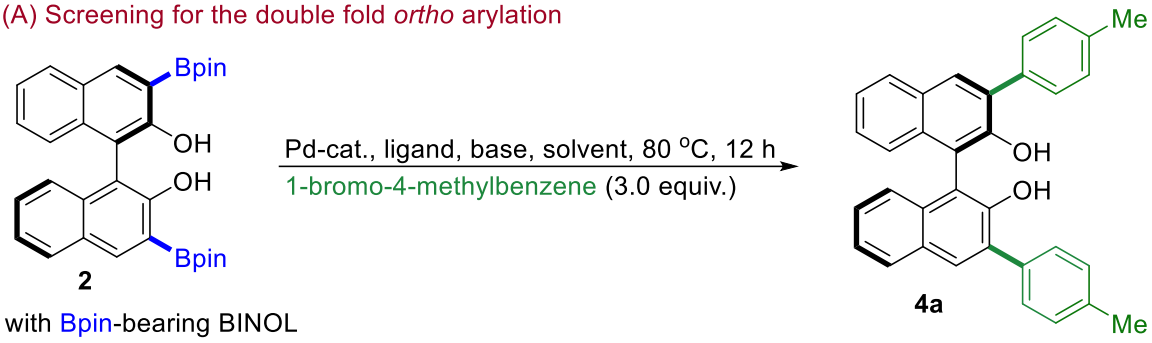
Entry	Boron source	Base	Solvent	Yield (%)
1.	B_2eg_2 (2.5 equiv.)	Et_3N (2.5 equiv.)	PhMe	Solvent borylation
2.	B_2eg_2 (2.5 equiv.)	Et_3N (2.5 equiv.)	CyH	Complex mixture
3.	B_2eg_2 (2.5 equiv.)	Et_3N (2.5 equiv.)	p-xylene	Solvent borylation
4.	B_2eg_2 (2.5 equiv.)	Et_3N (2.5 equiv.)	THF	53%[b]
5.	B_2eg_2 (4.0 equiv.)	Et_3N (4.0 equiv.)	THF	79%[b]
6.	HBpin (4.0 equiv.)	Et_3N (4.0 equiv.)	THF	Complex mixture
7.	B_2pin_2 (4.0 equiv.)	Et_3N (4.0 equiv.)	THF	Complex mixture

[a]Reactions were conducted with 0.1 mmol scale. [b]Isolated yield upon transesterification with pinacol.

However, we tried to isolate the Beg borylated product but we were unsuccessful due to the instability of corresponding borylated products. That is why after borylation reaction we transesterified the Beg group to stable Bpin group by employing the crude borylated mass with 2.5 equivalent of pinacol in dry chloroform. Finally, we obtained the borylated product in 53% yield **(Table 1; entry 4)**. Interestingly, when the amount of B_2eg_2 and Et_3N increased from 2.0 equivalent to 4.0 equivalent, the yield of the borylation reaction was increased to 79% after transesterification **(Table 1; entry 5)**. Notably, in this case, we observed some amount of mono borylated product. But, due to the proto-deborylation, we were failed to calculate the percenrage of mono and diborylated product. However, when HBpin and B_2pin_2 were used as a boron source for this reaction, we noticed non-selective borylation reaction **(Table 1; entry 6 and entry 7)**.

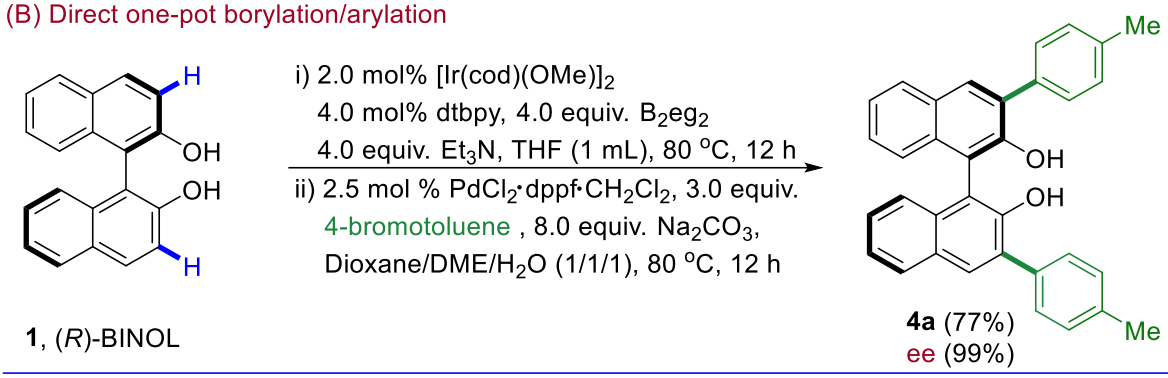
Table 2: ***Optimization of Double-Fold Ortho Arylation***

(A) Screening for the double fold *ortho* arylation



#	Catalyst (mol%)	Ligand	Base(eq.)	Solvent	Conv.[b]
1.	$Pd(PPh_3)_4$ (5)	-	K_2CO_3 (2)	PhMe/H_2O (6/1)	nr
2.	$Pd(PPh_3)_4$ (5)	-	K_2CO_3 (2)	DME/H_2O (1/1)	nr
3.	$Pd(PPh_3)_4$ (5)	-	CsF (3)	THF/H_2O (10/1)	nr
4.	Pd_2dba_3·$CHCl_3$ (2)	P(*o*-tolyl)$_3$ (4)	K_2CO_3 (2)	THF/H_2O (10/1)	85
5.	$PdCl_2$·dppf·DCM (2.5)	-	Na_2CO_3 (8)	Dioxane/DME/H_2O (1/1/1)	90 (79)[c]

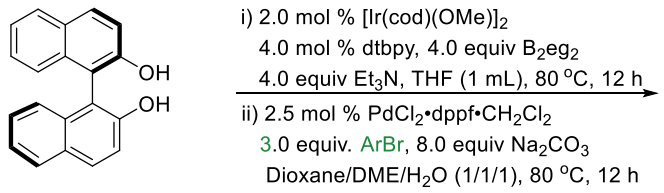
(B) Direct one-pot borylation/arylation



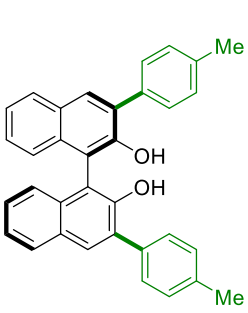
[a]Reactions were conducted with 0.1 mmol scale. [b]Conversions are based on crude NMR analysis [c]In parentheses, isolated yields are reported.

After successful optimization of this *o*, *o*'-diborylation reaction, we started investigation to find out a suitable reaction conditions for the o,o'-diarylation of BINOL. At first, *ortho,ortho'*-diborylated BINOL was subjected with 4-bromo toluene in presence of 5.0 mol% tetrakis(triphenylphosphine)palladium(0) and potassium carbonate base in the solvent toluene and water at 80 °C. However, no desired product (diaryl BINOL) formation was observed (**Table 2A**; **entry 1**).

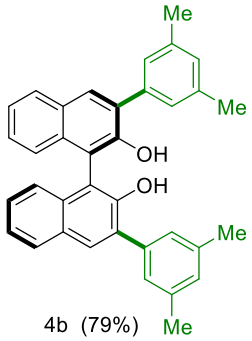
Table 3: ***Scope of Double-Fold Ortho Borylation/Arylation***[a]



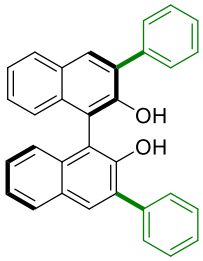
1: (*R*)-BINOL; **5**: H8-BINOL — **4, 6**



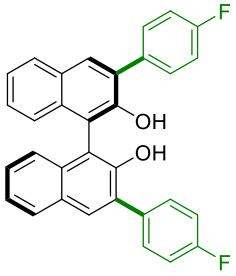
[a]4a (73%)
ee: (99%)
5.0 mmol scale



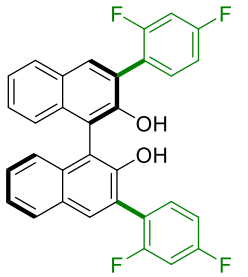
4b (79%)
ee: (91%)



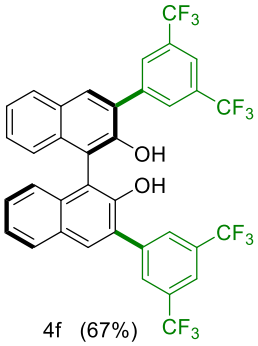
4c (70%)
ee: (99%)



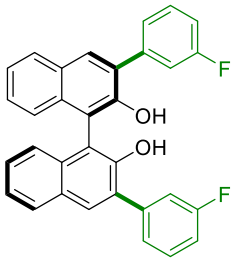
4d (65%)
ee: (93%)



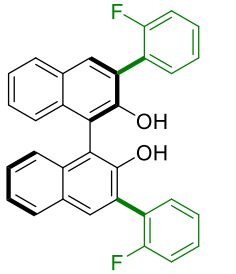
4e (69%)
ee: (99%)



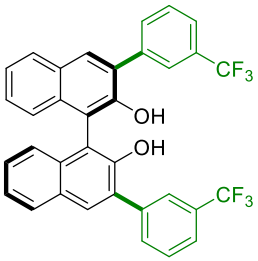
4f (67%)
ee: (93%)



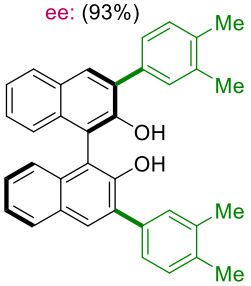
4g (68%)
ee: (98%)



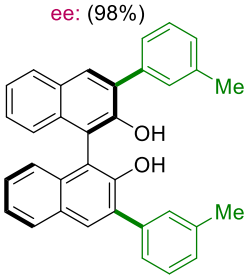
4h (62%)
ee: (94%)



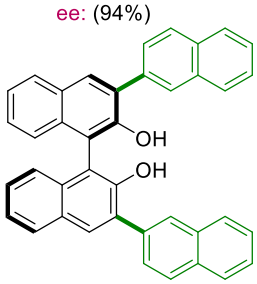
4i (61%)
ee: (94%)



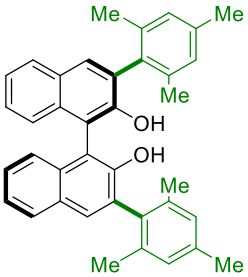
4j (69%)
ee: (98%)



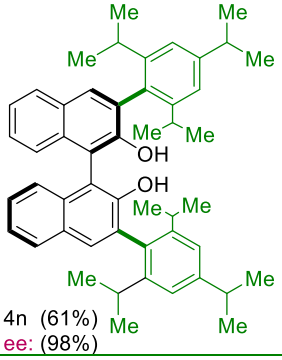
4k (66%)
ee: (98%)



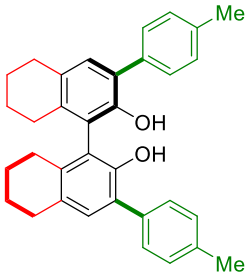
4l (65%)
ee: (>99%)



4m (68%)
ee: (94%)



4n (61%)
ee: (98%)



6 (81%)
ee: (98%)

[a] Scale of reaction 0.1 mmol; isolated yields. [b] Reaction scale 5.0 mmol.

Employment of the additional solvents and bases were also found to be ineffective for arylation reaction. Surprisingly, the use of 2.0 mol% Pd_2dba_3·$CHCl_3$ catalyst and 4.0 mol%

o-tolyl phosphine ligand afforded 85% conversion of the desired *o,o′*-diarylated product **(Table 2A; entry 4)**. Use of $PdCl_2$·dppf·DCM catalyst and sodium carbonate base in dioxane/DME/H_2O (1/1/1) solvent system gave 90% conversion of the desired arylated product **(Table 2A; entry 5)**. After the successful optimization, we combined the borylation and arylation protocol in one-pot method (depicted in **Table 2B**), which produced the expected diarylated BINOL in 77% yield and high enantiomeric excess (99%).

Next, we investigated the scope of this Ir-catalyzed double-fold borylation and successive arylation reaction (**Table 3**). For instance, electron donating and electronically neutral aryl bromides gave excellent outcome under this developed protocol (**entry 4b,4c, 4j & 4k**). Moreover, electronically poor aryl bromides are found to be suitable under this one-pot method producing high yield and enantioselectivity (**entry 4d-4i**). Interestingly, this one-pot borylation/arylation strategy is also fully compatible with sterically hindered aryl coupling partners, which afforded good yield and enantiomeric excess (**entry 4l- 4n**). Delightfully, applying our developed double-fold borylation/arylation strategy, we were able to synthesize the chiral 3,3′-H_8-BINOLs[29,30] with high yield and enantioselectivity **(entry 6)**, albeit its preparative method was not simple and also needed multistep sequences.

To highlight the synthetic efficacy of these double-fold borylation/arylation strategy, a gram scale (5.0 mmol scale) reaction was performed using 4-bromotoluene as coupling partner, which produced corresponding 3,3′-diaryl BINOL. The yield of this reaction was 73% and enantiomeric excess was 99% **(entry 4a)**.

2.3 Conclusion

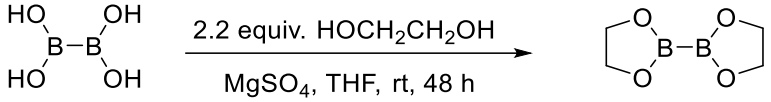
In closing, a double-fold *ortho, ortho′*-diborylation/arylation strategy of BINOLs have been developed. The observed *ortho* selectivity is fully controlled by an electrostatic interaction. This established borylation protocol was fruitfully united with Suzuki cross-coupling reaction as one-opt method. A variety of 3,3'-diaryl BINOLs with high yield and enantioselectivity were synthesized using this one pot protocol. A gram scale synthesis of valuable chiral 3,3′-biaryl BINOL compound from cheap starting material (*R*)-BINOL makes our method more synthetically useful.

2.4 Experimental Section

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBpin), bis(pinacolato)diboron (B_2pin_2), tetrahydroxydiboron were procured from Sigma-Aldrich. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(cod)(OMe)]_2$ was procured from Sigma-Aldrich. Tetrahydrofuran (THF) were refluxed over sodium/benzophenone ketyl, distilled and degassed twice before borylation. Column chromatography was performed on flash silica gel (ACME, India). Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm).

^{1}H-NMR and ^{13}C-NMR and ^{11}B-NMR spectra were recorded on Bruker 400 MHz NMR spectrometer. All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet). High-resolution mass spectra (HRMS) were obtained at the Centre of Biomedical Research Mass Spectrometry Service Center using a Waters GCT Premier instrument run on electron ionization (EI) direct probe or a Waters QTOF Ultima instrument run on electrospray ionization (ESI+). HPLC were performed on Agilent Technologies 1260 infinity.

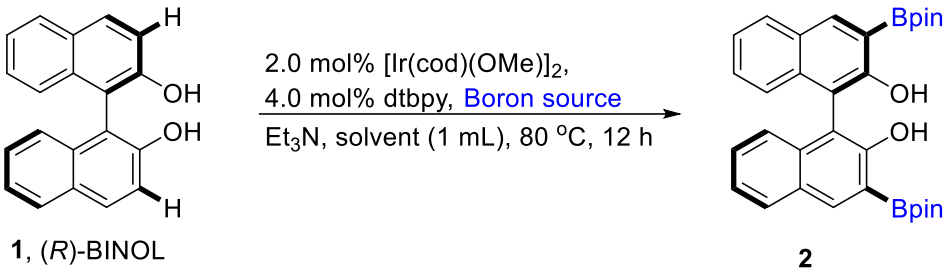
2.4.1 Preparation of B_2eg_2



33.3 mmol — Yield: 74%

To a 250 mL oven dried round bottom flask, tetrahydroxydiboron (3.0 g, 33.32 mmol), anhydrous $MgSO_4$ (2.0 g) and THF (100 mL) was added. Ethyleneglycol (3.98 mL, 2.2 equiv.) was then added. The resulting mixture was stirred at rt for 48 h under N_2 atmosphere. After 48 h, $MgSO_4$ was filtered using sintered and solvent was evaporated. The crude white material was then sublimed to get 3.50 g B_2eg_2 (74%) as white crystalline solid. Spectral data are in accordance with the reported data.[28]

2.4.2 Isolation of Bis-borylated Compound 2



1, (*R*)-BINOL

2

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with *(R)*-BINOL (28.6 mg, 0.1 mmol), dry THF (1.0 mL), $[Ir(cod)(OMe)]_2$ (1.3 mg, 2.0 mol%), dtbpy (1.1 mg, 4.0 mol%), B_2eg_2 (56.8 mg, 4.0 equiv.) and Et_3N (55.8 µL, 4 equiv.). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h, solvent was evaporated and transesterification was done with pinacol (47.3 mg, 4.0 equiv.) using dry $CHCl_3$ (2.0 mL) and stirred for 1 h. Solvent was evaporated and chromatographic separation with silica gel (*n*-hexane/dichloromethane/MeOH= 5/1/1) gave 42.5 mg of (*R*)-(+)-3,3'-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-binaphthalene]-2,2'-diol (**2)** in 79% yield.

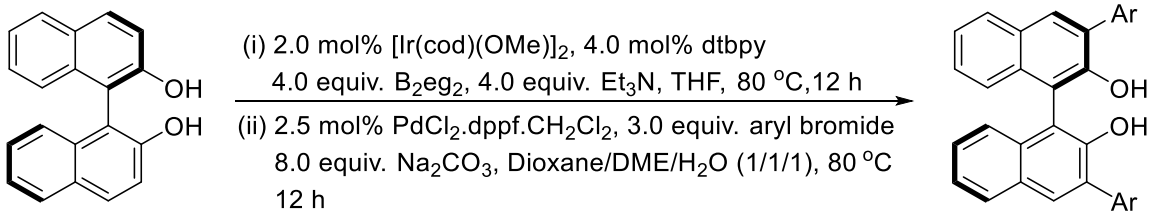
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 2H), 7.93 (s, 2H), 7.88–7.86 (m, 2H), 7.29–7.26 (m, 4H), 7.19–7.16 (m, 2H), 1.39 (s, 24H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 138.2, 136.6, 128.9, 128.3, 127.9, 124.8, 123.0, 115.4, 84.7, 24.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2

HRMS (ESI) *m/*z calcd for $C_{32}H_{36}B_2O_6$ $[M+H]^+$ 539.2776, found 539.2778.

2.4.3 *General Procedure for One-Pot Borylation and Suzuki Cross-Coupling Synthesis of ortho, ortho' di-[1,1'-binaphthalene]-2,2'-diol:*



1, *(R)*-BINOL
(0.1 mmol)

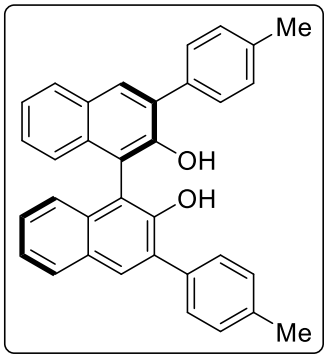
In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with *(R)*-BINOL (28.6 mg, 0.1 mmol), dry THF (1.0 mL), $[Ir(cod)(OMe)]_2$ (1.3 mg, 2.0 mol%), dtbpy (1.1 mg, 4.0 mol%), B_2eg_2 (56.8 mg, 4.0 equiv.) and Et_3N (55.7 µL, 4.0 equiv.). The

microreactor was capped with a teflon pressure cap and placed into a pre-heated aluminum block at 80 ^{o}C. After 12 h, solvent was evaporated and next step was carried out without purification. The crude mixture was then charged with $PdCl_2$•dppf•CH_2Cl_2 (2.0 mg, 2.5 mol%), Na_2CO_3 (84.8 mg, 8.0 equiv.), aryl bromide (3.0 equiv.), Dioxane/DME (1/1, 1.0 mL). Degassed water (0.5 mL) was added outside the glove box. Then the microreactor was capped with a teflon pressure cap and placed into a pre-heated aluminum block at 80 ^{o}C. After 12 h, reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent was evaporated and chromatographic separation with silica gel (ethyl acetate in hexane as eluent) gave corresponding *ortho, ortho' di*-[1,1'-binaphthalene]-2,2'-*diol.*

2.4.4 *Substrate Scope for Double-Fold Ortho Borylation/Arylation*

Synthesis of (R)-(+)-3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(3,5-dimethylphenyl)-[-1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-4-methylbenzene used as a coupling partner.



Reaction time: 24 h; 77% isolated yield, (eluent: 8% ethyl acetate in hexane).

Properties: White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.91 (d, *J* = 8 Hz, 2H), 7.63 (d, *J* = 8 Hz, 4H), 7.40–7.36 (m, 2H), 7.33–7.29 (m, 6H), 7.23–7.21 (m, 2H), 5.36 (s, 2H), 2.43 (s, 6H).

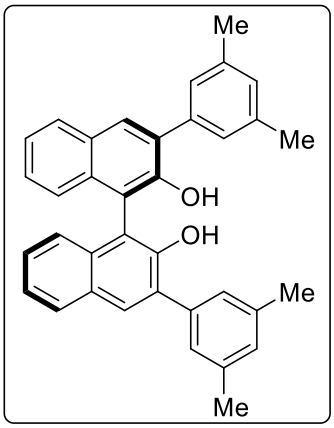
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 137.6, 134.5, 132.8, 131.1, 130.6, 129.4, 129.2, 128.3, 127.1, 124.3, 124.2, 112.4, 21.2.

HRMS (ESI) *m/z* calcd for $C_{34}H_{26}O_2$ $[M+H]^+$ 467.2011, found 467.2012.

HPLC Conditions: Detector wavelength- 254 nm, Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 17.21 min. t_R (minor) = 26.56 min., %ee = 99%.

Synthesis of (R)-(+)-3,3'-bis(3,5-dimethylphenyl)-[-1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(3,5-dimethylphenyl)-[-1,1'-binaphthalene]-2,2'-diol was prepared following the general formula **2.4.3**. Here 1-bromo-3,5-dimethylbenzene used as a coupling partner.



Spectral data are in accordance with the reported data.[21]

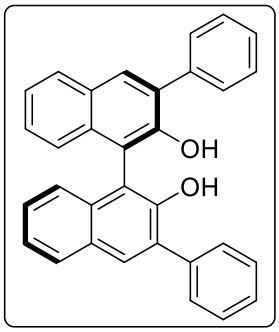
Reaction time: 24 h; 79% isolated yield, (eluent: 5% ethyl acetate in hexane).

Properties: White solid

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 16.80 min., t_R (minor) = 8.13 min., %ee = 91%.

Synthesis of (R)-(+)-3,3'-diphenyl-[-1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-diphenyl-[-1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here bromobenzene used as a coupling partner.



Reaction time: 24 h; 70% isolated yield, (eluent: 5% ethyl acetate in hexane)

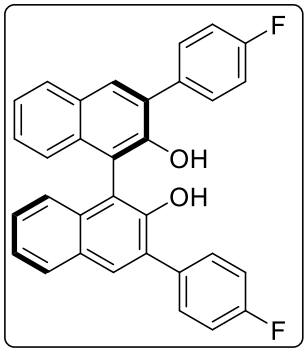
Properties: White solid

Spectral data are in accordance with the reported data.[21]

HPLC Conditions: Chiralcel® OD-H Column, 3% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 36.69 min., t_R (minor) = 52.42 min., %ee = 99%.

Synthesis of (R)-(+)-3,3'-bis(4-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol:

(R)-(+)-3,3'-bis(4-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-4-fluorobenzene used as a coupling partner.



Reaction time: 24 h; 65% isolated yield, (eluent: 8% ethyl acetate in hexane)

Properties: White solid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.93 (d, *J* = 8 Hz, 2H), 7.74–7.70 (m, 4H), 7 .42–7.40 (m, 2H), 7.36–7.32 (m, 2H), 7.23–7.16 (m, 6H), 5.33 (s, 2H).

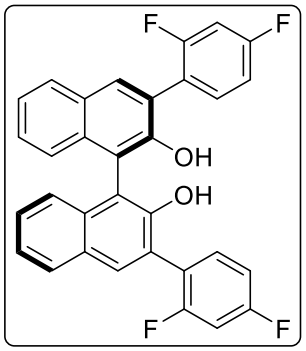
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (d, J_{C-F} = 245.6 Hz), 150.1, 133.4 (d, J_{C-F} = 3.3 Hz), 132.8, 131.4, 131.3, 131.2, 129.5 (d, J_{C-F} = 23.7 Hz), 128.4, 127.5, 124.5, 124.1, 115.3 (d, J_{C-F} = 21.3 Hz), 112.0.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 497.1329, found 497.1329.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 18.77 min., t_R (minor) = 37.63 min., %ee = 93%.

Synthesis of (R)-(+)-3,3'-bis(2,4-difluorophenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(2,4-difluorophenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here, 1-bromo-2,4-difluorobenzene used as a coupling partner.



Reaction time: 24 h; 69% isolated yield, (eluent: 7% ethyl acetate in hexane).

Properties: White solid.

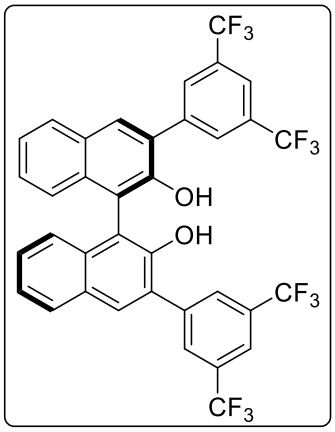
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.55 (m, 2H), 7.39 (m, 4H), 7.25 (m, 2H), 6.98 (m, 4H), 5.27 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (d, *J* = 11.7 Hz), 161.8 (dd, *J* = 11.9 Hz, *J* = 2.8 Hz), 159.3 (d, *J* = 11.9 Hz), 150.7, 133.4, 132.9 (m), 129.4, 128.8, 128.1, 124.8, 124.6, 124.4, 121.6 (dd, *J* = 15.9 Hz, *J* = 3.9Hz), 111.8, 111.5 (dd, *J* = 21.1 Hz, J = 3.7 Hz), 104.4 (d, *J* = 25.7 Hz).

HRMS (ESI) *m/z* calcd for $C_{32}H_{18}F_4O_2$ $[M+H]^+$ 511.1321 found 511.1326.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 0.5 mL/min: t_R (major) = 25.86 min., t_R(minor) = 29.54 min. %ee = 99%.

Synthesis of (R)-(+)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-3,5-bis(trifluoromethyl)benzene used as a coupling partner.



Properties: White solid

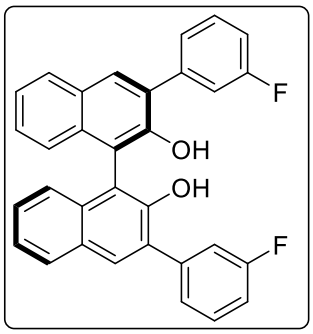
Reaction time: 24 h; 88% isolated yield, (eluent: 3% ethyl acetate in hexane).

Spectral data are in accordance with the reported data.[21]

HPLC Conditions: Chiralcel® OJ-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 16.47 min., t_R (minor) = 10.95 min., %ee = 93%.

Synthesis of (R)-(+) -3,3'-bis(3-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+) -3,3'-bis(3-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general formula **2.3.4**. Here 1-bromo-3-fluorobenzene used as a coupling partner.



Reaction time: 24 h; 68% isolated yield, (eluent: 8% ethyl acetate in hexane).

Properties: White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.39-7.33 (m, 4H), 7.32-7.24 (m, 4H), 7.21-7.17 (m, 2H), 7.09-7.06 (m, 2H), 6.97-6.92 (m, 2H), 5.19 (s, 2H).

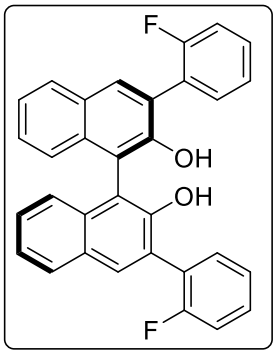
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, J_{C-F} = 244 Hz), 150.0, 139.6 (d, J_{C-F} = 8 Hz), 132.9, 131.6, 129.8 (d, J_{C-F} = 8.3 Hz), 129.4, 129.3, 128.5, 127.7, 125.2 (d, J_{C-F} = 2.8 Hz), 124.6, 124.0, 116.7 (d, J_{C-F} = 22 Hz), 114.5(d, J_{C-F} = 20.9), 112.1.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 475.1510, found 475.1502

HPLC Conditions: Chiralcel® OJ-H Column, 60% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) =18.01min., t_R (minor) = 31.72, %ee = 98%.

Synthesis of (R)-(+)-3,3'-bis(2-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(2-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-2-fluorobenzene used as a coupling partner.



Reaction time: 24 h; 94% isolated yield, (eluent: 8% ethyl acetate in hexane).

Properties: White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.45 (dt, *J* = 1.6 Hz, J = 7.2 Hz, 2H), 7.30-7.21 (m, 6H), 7.16-7.04 (m, 6H), 5.15 (s, 2H).

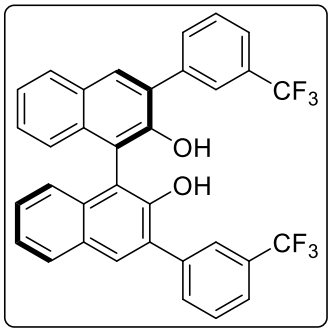
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (d, J_{C-F} = 246.4 Hz), 150.4, 133.1, 132.5(d, J_{C-F} = 1.1 Hz), 131.9 (d, J_{C-F} = 3.3 Hz), 129.7 (d, *J* = 8.1 Hz), 129.1, 128.5, 127.7, 125.3, 125.2, 125.1, 124.3 (d, *J* =13.7 Hz), 124.0 (d, *J* = 3.6 Hz), 115.7 (d, *J* = 22.1 Hz), 111.6.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 497.1329, found 497.1328.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 21.69 min., t_R (minor) = 14.39 min., %ee = 94%.

Synthesis of (R)-(+)-3,3'-bis(3-(trifluoromethyl) phenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(3-(trifluoromethyl) phenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-3-(trifluoromethyl)benzene used as a coupling partner.



Reaction time: 24 h; 61% isolated yield, (eluent: 8% ethyl acetate in hexane)

Properties: White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.92 (s, 2H), 7.84-7.81 (m, 4H), 7.55-7.45 (m, 4H), 7.33-7.22 (m, 4H), 7.12-7.10 (m, 2H), 5.23 (s, 2H).

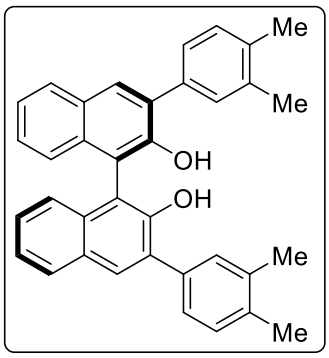
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 138.2, 133.0, 132.0, 130.7 (q, J_{C-F} = 32 Hz), 129.4, 129.2, 128.7, 128.6, 127.9, 126.8 (q, J_{C-F} = 3.8 Hz), 124.7, 124.3 (q, J_{C-F} = 38 Hz), 124.1 (q, J_{C-F} = 270.8 Hz), 124.0, 111.8.

HRMS (ESI) *m/z* calcd for $C_{34}H_{20}F_6O_2$ $[M+H]^+$ 575.1446, found 575.1433.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 11.15 min., t_R (minor) = 7.19 min., %ee = 94%.

Synthesis of (R)-(+)-3,3'-bis(3,4-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-bis(3,4-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here, 1-bromo-3,4-dimethylbenzene used as a coupling partner.



Reaction time: 24 h; 69% isolated yield, (eluent: 5% ethyl acetate in hexane).

Properties: White solid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.53-7.48 (m, 4H), 7.41-7.37 (m, 2H), 7.33-7.24 (m, 6H), 5.41 (s, 2H), 2.36-2.35 (12H, 2 singlets of CH_3 are overlapped).

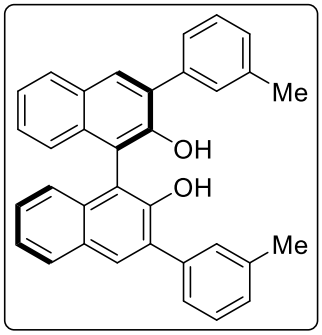
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 136.8, 136.3, 134.9, 132.8, 131.0, 130.7, 130.0, 129.4, 128.3, 127.0, 126.9, 124.3, 124.1, 112.5, 19.9, 19.6.

HRMS (ESI) *m/z* calcd for $C_{36}H_{30}O_2$ $[M+H]^+$ 495.2324, found 495.2290.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 16.79 min., t_R (minor) = 14.97 min. %ee = 98%

Synthesis of (R)-(+)- 3,3'-di-m-tolyl-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)- 3,3'-di-m-tolyl-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-3-methylbenzene used as a coupling partner.



Reaction time: 24 h; 66% isolated yield, (eluent: 5% ethyl acetate in hexane).

Properties: White solid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (m, 4H), 7.41 (t, *J* = 7.6 Hz, 4H), 7.33 (t, *J* = 8.0 Hz, 2H,), 7.26-7.24 (m, 4H), 5.41 (s, 2H), 2.46 (s, 6H).

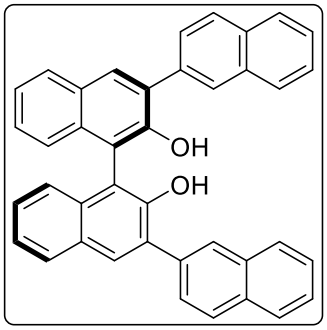
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 138.2, 137.3, 132.9, 131.2, 130.7, 130.2, 129.4, 128.5, 128.4, 128.3, 127.2, 126.6, 124.3, 124.2, 112.5, 21.5.

HRMS (ESI) *m/z* calcd for $C_{34}H_{26}O_2$ $[M+H]^+$ 467.2011, found 467.2011.

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 22.23 min., t_R (minor) = 19.86 %ee = 98%.

Synthesis of (R)-(+)-[3,3'-bis(2-naphthyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-[3,3'-bis(2-naphthyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 2-bromonaphthalene used as a coupling partner.



Reaction time: 24 h; 65% isolated yield, (eluent: 5% ethyl acetate in hexane).

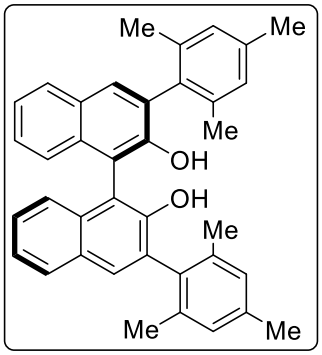
Properties: White solid

Spectral data are in accordance with the reported data.[21]

HPLC Conditions: Chiralcel® OD-H Column, 45% ^{i}PrOH/ hexanes, 1.0 mL/min: t_R (major) = 16.29 min., t_R (minor) = 53.53 min., %ee >99%.

Synthesis of (R)-(+)-3,3'-dimesityl-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-dimesityl-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 2-bromomesitylene used as a coupling partner.



Reaction time: 24 h; 68% isolated yield, (eluent: 5% ethyl acetate in hexane).

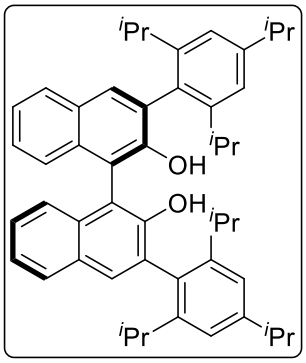
Properties: White solid

Spectral data are in accordance with the reported data.[21]

HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 5.54 min., t_R (minor) = 4.82 min., %ee = 94%.

Synthesis of (R)-(+)-3,3'-Di-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol:

(*R*)-(+)-3,3'-Di-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol was prepared following the general procedure **2.4.3**. Here 1-bromo-2,4,6-triisopropylbenzene used as a coupling partner.



Reaction time: 24 h; 61% isolated yield, (eluent: 5% ethyl acetate in hexane).

Properties: white solid

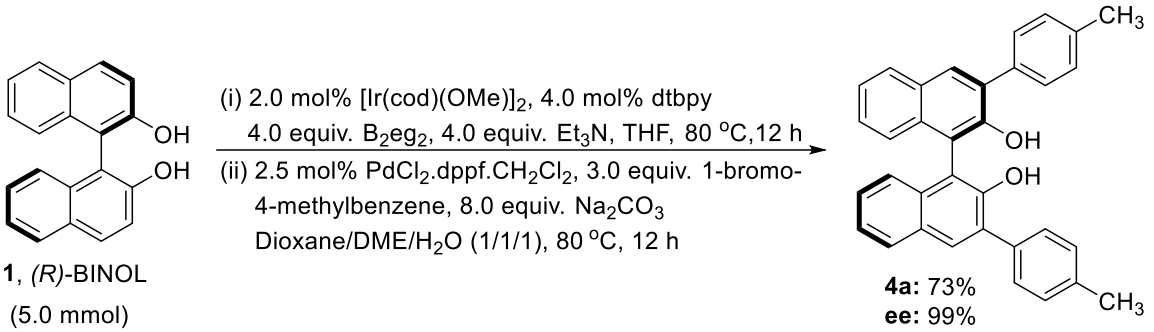
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 11.2 Hz, 2H), 7.76 (s, 2H), 7.35 (m, 6H), 7.13 (m, 4H), 4.91 (s, 2H), 2.96 (m, 2H), 2.86 (m, 2H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.10 (dd, *J* = 7.2 Hz, *J* = 9.6 Hz, 12H), 1.03 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 149.1, 147.8, 147.7, 133.4, 130.6, 130.4, 129.1, 129.0, 128.2, 127.1, 126.6, 124.5, 123.8, 121.2, 113.0, 115.0, 34.3, 30.9, 30.8, 24.3, 24.1, 24.0, 23.9, 23.7.

HRMS (ESI) *m/z* calcd for $C_{50}H_{58}O_2$ $[M+NH_4]^+$ 708.4819, found 708.4781.

HPLC Conditions: Chiralcel® OD-H Column, 0.1% ^{i}PrOH/hexanes, 0.5 mL/min: t_R (major) = 7.08 min., t_R (minor) = 6.67 min., %ee = 98%.

2.4.5 ***Gram scale synthesis of (R)-(+)-3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol***



1, *(R)*-BINOL
(5.0 mmol)

4a: 73%
ee: 99%

In an argon filled glove box, a 15.0 mL pressure tube was charged with *(R)*-BINOL (1.43 gm, 5.0 mmol), dry THF (8.0 mL), $[Ir(cod)(OMe)]_2$ (66.2 mg, 2.0 mol%), dtbpy (53.6 mg, 4.0 mol%), B_2eg_2 (2.8 gm, 4.0 equiv.) and Et_3N (2.7 mL, 4.0 equiv.). The pressure tube was capped with a teflon pressure cap and placed into a pre-heated oil bath at 80 °C. After 12 h, solvent was evaporated and next step was carried out without purification. The crude mixture was then charged with $PdCl_2$•dppf•CH_2Cl_2 (102.0 mg, 2.5 mol%), Na_2CO_3 (4.2 g, 8.0 equiv.), 1-bromo-4-methylbenzene (2.5 g, 3.0 equiv.), dioxane/DME (1/1, 6.0 mL). Degassed water (3.0 mL) was added outside the glove box. Then the pressure tube was capped with a teflon pressure cap and placed into pre-heated oil bath at 80 °C. After 12 h, reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent was evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 1.7 gm of *(R)*-(+)-3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol (**4a)** in 73% yield.

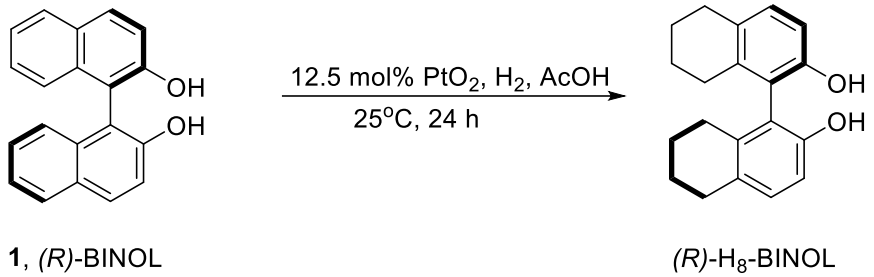
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.91 (d, *J* = 8 Hz, 2H), 7.63 (d, *J* = 8 Hz, 4H), 7.40–7.36 (m, 2H), 7.33–7.29 (m, 6H), 7.23–7.21 (m, 2H), 5.36 (s, 2H), 2.43 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 137.6, 134.5, 132.8, 131.1, 130.6, 129.4, 129.2, 128.3, 127.1, 124.3, 124.2, 112.4, 21.2.

HRMS (ESI) *m/z* calcd for $C_{34}H_{26}O_2$ $[M+H]^+$ 467.2011, found 467.2012.

HPLC Conditions: Detector wavelength- 254 nm, Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 17.21 min. t_R (minor) = 26.56 min., %ee = 99%.

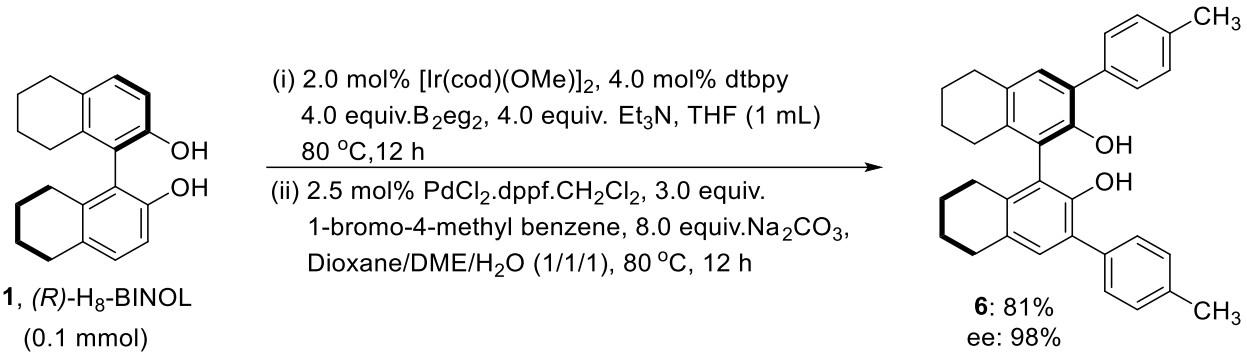
2.4.6 *Synthesis of (R)-H_8-BINOL*



1, *(R)*-BINOL *(R)*-H_8-BINOL

To a two neck round bottom flask containing *(R)*-BINOL (1.25 g, 4.37 mmol) and PtO_2 (0.125 g, 0.55 mmol), acetic acid (35 mL) was added. The flask was evacuated and backfilled with H_2 three times. The suspension was stirred with a balloon of H_2 gas for 24 h at 25 °C. After completion of reaction, the reaction mixture was filtered through a pad of celite using ethyl acetate. Evaporation of solvent yielded pure *(R)*-H_8-BINOL as a white solid (1.27 g, 98%). Spectral data are in accordance with the reported data.[31]

2.4.7 *Synthesis of 3,3'-di-p-tolyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol*



1, *(R)*-H_8-BINOL (0.1 mmol)

6: 81%
ee: 98%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with *(R)*-H_8-BINOL (29.6 mg, 1 mmol), dry THF (1.0 mL), $[Ir(cod)(OMe)]_2$ (1.3 mg, 2.0 mol%), dtbpy (1.1 mg, 4.0 mol%), B_2eg_2 (56.8 mg, 4.0 equiv.) and Et_3N (55.8 μL, 4.0 equiv.). The microreactor was capped with a teflon pressure cap and placed into a pre-heated aluminum block at 80 °C. After 12 h, solvent was evaporated and dry dioxane/DME (1.0 mL) was added. In a glove box, this microreactor was then charged with $PdCl_2$•dppf•CH_2Cl_2 (2.0 mg, 2.5 mol%), Na_2CO_3 (84.8 mg, 8.0 equiv.) and 1-bromo-4-methylbenzene (51.3 mg, 3.0 equiv.). Degassed water (0.5 mL) was added outside the glove box. Then the microreactor was capped with a teflon pressure cap and placed into a pre-heated aluminum

block at 80 ^{o}C. After 12 h, reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 38.6 mg of *(R)*-(+)-3,3'-di-p-tolyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol **(**81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.0 Hz, 4H,), 7.24 (d, *J* = 8.0 Hz, 4H), 7.13 (s, 2H), 4.90 (s, 2H), 2.81-2.78 (m, 4H), 1.77-1.71 (m, 8H), 0.90-0.83 (m, 4H).

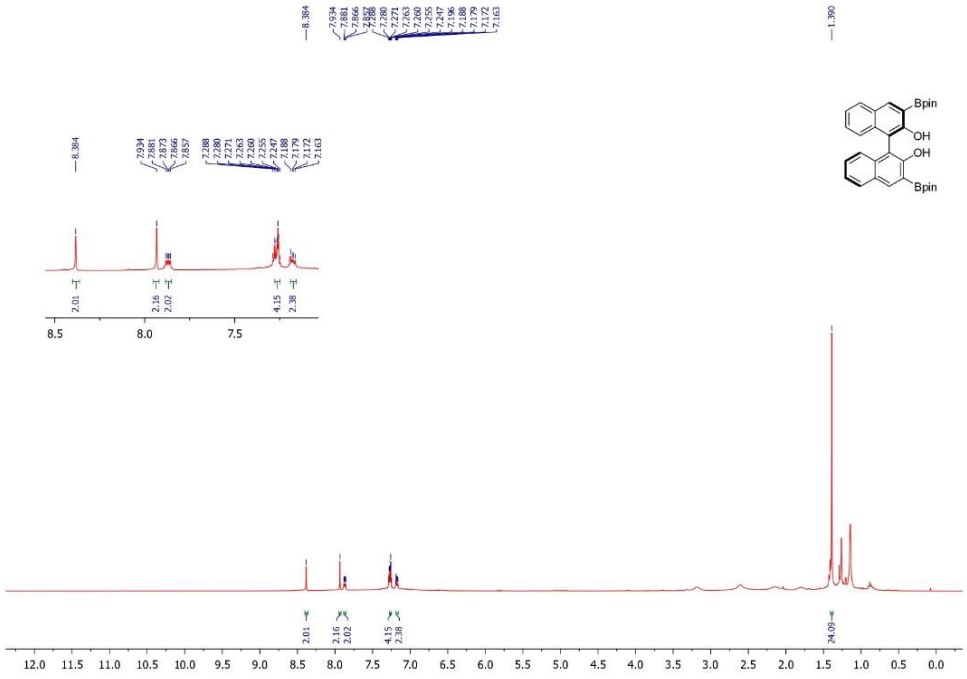
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 136.8, 136.3, 134.9, 131.5, 130.1, 129.1, 126.0, 120.2, 29.3, 27.1, 23.08, 23.06, 21.2

HRMS (ESI) *m/z* calcd for $C_{34}H_{34}O_2$ $[M+NH_4]^+$ 492.2903, found 492.2888.

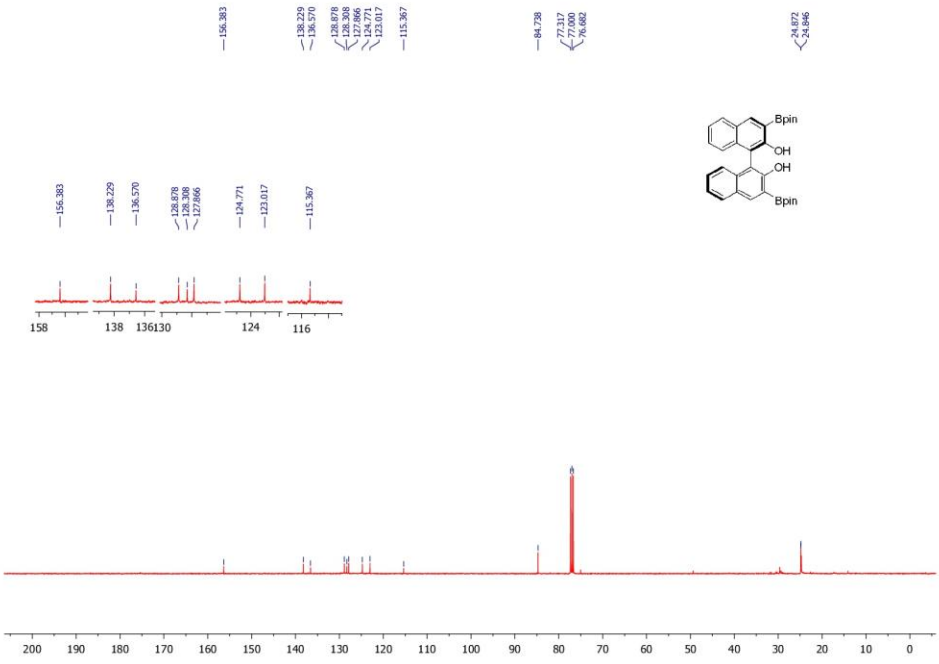
HPLC Conditions: Chiralcel® OD-H Column, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 10.53 min., t_R (minor) = 14.36 min., %ee = 98%.

2.4.8 Spectral Copies

^{1}H and ^{13}C-NMR Spectra of Bis-borylated Compound 2:

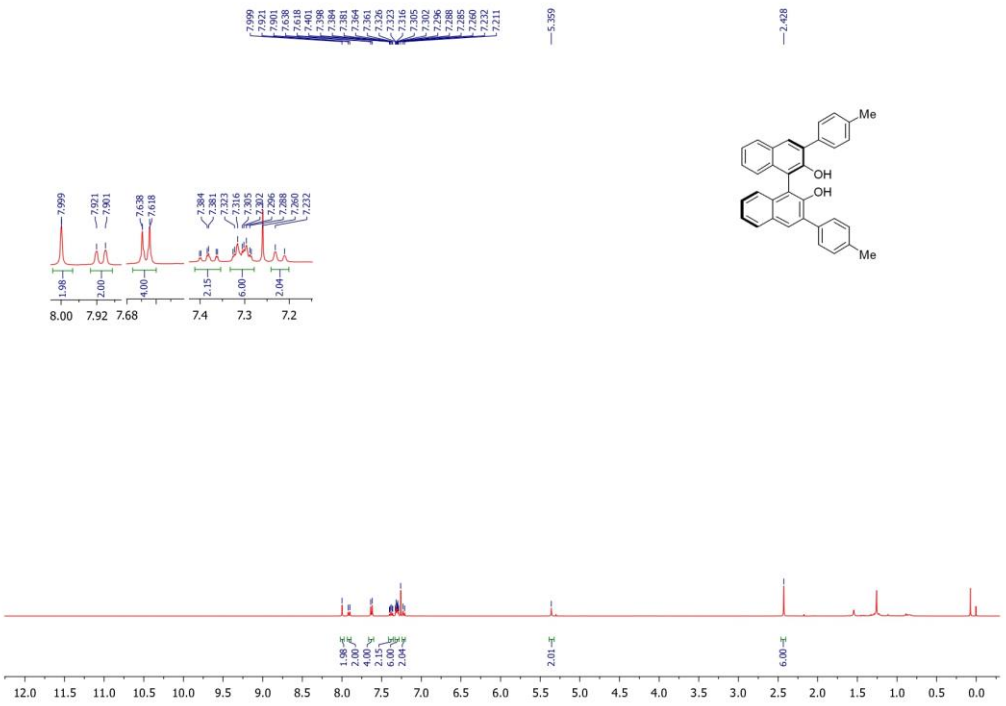


^{1}H-NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

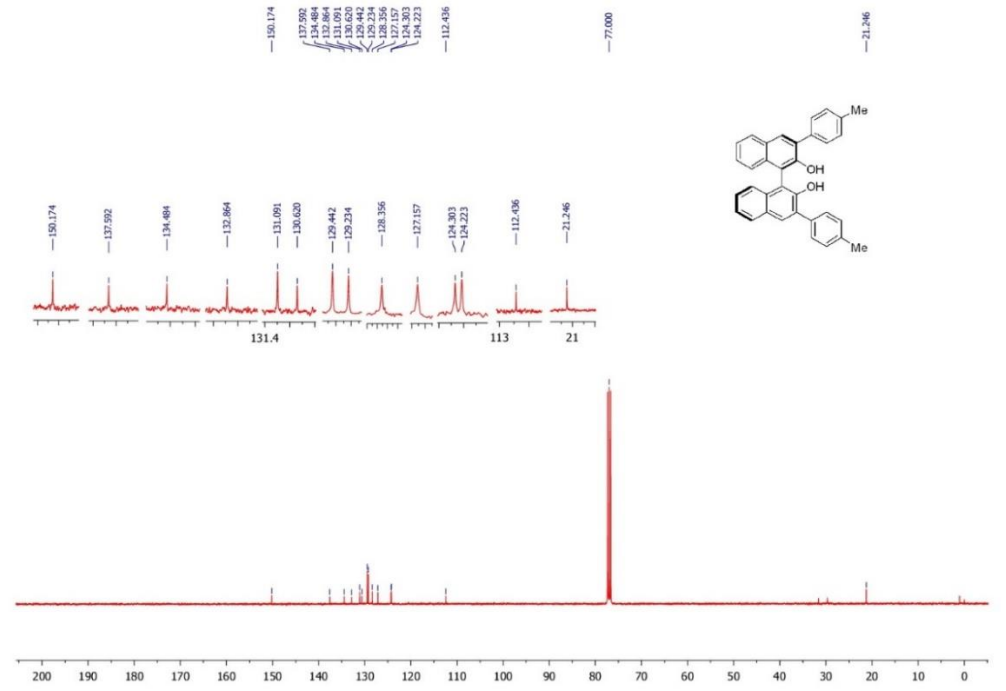


^{13}C-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

***^{1}H and ^{13}C-NMR Spectra of (R)-(+)-3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol*:**

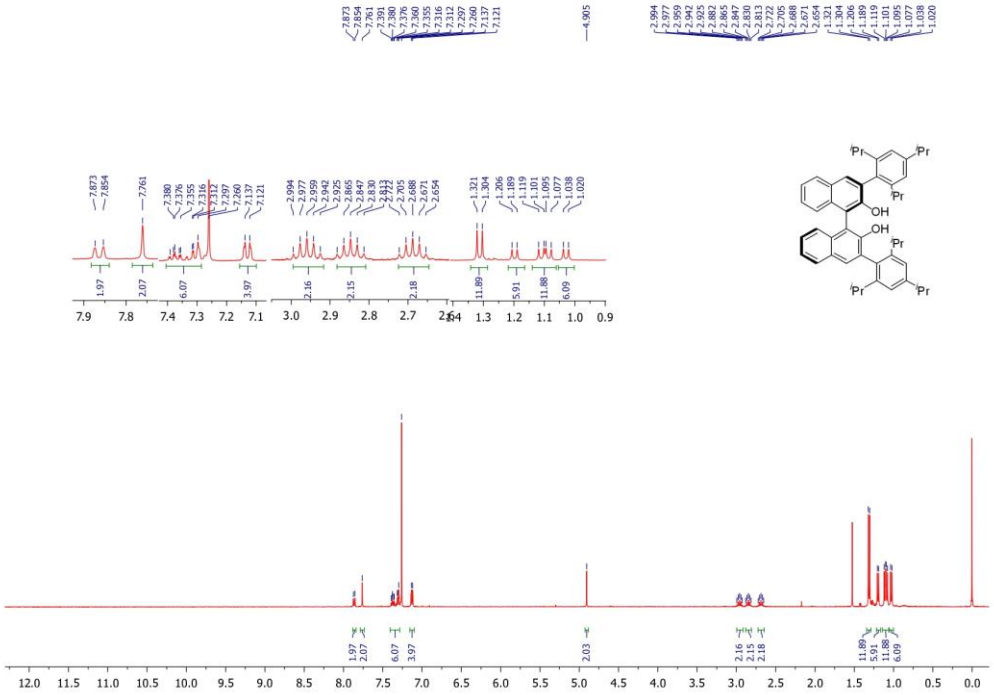


^{1}H-NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

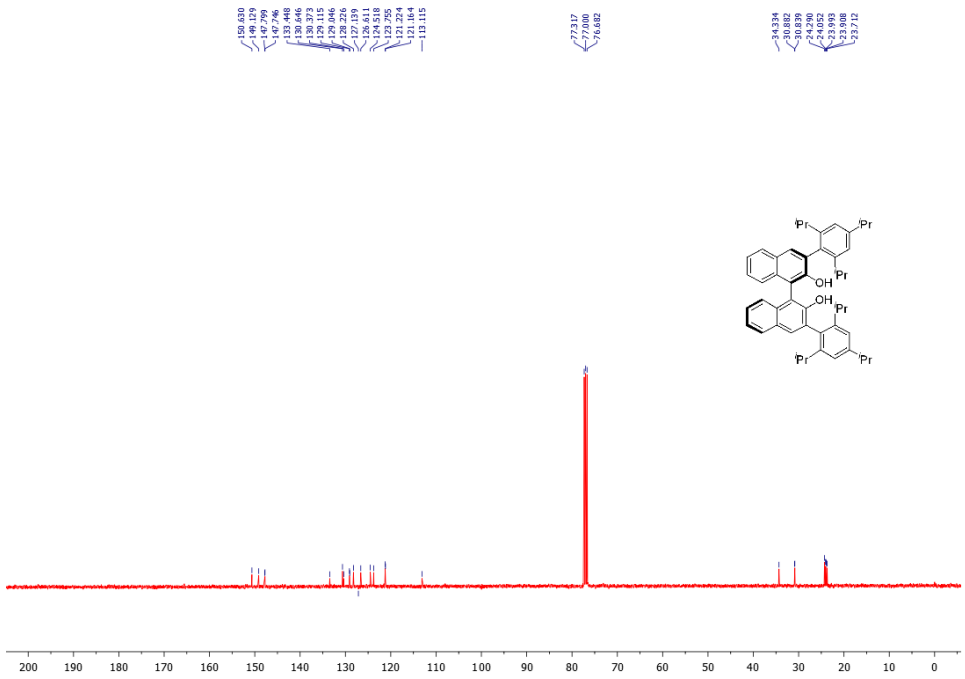


^{13}C-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

^{1}H and ^{13}C-NMR Spectra of (R)-(+)-3,3'-Di-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol:

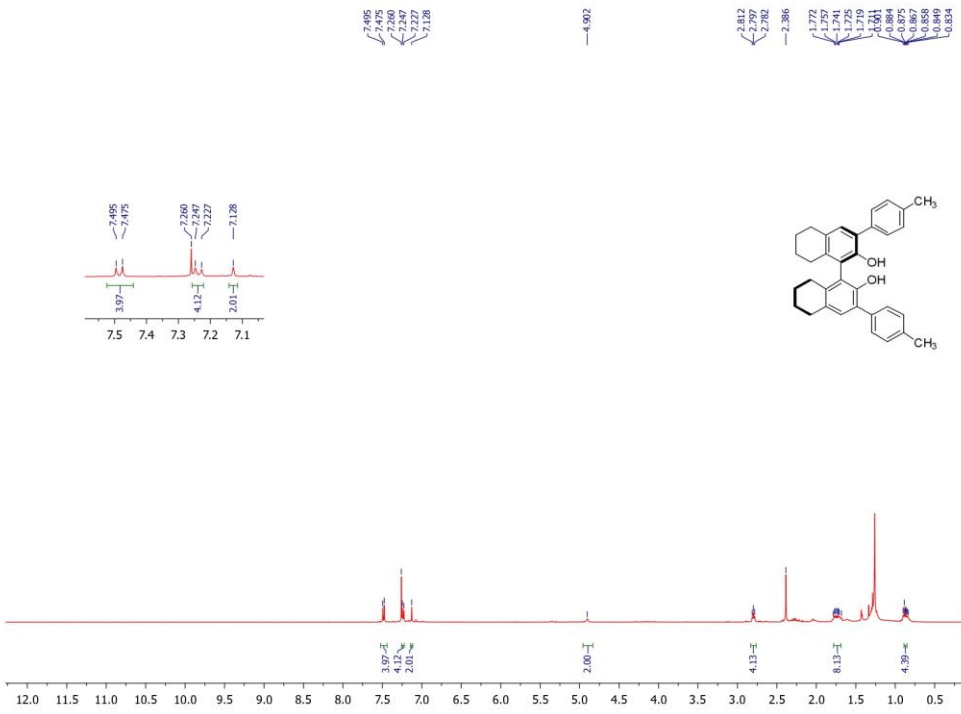


^{1}H-NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

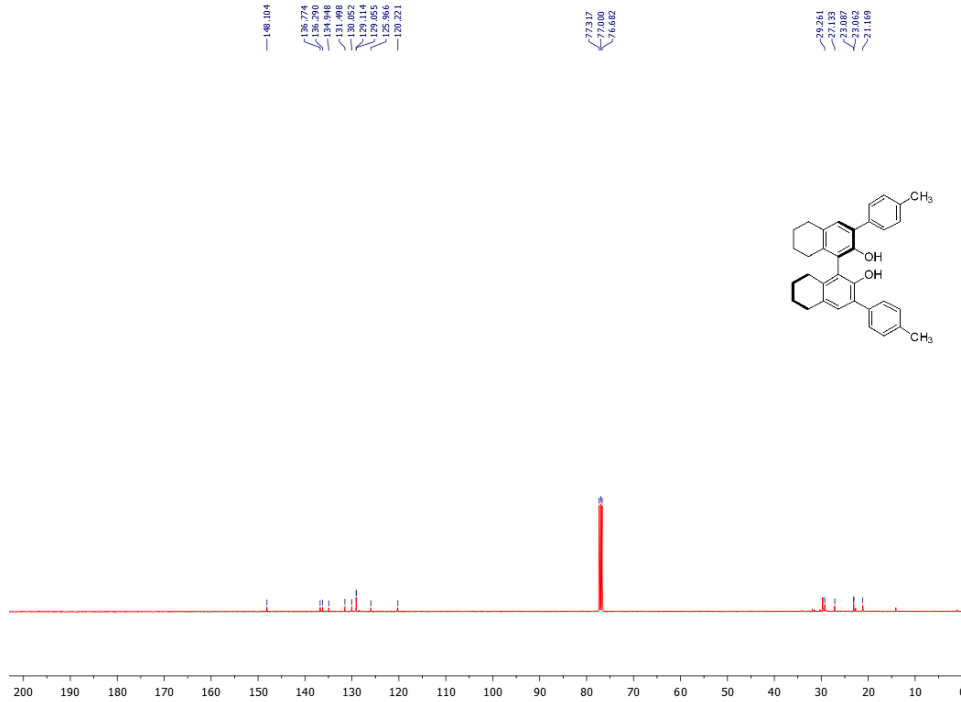


^{13}C-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

^{1}H and ^{13}C-NMR Spectra of (R)-(+)-3,3'-Di-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol:



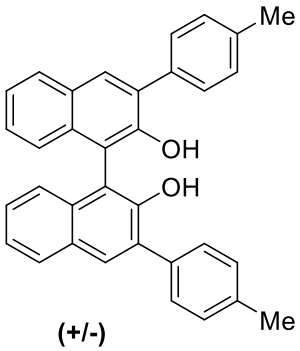
^{1}H-NMR (25 ^{o}C, 400 MHz, $CDCl_3$)



^{13}C-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

2.4.9 HPLC Data

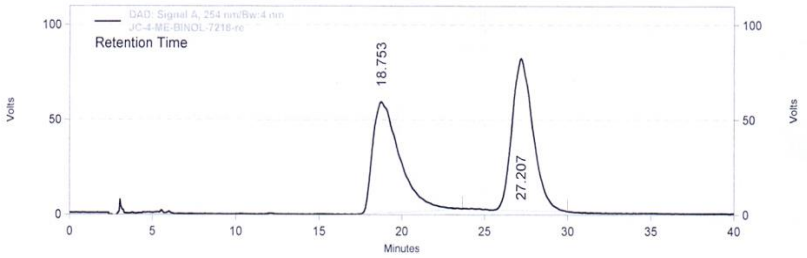
HPLC data of 3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol:



(+/-)

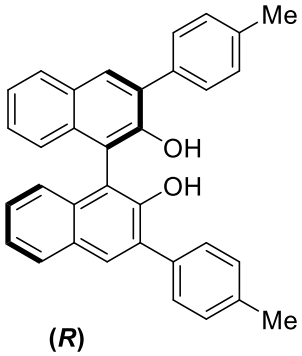
Area % Report

Data File: C:\Users\hplc\Desktop\Jagriti\JC-4-ME-BINOL-7218-re.rslt\JC-4-ME-BINOL-7218-re.dat
Method: C:\Enterprise\Projects\Method\untitled.met
Acquired: 2/7/2018 4:48:53 PM (GMT +05:30)
Printed: 2/10/2018 8:50:54 PM (GMT +05:30)



DAD: Signal A, 254 nm/Bw:4 nm
Results

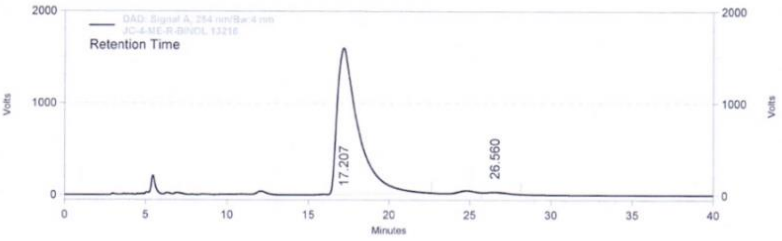
Retention Time	Area	Area %	Height	Height %
18.753	13944386	48.80	123012	42.30
27.207	14632451	51.20	167772	57.70
Totals	28576837	100.00	290784	100.00



(*R*)

Area % Report

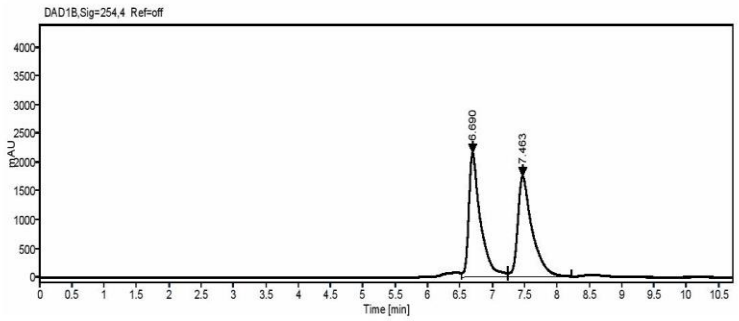
Data File: D:\Projects\Data\Trial\Jagriti\JC-4-ME-R-BINOL 13218.rslt\JC-4-ME-R-BINOL 13218.dat
Method: C:\Enterprise\Projects\Method\untitled.met
Acquired: 2/13/2018 4:16:44 PM (GMT +05:30)
Printed: 2/13/2018 6:33:07 PM (GMT +05:30)

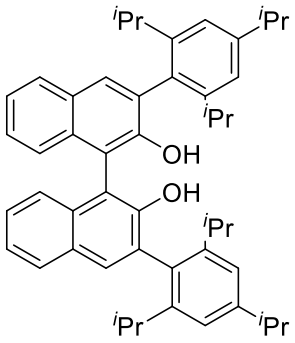


DAD: Signal A, 254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
17.207	302258284	99.47	3334471	99.31
26.560	1624905	0.53	23098	0.69
Totals	303883189	100.00	3357569	100.00

HPLC data of 3,3'-Di-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol:

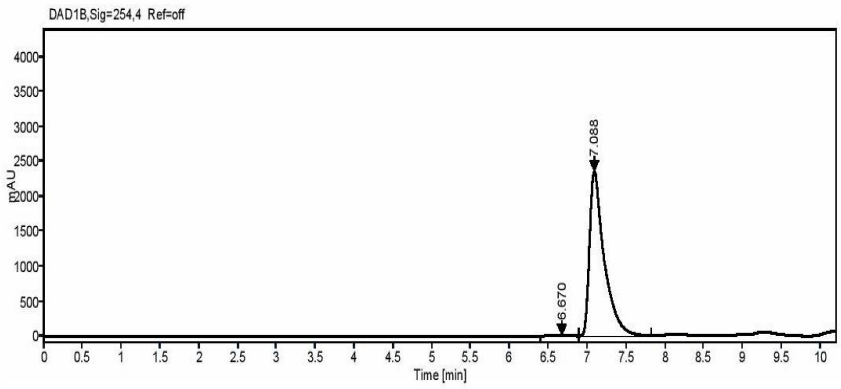


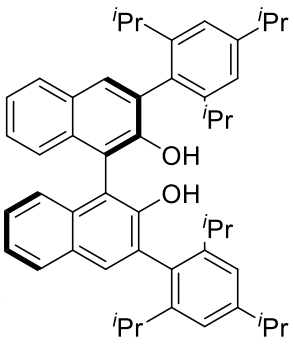


(+/-)

Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
6.690	VM m	0.18	27183.60	2161.88	50.26	
7.463	MM m	0.22	26896.99	1747.80	49.74	
		Sum	54080.59			





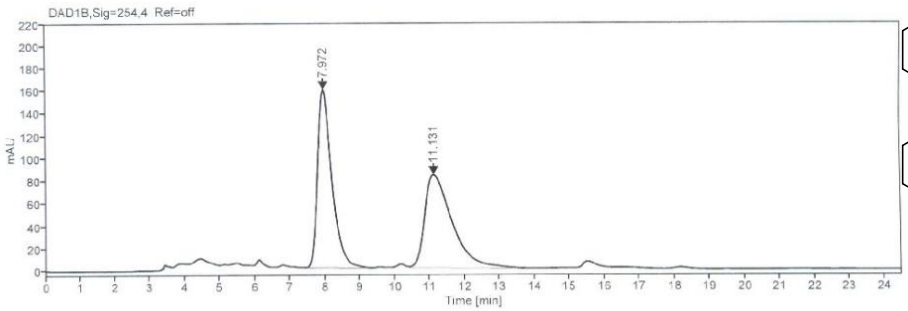
(*R*)

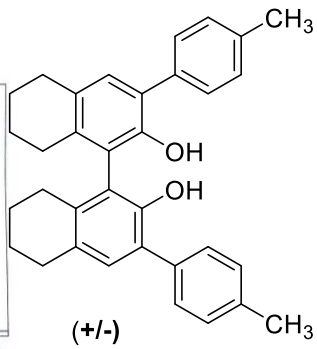
Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
6.670	MM m	0.23	251.74	14.36	0.80	
7.088	MV m	0.19	31274.78	2363.33	99.20	
		Sum	31526.51			

HPLC data of 3,3'-di-p-tolyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol:

Instrument:	HPLC	**Injection date:**	2018-08-22 23:25:27+05:30
Inj. volume:	0.000	**Location:**	
Acq. method:	Test.amx	**Type:**	Sample
Processing method:	GC_LC Area Percent_DefaultMethod.pmx	**Sample amount:**	0.00
Manually modified:	Manual Integration		



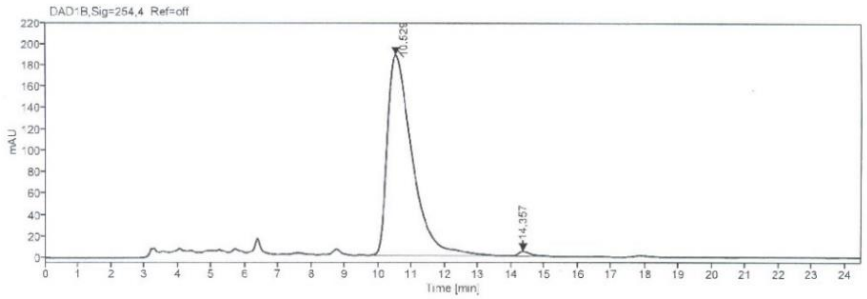


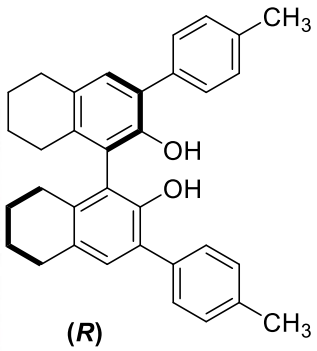
(+/-)

Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
7.972	BB	1.89	4509.69	158.12	49.67	
11.131	VB	3.50	4570.42	82.86	50.33	
		Sum	9080.11			

Instrument:	HPLC	**Injection date:**	2018-08-23 10:01:20+05:30
Inj. volume:	0.000	**Location:**	
Acq. method:	Test.amx	**Type:**	Sample
Processing method:	GC_LC Area Percent_DefaultMethod.pmx	**Sample amount:**	0.00
Manually modified:	Manual Integration		





(***R***)

Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
10.529	VB	4.21	9735.22	187.66	98.97	
14.357	BM m	0.36	100.98	4.21	1.03	
		Sum	9836.20			

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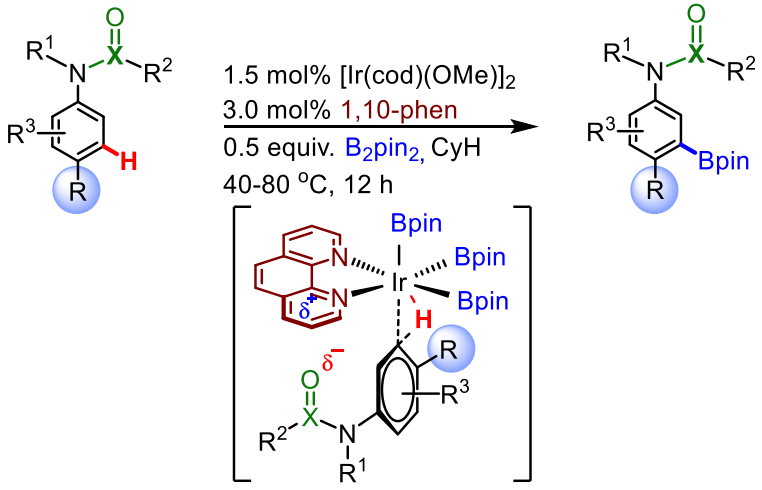
CHAPTER 3

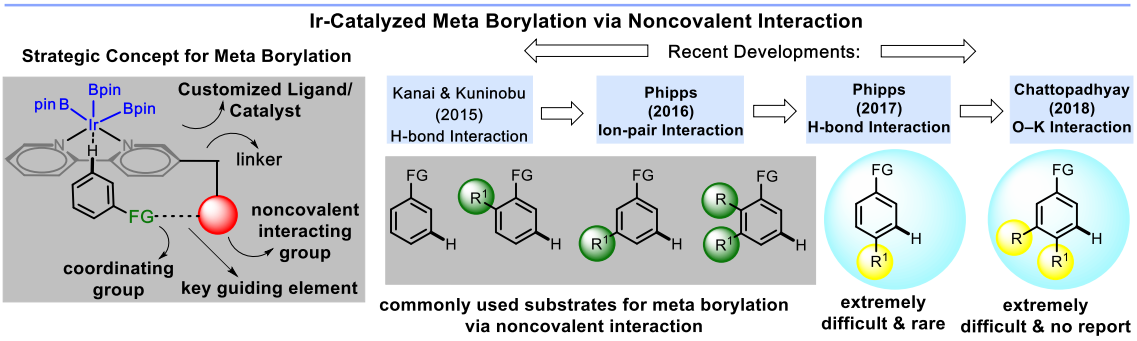
Meta Selective C-H Borylation of Sterically Biased and Unbiased Substrates Directed by Electrostatic Interaction

Electrostatically Directed Meta Borylation



3.1 Introduction

Over the past few decades, transition metal-catalyzed carbon-hydrogen bond functionalization[1-5] has experienced considerable recognition from organic chemist to build carbon-carbon bond and carbon-heteroatom bonds for the preparation of high value-added molecules. However, owing to the numerous carbon hydrogen bonds in organic compounds, site selective[6-10] functionalization remains a major challenge.



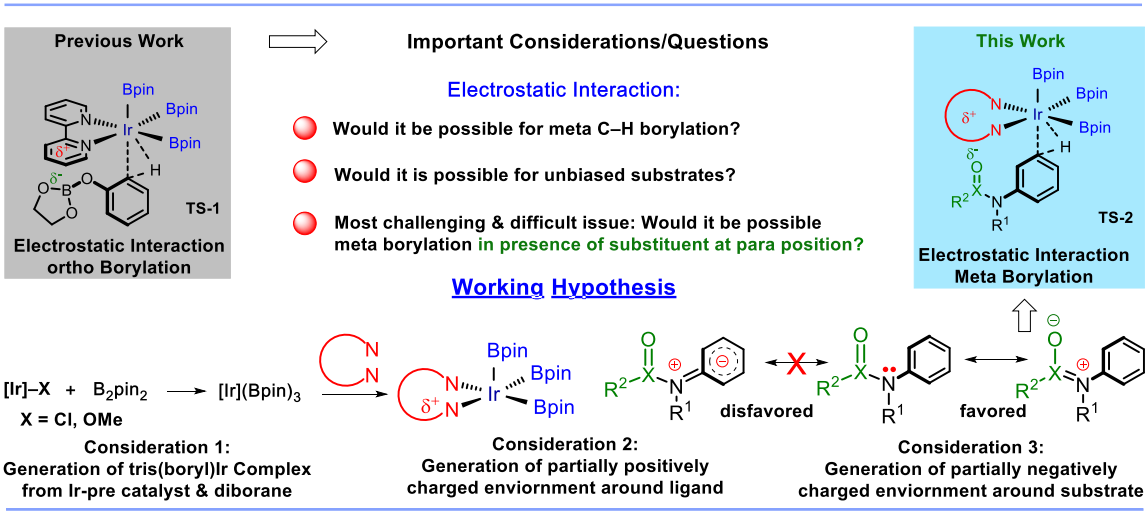
Scheme 3.1: Previous Reports of *Meta* Borylation

In contrast to the well-developed *ortho* functionalization reaction,[11-14] research towards the *meta* and *para* functionalization[15,16] has been scarce. The major issue of achieving remote arene C-H functionalization (*m* & *p*) is steric crowding. Moreover, remote C-H bond (*meta* and *para*) functionalization often needs installation and deletion of a bulky directing template which restricts its practical application.

In recent years, borylation of arenes using iridium catalyst[17-20] have been extensively used in chemical synthesis due to its competence to deliver very beneficial aryl organoboronate ester intermediates which can be easily transformed to a variety of important synthons.[21-24] Although, significant efforts have been made in *ortho* borylation reaction counting traditional metalation strategy,[25,26] in contrast, there are few reports of remote borylation reaction. Earlier, Smith, Maleczka along with Hartwig[27-30] reported *meta* borylation with only 1,3-disubstituted aromatic systems. Recently, in addition to the directed *meta* borylation,[31,32] many remote *meta* selective C-H borylations have been established utilizing non covalent interactions (**Scheme 3.1**).[33-39] Moreover, noncovalent interaction and LA-LB interaction has been found for *para* borylation also.[40-43]

Nevertheless, despite the significant contribution of noncovalent interaction in borylation, there are some restrictions which limits its application. Firstly, due to the weak nature of

the noncovalent interaction, substrates bearing substitution adjacent to the borylation site faces several competitive reactions. For instance, *meta* borylation of *para*-substituted arenes is still a formidable task. The reason behind is that the steric crowding inhibits noncovalent interaction which resulted in no borylation. Secondly, requirement of special type of ligands and catalysts limits the generality of the reaction toward synthetic application.[28] In this project, we report a new *meta* borylation concept of arenes bearing trifluoro acetyl group (-$COCF_3$), methane sulfonyl group (-SO_2CH_3), triflate group (-SO_2CF_3), pivaloyl group (-CO^tBu) and acetyl group (-$COCH_3$) at benign reaction conditions under Ir-catalysis using an electrostatic interaction. Especially, our developed idea empowers borylation at the *meta* position of 4-substituted substrates. Very recently, Smith, Maleczka, and Singleton accomplished an electrostatically directed phenols *ortho* borylation strategy (**Scheme 3.2, TS-1**).[44] Inspired by this stimulating result, we hypothesized that whether this electrostatic model could be used for the remote borylation especially for the *meta* borylation of arenes or not.



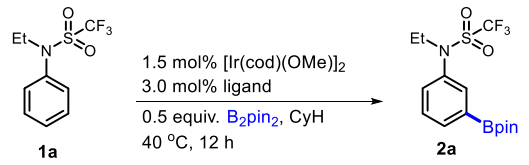
Scheme 3.2: Present Work of *Meta* Borylation

Following this hypothesis, we portrayed a plan which have following four important considerations: (i) at first, formation of Ir-trisboryl complex using iridium precatalyst and B_2Pin_2, (ii) use of the commercial inexpensive nitrogen containing ligands in place of specially designed ligand framework for the in-situ generation of the positively charged 5-coordinated iridium-complex. (iii) a proper fitting an electrostatic interaction between the arene and ligand (**Scheme 3.2, TS-2**).

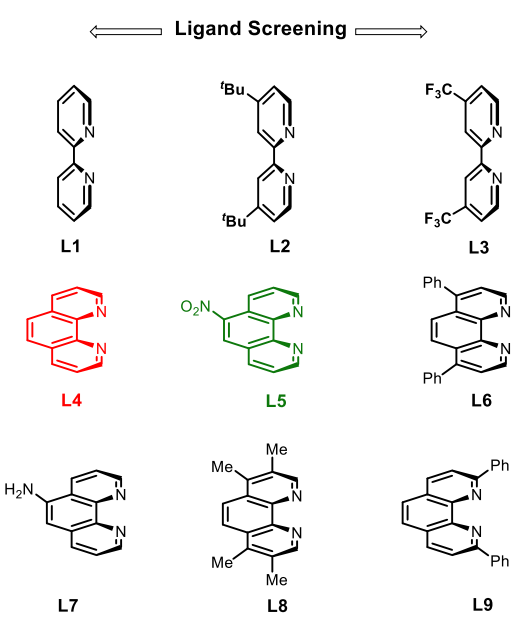
3.2 Results and Discussion

We started our investigations with substrate (**1a**) having an ethyl protected *N*-Tf group [(Et)N-SO_2CF_3] with the readily available ligands (**Table 1**). Utilizing the concept of an electrostatic interaction, at first, we performed a borylation reaction using bipyridine (**L1**) and B_2pin_2 (1.0 equiv.) at 40 °C (**entry 1**) that resulted in high *meta* selectivity along with the significant amount of the diborylated products. Next, we started optimization using 0.5 equiv. of B_2pin_2 to suppress the formation di borylated products. The selectivity was measured by GC/MS analysis of the crude borylated mass. Consequently, we conducted borylation reactions using various bipyridine ligands such as **L1**, **L2** and **L3** with the less amount of the boron source.

Table 1: Reaction Optimization



#	ligand	B_2pin_2	*meta*/*para*	Conv. (%)
1	L1	1.0 (equiv.)	5/1[a]	99
2	L1	0.5 (equiv.)	5.6/1	83
3	L2	0.5 (equiv.)	4.8/1	92
4	L3	0.5 (equiv.)	10.1/1	45
5	L4	0.5 (equiv.)	32/1	96 (91)
6	L5	0.5 (equiv.)	33/1	10
7	L6	0.5 (equiv.)	4/1	61
8	L7	0.5 (equiv.)	3.5/1	25
9	L8	0.5 (equiv.)	3.3/1	99
10	L9	0.5 (equiv.)	-	NR



Reactions were performed with 0.2 mmol scale. In parenthesis, Isolated yield is reported. Selectivity is based on GC/MS analysis of the reaction.[a]In addition to this meta/para isomer, significant diborylation occurred.

We noticed that as the electron deficiency of bipyridine ligands increases from **L1** to **L3,** *meta* selectivity of corresponding arenes also increases. For instance, ligand **L1** showed more *meta* to *para* selectivity (5.6/1, **entry 2**) compared to the electron rich **L2** ligand (4.8/1, **entry 3**) and an electron withdrawing group containing bipyridine ligand **L3** furnished high level of *meta* to *para* selectivity (10.1/1) although with less conversion (**entry 4**).

From the increasing trend of selectivity with electronically diverse bpy ligands, we can say that electron poor bis-CF_3 groups present in the **L3** bpy ligand drag the electron from the

ligand system, resulting more positive charge on the ligand system after coordination with the Ir-catalyst. This positively charged ligand system facilities an electrostatic interaction with the O atom of protecting group of arenes having partly developed negative charge.

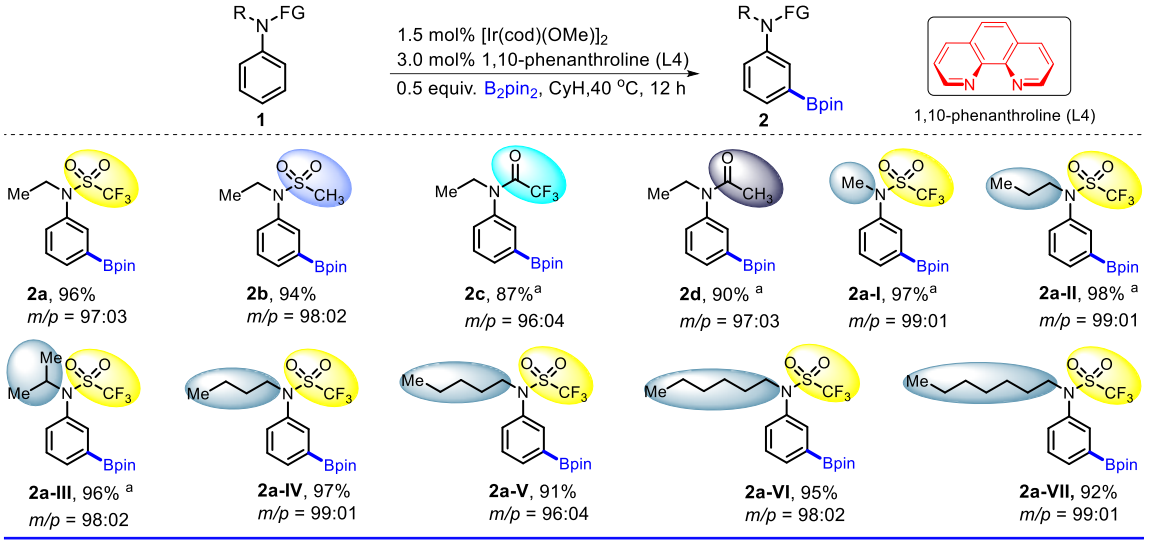
Next, we studied various electronically distinctive Phen ligands that are less developed in borylation reactions.[45,46] The Phen ligand is an electron-deficient heteroaromatic chelating ligand rigid and planar. In this ligand, two N-atoms are directed towards inside and are placed in close proximity in compared to the bpy ligand. A free rotation around the single bond can disturb the inward tendency of two nitrogen donor atoms. Due to the lack of π-electron, Phen ligand acts as an appropriate π-acceptor.[47] Thus, keeping these unique properties of Phen ligand, a borylation reaction with 1,10-phenanthroline ligand **(L4)** was conducted (**entry 5**). Remarkably, excellent *meta* selectivity (32/1) was observed with 91% isolated yield of **2a**. Moreover, phenanthroline ligand bearing electron poor group (**L5**) resulted in high *meta* to *para* selectivity (33/1) with poor conversion. Furthermore, electron donating ligand 5-amino phenanthroline ligand (**L7**) and 3,4,7,8-tetramethylphenanthroline ligand (**L8**) were subjected under the developed conditions which led to the poor regioselectivity (**entry 8 & 9**). While ligand **L6** gave moderate *meta* to *para* selectivity (**entry 7**), ligand **L9** resulted in no reaction. This can be rationalized by considering steric crowding between two bulky Ph substitutions present at C6 position of **L9** ligand.

With these encouraging results, we planned to investigate other types of functional groups such as *N*-ethylacetyl, *N*-ethyltriflate, *N*-ethyltrifluoroacetyl and *N*-ethylmethanesulfonyl applying our proposed electrostatic interaction. Pleasingly, all the above-mentioned functionality displayed high level of *meta* selectivity and the results are summarized in **Table 2** (**2a-2d**). Therefore, we tested borylation reaction with various alkyl groups encompassing substrates,[48] for instance, methyl, butyl, propyl, isopropyl, heptyl, hexyl and pentyl groups containing arenes (**1a-I to 1a-VII**) and noticed that longer chain length does not interfere in the *meta* selectivity.

Next, we explored the scope of various 4-substituted arenes under the developed *meta* borylation conditions (**Table 3**). Diverse range of *para* substituted arenes bearing Et(*N*)-SO_2CF_3 functional group are well-suited and afforded *meta* isomer solely with remarakable yields (**4a-I** to **4a-XV**). Moreover, we examined different types of functional groups other than Et(*N*)-triflate group such as Et(*N*)-trifluoroacetyl group, Et(*N*)-acetyl group, Et(*N*)-

methanesulfonyl group, and Et(*N*)-pivaloyl group with electronically and sterically diverse substituents.

Table 2: *Meta* Borylation of Monosubstituted Arenes

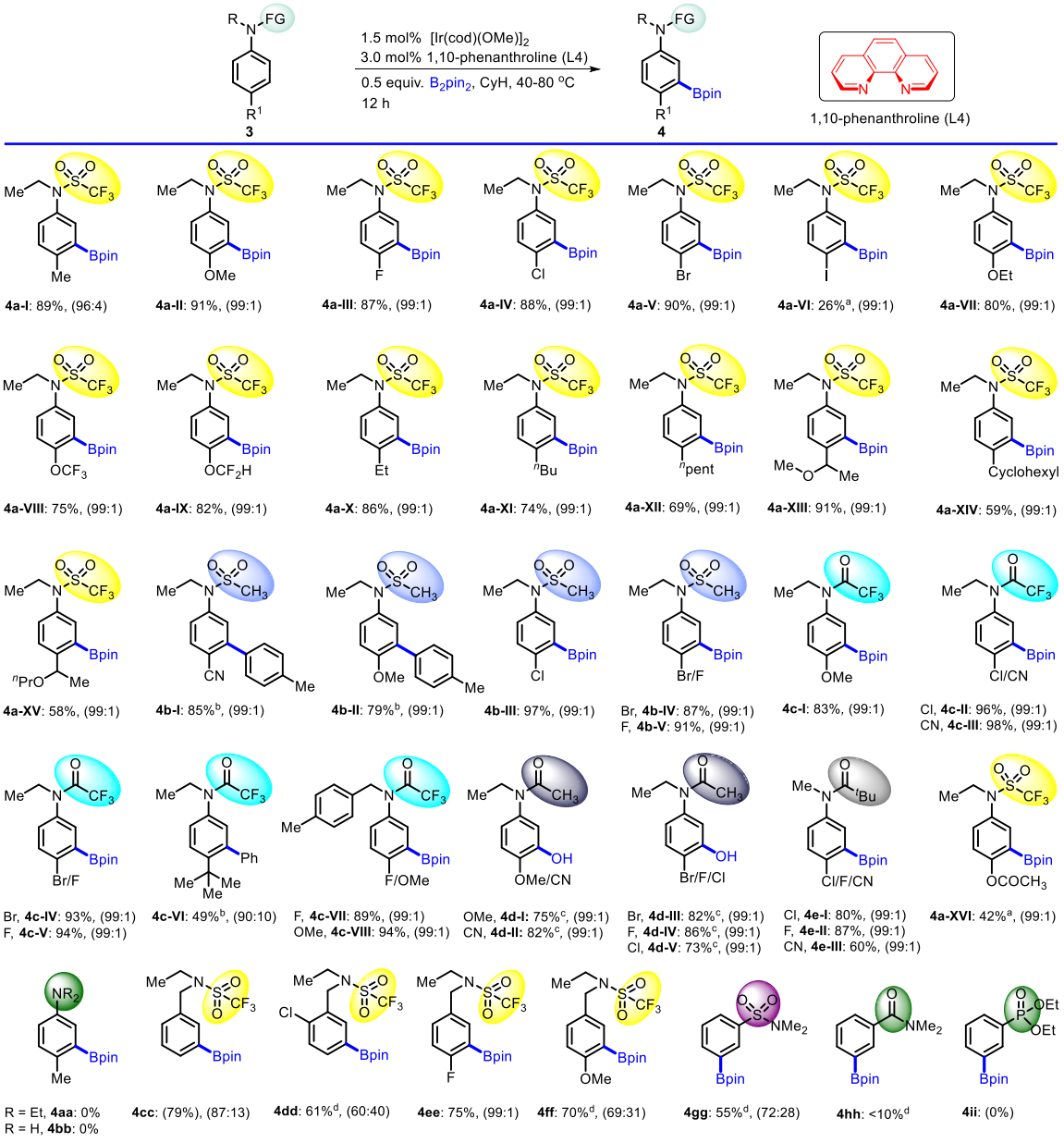


Reactions performed with 0.5 mmol scale. Isolated yields are given. [a]In these cases, very minor amount of *m,m'*-diborylation occurred. But, due to the stability issue, we were unable to isolate.

It was found that all the functional groups smoothly participated in the *meta* borylation reactions. Remarkably, arene having a larger ^{t}Bu group at the *para* position also furnished only *meta* isomer (*m*/*p* = 90/10*)* (**entry 4c-IV**). Owing to the instability of corresponding *meta* borylated product, we isolated it after cross-coupling reaction. Substrate (**3c-VII, 3c-VIII**) having a -Bn group in place of an ethyl group also afforded *meta* isomer with good selectively. Notably, the carbon hydrogen bonds of the benzyl moiety were untouched under the established conditions.

Importantly, when substrate **3aa** and **3bb** were employed to the borylation reaction, no borylation occurred. For this, we reasoned that due to the lack of any noncovalent interacting sites especially the aforementioned functional groups, meta borylation did not occur. Next, we became interested to test benzylamine substrates (**3cc-3ff**) having the longer distance in contrast to the anilines. Thus, we conducted borylation reactions with those substrates and observed that unsubstituted benzylamine (**3cc**) and 4-fluoro benzylamine (**3ee**) furnished good *meta* selectivity. But, the *meta* isomer ratio of 2-substituted benzyl amine e.g., 2-chloro (**3dd**) and 4-substituted benzyl amine e.g., 4-methoxy (**3ff**) was average, which is due to the lack of proper electrostatic interaction between Phen ligand and benzylamine substrates.

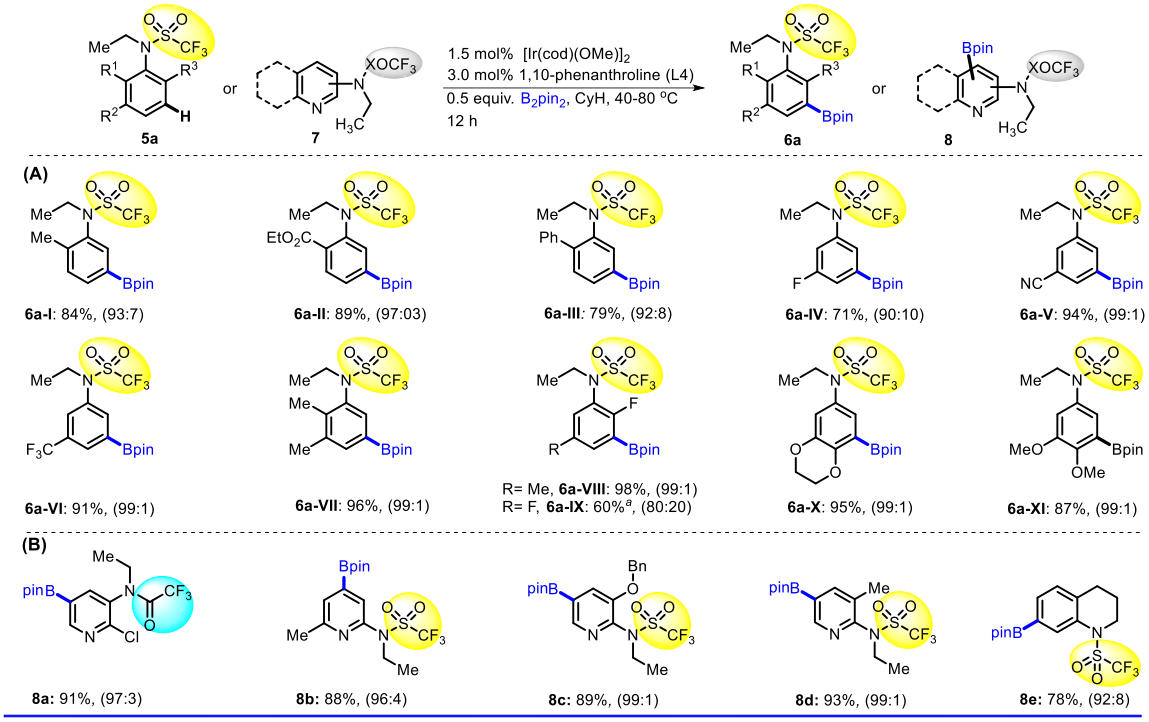
Table 3: Substrate Scope for 4-Substituted Arenes



All reactions were performed with 0.5 mmol scale. Isolated yields are reported. In parenthesis meta-/others isomeric ration given. Selectivity is based on the GC/MS analysis of the reaction. For details see, SI. aCrude NMR convesion is given. bProducts were isolated after cross coupling (SI for details). cProducts were isolated after oxidation. dGC/MS conversions are reported. Borylation of (3a-II) using L1 and L2 ligand afforded 49% and 53% conv. respectively.

For additional elucidation, we endeavored *meta* borylations with other types of arene systems. For example, we tested sulfonamide (**3gg**) under the optimized borylation conditions and found good *meta* to *para* (72:28) selectivity. We also examined benzamide (**3hh**) and phosphonate ester (**3ii**) under the developed *meta* borylation conditions. Unfortunately, both the substrates were found to be ineffective to produce borylated products, which demonstrated the absence of a suitable electrostatic interaction.

Table 4: Substrate Scope for Substituted Arenes



Reactions were performed with 0.5 mmol scale. Isolated yields are reported. In parenthesis meta-/others isomeric ration are given. Selectivity is based on the GC/MS analysis of the reaction. aGC/MS conversion is reported.

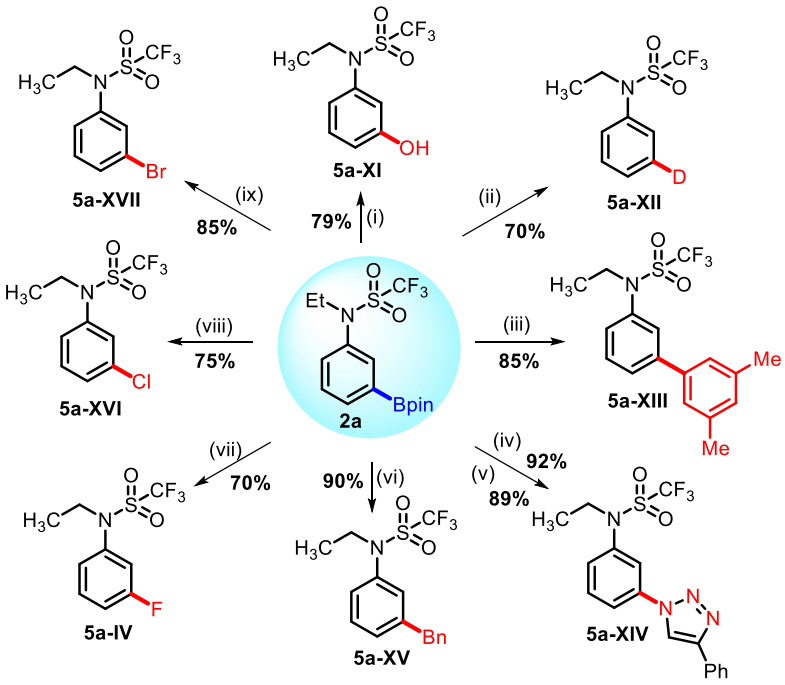
To realize the role of the **L1** and **L2** ligands, we conducted a borylation reaction with the *para* substituted arene (**3a-II**) in presence of **L1** & **L2**. It was found that whereas the ligand **L4** produced *meta* borylated product quantitatively, bipyridine ligand **L1** and dtbpy ligand **L2** also showed *meta* selectivity with 49% and 53% conversion individually. This outcome proves that along with 1,10-phen ligand (**L4**), substrate also has a significant role to yield better reactivity. This is because of the exceptional properties[47] of the Phen ligand (**L4**).

We next evaluated various substitutions on the arene ring (**Table 4**). At first, we tested challenging 2-substituted arenes having an (Et)N-SO_2CF_3 group such as, 2-Me, 2-CO_2Et, 2-Ph, employing the developed meta borylation conditions. Remarkably, all the substrates gave high *meta* selectivity with excellent isolated yields (entry **6a-I**- **6a-III**). Substrates containing difluoro groups at 2 and 5 positions gave good *meta* selectivity (entry **6a-IX**). Although the substrates **3a-III** having a -F substituent at *para* position and substrates **3b-I** containing a -CN substituent at *para* position (**Table 3**) furnished exclusively *meta* borylated product (which generally allows borylation adjacent to the fluoro and nitrile group), substrates **5a-IV** and **5a-V** (having 3-fluoro and 3-cyano group respectively, **Table 5**) did not furnish borylation entirely adjacent to -F and -CN groups but, rather, gave 90:10 and 99:1 *meta*/others selectivity. These observations are in accordance with the proposed

electrostatic interaction model. Moreover, di-substituted arenes (**5a-VII ,5a-VIII,5a-X& 5a-XI**) resulted in *meta* isomer as single products. Fascinatingly, we also observed that various protected heterocyclic substrates like 2-Cl pyridine (**7a**), 6-methyl pyridine(7b) and isoquinoline substrate (**5a-IX**) participates in borylation reaction yielding excellent meta borylated product with good isolated yield. 3-Substituted pyridine like **7c** having -OBn gorup at C3-position and **7d** having Me group at C3-position also afforded excellent selectivity under the developed meta borylation conditions.

To highlight the synthetic efficacy, we converted borylated material (**2a**) to the numerous valuable synthons using known synthetic transformations and the results are depicted in **Table 5**. For example, we transformed -Bpin group to hydroxy (-OH),[47] fluoro (-F),[49]chloro (-Cl),[50] bromo (-Br),[50] deuterium (-D),[51] aryl (-Ar),[21] benzyl (-Bz)[52] and azide ($-N_3$) followed by cycloaddition[53] (**Table 5**).

Table 5: Synthetic Transformations



Conditions: (i) 1.2 equiv. oxone, (3/1) acetone/water, 0 °C-rt, 2 h. (ii) 1.0 mol% $[Ir(cod)OMe]_2$, (4/1) (THF/D_2O), 80 °C, 12 h. (iii) 2.5 mol% $Pd(PPh_3)_4$, 2.0 equiv. K_2CO_3, 1.1 equiv. 5-bromo-m-xylene, (1/1) DME/H_2O, 100 °C, 12 h. (iv) 10 mol% $Cu(OAc)_2$, 1.5 equiv. NaN_3, MeOH, 55 °C, under air, 24 h. (v) 1.2 equiv. phenylacetylene, 3.0 mol% sodium ascorbate, H_2O, MeOH, rt, 24 h. (vi) 1.0 mol% $Pd_2(dba)_3.CHCl_3$, 4.0 mol% PPh_3, 4.0 equiv. K_2CO_3, 1.2 equiv. BnBr, (10/1) THF/H_2O, 100 °C, 24 h. (vii) 4.0 equiv. TFA, 2.0

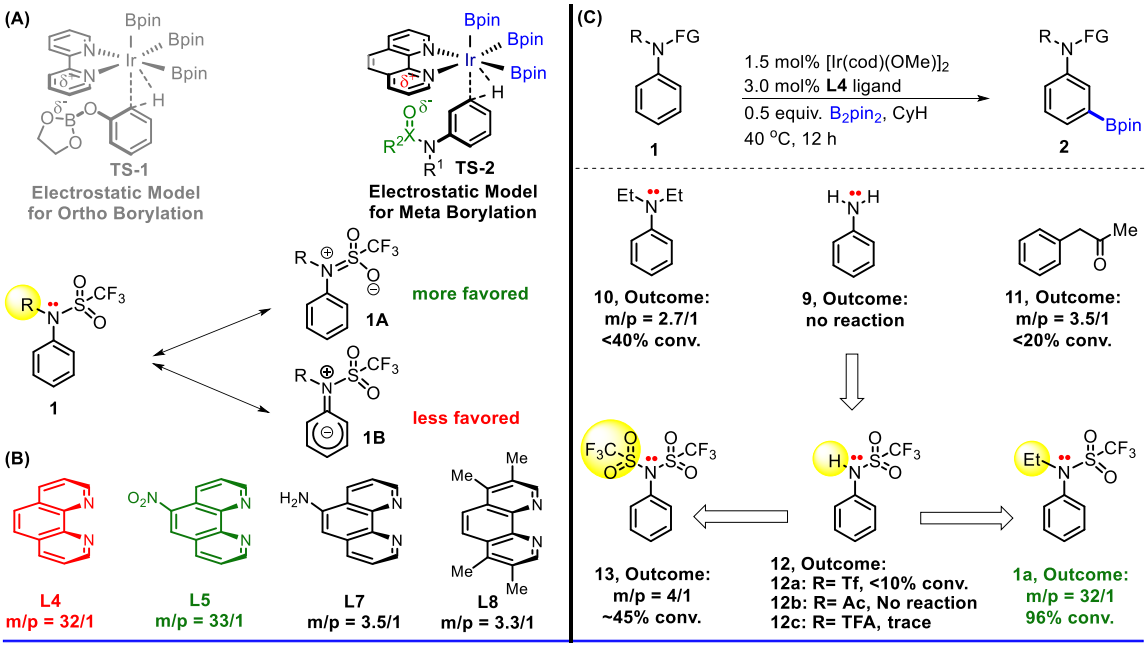
equiv. $Cu(OTf)_2$, CH_3CN, 60 °C, 20 h. (viii) 3.0 equiv. $CuCl_2$, (1/1) $MeOH/H_2O$, 80 °C, 12 h. (ix) 3.0 equiv. $CuBr_2$, (1/1) $MeOH/H_2O$, 80 °C, 12 h.

3.3 Mechanistic Investigation

The typical borylation reaction mechanism of arene was reported[54] previously, and our developed *meta* borylation probably followed the same pathway. But, to gain more insight of the proposed electrostatic model (**Scheme 3.3A, TS-2**), we first surveyed various electronically different ligands. Previously, it has been established that, for *ortho* borylation directed by an electrostatic interaction (**TS-1**),[44] an electronically diverse ligand framework changes the *ortho* selectivity.

Accordingly, we checked various electronic outcome of several Phen ligands.[47] We noticed that our borylation reaction ensues the identical trend (**Scheme 3.3B**) that is in line with the former electrostatic model for the *ortho* borylation of phenol. For detailed mechanistic investigations, we performed several control experiments. As per our proposed hypothesis, we assumed that presence of strong electron withdrawing $-SO_2CF_3$ group will not allow the lone-pair of attached *N* atom to delocalize through arene ring rather it will be delocalized through the $-SO_2CF_3$ group (**Scheme 3.3A**).

Scheme 3.3: Validation of Proposed Electrostatic Model



All the reactions were conducted with 0.2 mmol scale. GC/MS ratios are given. GC/MS conversions are reported of the crude reaction.

Therefore, in arene (**1**), a fractional negative charge will develop on the O atom of the sulfonyl group (**1A**) in place of the arene ring (**1B**). Arene ring would then interact the ligand having a partial positive charge. We visualize that, if this speculation is accurate, then a functional group modification of the N atom should disturb the *meta* selectivity. Ensuing this speculation, we executed a reaction with arenes having different functionality (**Scheme 3.3 C**) and observed that substrates deprived of appropriate functional groups (**11,9, &10**) led to either no reaction or a mixture of isomers.

Next, we conducted a borylation reaction with substrate **12a** having a free NH group along with a Tf group and we noticed less than 10% conversion. This result signifies that enhancement of electron delocalization by confining the chelation with iridium is possible if N atom is protected. However, acetyl protected (**12b**) and trifluoroacetic acid group protected (**12c**) arenes gave more or less identical results. Moreover, di triflate ($-SO_2CF_3$) group protected aniline (**13**) furnished a 4/1 mixture of *meta* to *para* isomer with 45% conversion. Hence, this observation specifies the requirement of an alkyl group because in presence of two triflate group, electron density on one sulfonyl oxygen atom will be less because lone pair of aniline nitrogen atom will be delocalized over two sulfonyls group. Overall, the above-mentioned mechanistic experiments suggest that the *meta* selectivity is governed by an unprecedented electrostatic interaction.

3.4. Conclusion

In closing, we have discovered a highly selective *meta* borylation concept of *N*-protected anilines and other arene systems via an electrostatic interaction. Scope of this catalytic system is remarkable. The developed method is capable to borylate 4-substituted arenes, which was a formidable task. Though maximum Ir-catalyzed remote borylation reactions necessitate at least 1.0 equiv. of B_2pin_2, our protocol entails only 0.5 equiv. of B_2pin_2, representing the usefulness of our catalytic method.[56] We believe that the strategy will be widely used in pharmaceutical industries, natural product synthesis and drug discovery.

3.5 Experimental Section

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBpin), bis(pinacolato)diboron (B_2pin_2) were procured from Sigma-Aldrich. Bis(1,5-cyclooctadiene)di-μ-methoxy-diiridium(I) $[Ir(cod)(OMe)]_2$ and di-μ-chlorobis[(1,2,5,6-η)-1,5-cyclooctadiene]diiridium ($[Ir(cod)Cl]_2$) were procured from Sigma-Aldrich. Tetrahydrofuran (THF), 1,4-dioxane, *p*-xylene, cyclohexane and toluene (PhMe) were refluxed over sodium/benzophenone ketyl, distilled and degassed twice before reaction. Dichloromethane (DCM), acetonitrile (MeCN) and dimethylformamide (DMF) were distilled over CaH_2. Methanol (MeOH) was dried over magnesium (activated with iodine). Column chromatography was performed on flash silica gel (ACME). Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm). ^{1}H, ^{13}C and ^{11}B NMR spectra were recorded on Bruker 400 MHz NMR spectrometer.

The boron bearing carbon atom was not observed in ^{13}C-NMR spectra due to the quadrupolar relaxation. Due to low solubility and relaxation problem of some borylated compounds, few carbon peaks are missing and the peak corresponding to the Bpin group has appeaed with low intensity. All coupling constants (J) are apparent, J values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet, ddd = doublet of doublets of doublets). High-resolution mass spectra (HRMS) were obtained at the Centre of Biomedical Research Mass Spectrometry Service Center using a Waters GCT Premier instrument run on electron ionization (EI) direct probe or a Waters QTOF Ultima instrument run on electrospray ionization (ESI). GC/MS (Agilent Technology) was obtained from Centre of Biomedical Research Institute and for the analysis RAM temperature was used 50 ^{o}C for each sample.

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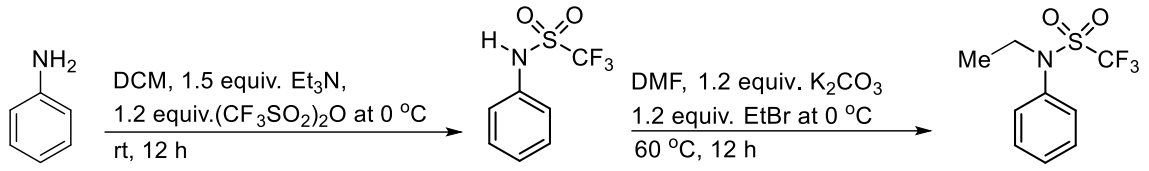
Synthesis of N-ethyl-1,1,1-trifluoro-N-phenylmethanesulfonamide:



10 mmol

79% yield

Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (10% ethyl acetate in hexane as eluent) gave 1.91 g (85%) of 1,1,1-trifluoro-*N*-phenylmethanesulfonamide as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.2 Hz, 2H), 7.27-7.34 (m, 3H), 6.78 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.6, 129.7, 127.7, 123.7, 119.7 (q, *J* = 320.5 Hz).

HRMS (ESI) *m/z* calcd $C_7H_6F_3NO_2S$ $[M+Na]^+$ 247.9969, found 247.9963.

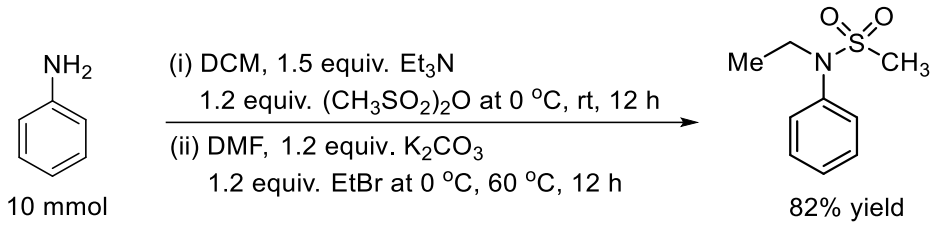
Step-II: In a 50 mL round-bottom flask, 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (1.13 g, 5.0 mmol**)** was dissolved in dry DMF (10.0 mL) and K_2CO_3 (829.2 mg, 1.2 equiv.) added. The reaction mixture was cooled to 0 ^oC and stir for 5 minute. Then, EtBr (447.9 µL, 1.2 equiv.) was added dropwise at 0 ^oC and then reaction mixture was warmed to room temperature and reflux it at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane as eluent) gave 1.00 g (79%) of *N*-ethyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 – 7.46 (m, 3H), 7.32 – 7.34 (m, 2H), 3.87 (q, *J* = 6.8 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 136.6, 129.6, 129.3, 129.2, 120.4 (d, *J* = 322 Hz), 48.7, 14.2.

HRMS (ESI) *m/z* calcd for $C_9H_{10}F_3NO_2S$ $[M+H]^+$ 254.0463, found 254.0460.

Synthesis of N-ethyl-1,1,1-trifluoro-N-phenylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 15 minutes. Then, $(CH_3SO_2)_2O$ (2.10 gm, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding *N*-SO_2CH_3 protected aniline quantitatively which was used directly without further purification for the next step.

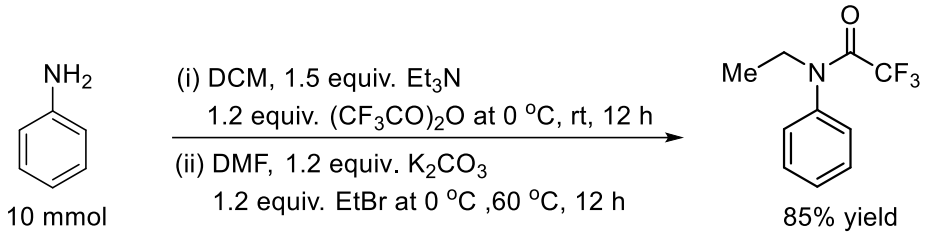
Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 5 minutes. Then, EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC and reaction mixture was warmed to room temperature and heated it at 60 ^oC for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and chromatographic separation with silica gel (20% ethyl acetate in hexane as eluent) gave 1.63 g (82%) of *N*-ethyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.43 (m, 2H), 7.33 – 7.35 (m, 3H), 3.74 (q, *J* = 7.2 Hz, 2H), 2.88 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.9, 129.4, 128.7, 128.1, 45.7, 37.3, 14.4.

HRMS (ESI) *m/z* calcd for $C_9H_{13}NO_2S$ $[M+H]^+$ 200.0745, found 200.0738.

Synthesis of N-ethyl-2,2,2-trifluoro-N-phenylacetamide:



Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3CO)_2O$ (1.67 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-$COCF_3$ protected aniline quantitatively which was used directly without further purification for the next step.

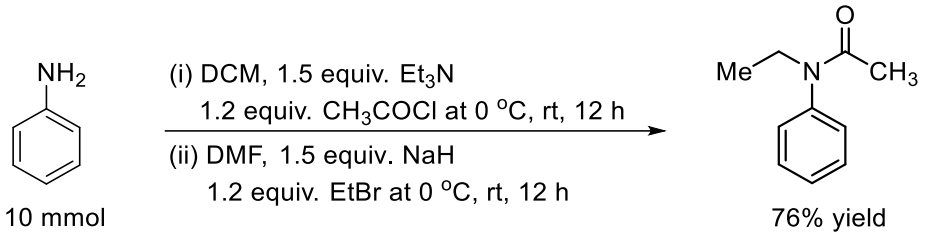
Step-II: In a 50 mL round-bottom flask crude material was dissolved in DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and heated it at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (15% ethyl acetate in hexane as eluent) gave 1.84 g (85%) of *N*-ethyl-2,2,2-trifluoro-*N*-phenylacetamide as colourless liquid.

^1H NMR (400 MHz, $CDCl_3$): 7.40-7.42 (m, 3H), 7.20 (d, J = 8.0 Hz, 2H), 3.78 (q, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.32 (d, J = 35.2 Hz), 138.8, 129.3, 128.9, 128.3, 116.3 (q, J = 286.6 Hz), 46.8, 12.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_{10}F_3NO$ $[M+H]^+$ 218.0793, found 218.0790.

Synthesis of N-ethyl-N-phenylacetamide:



10 mmol

76% yield

Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, CH_3COCl (856.25 µL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-$COCH_3$ protected aniline quantitatively which was used directly without further purification for the next step.

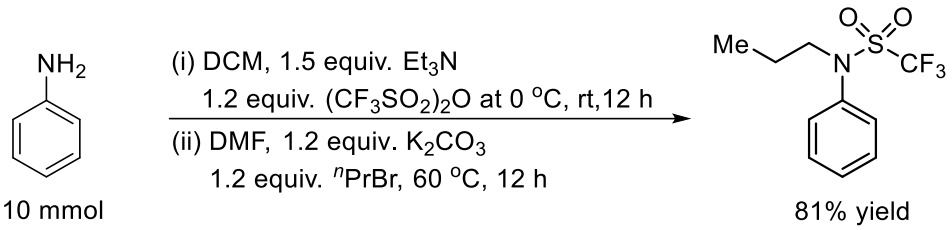
Step-II: In a 50 mL round-bottom flask crude material was dissolved in DMF (15.0 mL) and NaH (360 mg, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and stirred for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (30% ethyl acetate in hexane as eluent) gave 1.24 g (76%) of *N*-ethyl-*N*-phenylacetamide as colourless liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 3.72 (q, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 142.8, 129.5, 128.1, 127.7, 43.7, 22.7, 13.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_{13}NO$ $[M+H]^+$ 164.1075, found 164.1066.

Synthesis of N-phenyl-N-propylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

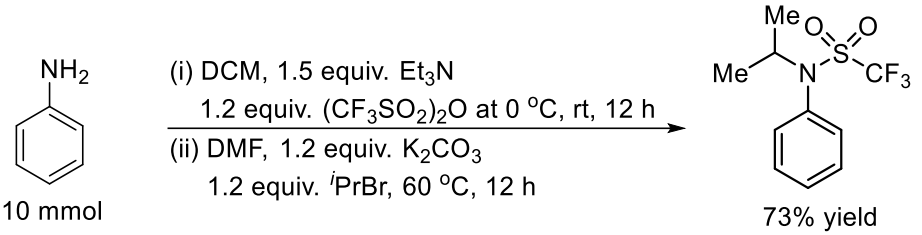
Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture was stirred for 5 minutes. Then 1-Bromopropane (1.09 mL, 1.2 equiv.) was added at room temperature and after that reaction mixture was heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 2.16 g (81%) of *N*-phenyl-*N*-propylmethanesulfonamide as colorless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.45 (m, 3H), 7.34 (d, *J* = 7.2 Hz, 2H), 3.76 (t, *J* = 7.2 Hz, 2H), 1.48 – 1.57 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.5, 129.1, 129.0, 120.5 (q, *J* = 322.3 Hz), 54.9, 21.5, 10.5.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}F_3NO_2S$ $[M+H]^+$ 268.0619, found 268.0610.

Synthesis of 1,1,1-trifluoro-N-isopropyl-N-phenylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

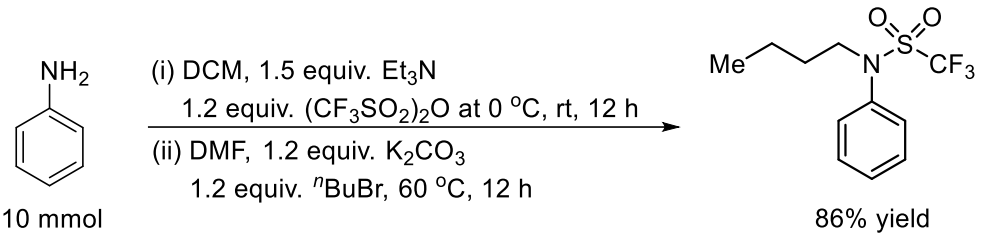
Step-II: In a 50 mL round-bottom flask crude material was dissolved in DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture was stirred for 5 minutes. Then 2-Bromopropane (1.13 mL, 1.2 equiv.) was added at room temperature and reaction mixture was heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 1.95 g (73%) of 1,1,1-trifluoro-*N*-isopropyl-*N*-phenylmethanesulfonamide as colourless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.47 (m, 3H), 7.24 – 7.26 (m, 2H), 4.51 – 4.61 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5, 132.0, 129.6, 129.1, 120.2 (q, *J* = 321.0 Hz), 54.2, 22.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}F_3NO_2S$ $[M+Na]^+$ 290.0439, found 290.0435.

Synthesis of N-butyl-1,1,1-trifluoro-N-phenylmethanesulfonamide:



10 mmol

86% yield

Step-I: In a 100 mL round-bottom flask aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

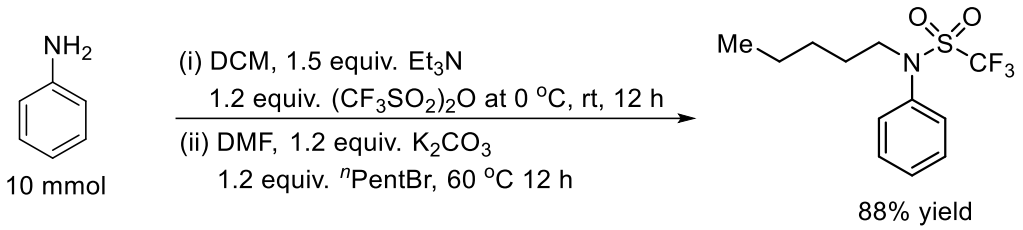
Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture stirred for 5 minutes. Then 1-Bromobutane (1.29 mL, 1.2 equiv.) was added at room temperature and reaction mixture was heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 2.42 g (86%) of *N*-butyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide as colorless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.46 (m, 3H), 7.33-7.34 (m, 2H), 3.79 (t, *J* = 7.2 Hz, 2H), 1.43-1.52 (m, 2H), 1.29-1.39 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.5, 129.1, 129.0, 120.5 (q, *J* = 322.4 Hz), 53.1, 30.2, 19.2, 13.4.

HRMS (ESI) *m/z*calcd for $C_{11}H_{14}F_3NO_2S$ $[M+H]^+$ 282.0776, found 282.0772.

Synthesis of 1,1,1-trifluoro-N-pentyl-N-phenylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

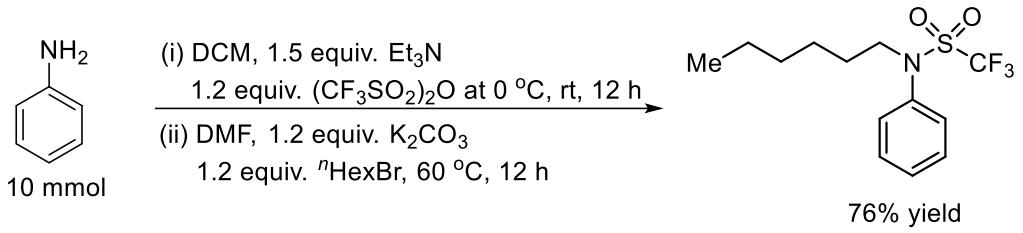
Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture stirred for 5 minutes. Then 1-Bromopentane (1.49 mL, 1.2 equiv.) was added at room temperature and reaction mixture was heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and chromatographic separation with silica gel (1% ethyl acetate in hexane as eluent) gave 2.60 g (88%) of 1,1,1-trifluoro-*N*-pentyl-*N*-phenylmethanesulfonamide as colorless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.45 (m, 3H), 7.32-7.34 (m, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 1.42-1.57 (m, 2H), 1.27-1.30 (m, 4H), 0.86 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.5, 129.1, 129.0, 120.1 (q, *J* = 322.4 Hz), 53.3, 28.1, 27.9, 22.1, 13.8.

HRMS (ESI) *m/z*calcd for $C_{12}H_{16}F_3NO_2S$ $[M+H]^+$ 296.0932, found 296.0929.

Synthesis of 1,1,1-trifluoro-N-hexyl-N-phenylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

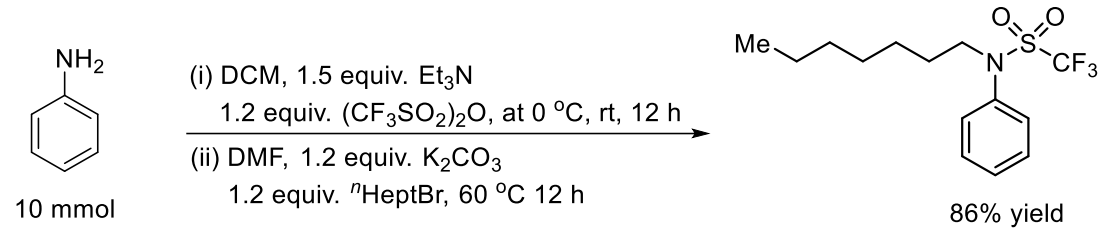
Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture stirred for 5 minutes. Then 1-Bromohexane (1.68 mL, 1.2 equiv.) was added at room temperature and reaction mixture was heated at 60 °C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (1% ethyl acetate in hexane as eluent) gave 2.35 g (76%) of 1,1,1-trifluoro-*N*-hexyl-*N*-phenylmethanesulfonamide as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.45 (m, 3H), 7.34 (d, *J* = 6.8 Hz, 2H), 3.79 (t, *J* = 6.8 Hz, 2H), 1.46 – 1.54 (m, 2H), 1.26 – 1.35 (m, 6H), 0.87 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.5, 129.1, 129.0, 120.5 (q, *J* = 322.5 Hz), 53.3, 31.1, 28.2, 25.6, 22.4, 13.8.

HRMS (ESI) *m/z* calcd for $C_{13}H_{18}F_3NO_2S$ $[M+Na]^+$ 332.0908, found 332.0905.

Synthesis of 1,1,1-trifluoro-N-heptyl-N-phenylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask, aniline (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

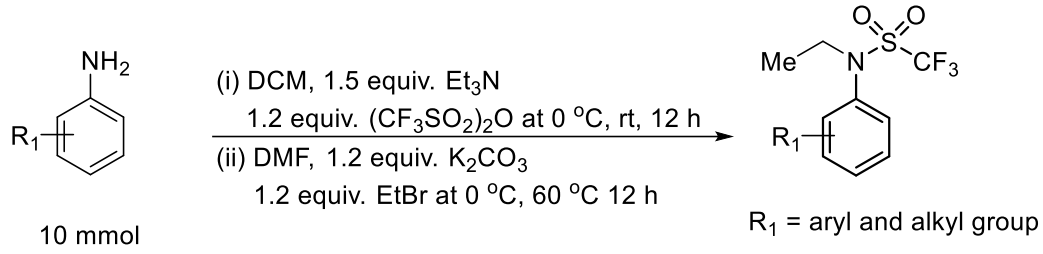
Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture stirred for 5 minutes. Then 1-Bromoheptane (1.89 mL, 1.2 equiv.) was added at room temperature and reaction mixture was heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (1% ethyl acetate in hexane as eluent) gave 2.78 g (86%) of 1,1,1-trifluoro-*N*-heptyl-*N*-phenylmethanesulfonamide as colorless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.45 (m, 5H), 3.78 (t, *J* = 6.4 Hz, 2H), 1.46 – 1.53 (m, 2H), 1.24 – 1.30 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.5, 129.1, 129.0, 120.5 (q, *J* = 322.5 Hz), 53.3, 31.6, 28.6, 28.2, 25.9, 22.5, 14.0.

HRMS (ESI) *m/z*calcd for $C_{14}H_{20}F_3NO_2S$ $[M+H]^+$ 324.1245, found 324.1244.

3.5.1 General Procedure for the Synthesis of Substituted N-ethyl-1,1,1-trifluoro-N-phenylmethanesulfonamide

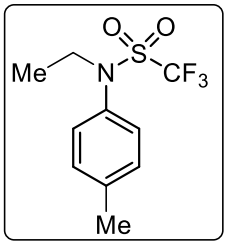


Step-I: In a 100 mL round-bottom flask, corresponding aniline (10 mmol), 20 mL dry DCM and Et_3N (2.10 mL,1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stirred for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask, crude material was dissolved in DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and heated it at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel gave corresponding substituted *N*-ethyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide.

N-ethyl-1,1,1-trifluoro-N-(p-tolyl) methane sulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(*p*-tolyl) methane sulfonamide was prepared by using general procedure **3.5.1.** Here, we used *p*-toluidine as a starting material.



Reaction time: 24 h; 88% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

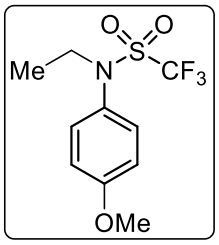
^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.24 (m, *J* = 8.4 Hz, 4H), 3.82 (q, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 133.9, 130.2, 129.0, 120.4 (d, *J* = 322.1 Hz), 48.7, 21.1, 14.2.

HRMS (ESI) *m/z*calcd for $C_{10}H_{12}F_3NO_2S$ [M+Na] 290.0439, found 290.0434.

N-ethyl-1,1,1-trifluoro-N-(4-methoxyphenyl) methane sulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-methoxyphenyl) methane sulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-methoxyaniline as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

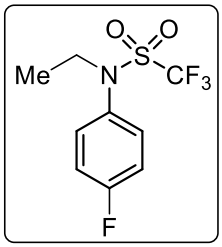
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.81 (dd, *J* = 10.2, 4.7 Hz, 5H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 130.5, 128.9, 114.6, 120.4 (q, *J* = 322.2 Hz), 55.4, 48.8, 14.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}F_3NO_3S$ $[M+Na]^+$ 427.1686, found 427.1682.

N-ethyl-1,1,1-trifluoro-N-(4-fluorophenyl) methane sulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-fluorophenyl) methane sulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-fluoroaniline as a starting material.



Reaction time: 24 h; 89% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

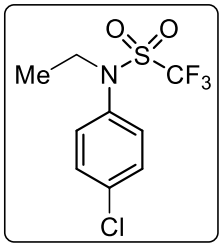
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.32 (m, 2H), 7.11 (t, *J* = 8.4 Hz, 2H), 3.82 (dd, *J* = 14.0, *J* = 6.8 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (d, *J* = 248.6 Hz), 132.4 (d, *J* = 3.3 Hz), 131.2 (d, *J* = 9.0 Hz), 120.3 (q, *J* = 321.8 Hz), 116.6 (d, *J* = 22.9 Hz), 48.8, 14.1.

HRMS (ESI) *m/z*calcd for $C_9H_9F_4NO_2S$ $[M+H]^+$ 272.0368, found 272.0361.

N-(4-chlorophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-chlorophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-chloroaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

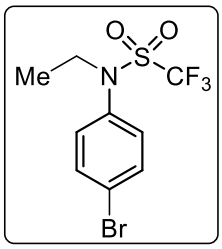
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 3.84 (dd, *J* = 13.2, 6.4 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 135.1, 130.5, 129.8, 120.3 (q, *J* = 321.8 Hz), 48.7, 14.1.

HRMS (ESI) *m/z* calcd for $C_9H_9ClF_3NO_2S$ $[M+H]^+$ 288.0073, found 288.0070.

N-(4-bromophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-bromophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-bromoaniline as a starting material.



Reaction time: 24 h; 89% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

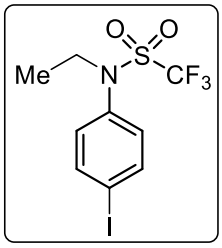
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 3.89 – 3.77 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 132.8, 130.8, 123.4, 120.2 (q, *J* = 321.9 Hz), 48.7, 14.2.

HRMS (ESI) *m/z* calcd for $C_9H_9BrF_3NO_2S$ $[M+H]^+$ 331.9568, found 331.9559.

N-ethyl-1,1,1-trifluoro-N-(4-iodophenyl) methane sulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-iodophenyl) methane sulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-iodoaniline as a starting material.



Reaction time: 24 h; 81% isolated yield, (eluent: 2% ethyl acetate in hexane). Properties: Colorless Liquid

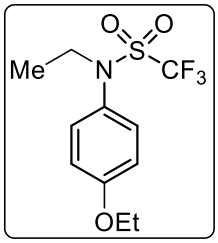
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.82-3.83 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 136.3, 131.0, 120.2 (q, J = 321.9 Hz), 95.0, 48.6, 14.2.

HRMS (ESI) *m/z* calcd for $C_9H_9F_3INO_2S$ $(M+H)^+$ 506.0281 found 506.0272.

N-(4-ethoxyphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-ethoxyphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-ethoxyaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

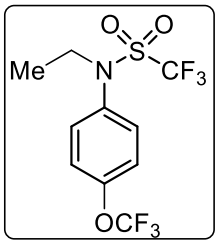
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.04 (q, J = 6.8 Hz, 2H), 3.79-3.81 (m, 2H), 1.42 (t, J = 6.8 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 130.5, 128.7, 120.4 (q, *J* = 322.1 Hz), 115.1, 63.8, 48.8, 14.7, 14.2.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}F_3NO_3S$ $(M+Na)^+$ 297.0646 found 297.0640.

N-ethyl-1,1,1-trifluoro-N-(4-(trifluoromethoxy)phenyl) methane sulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-(trifluoromethoxy) phenyl) methane sulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-(trifluoromethoxy)aniline as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

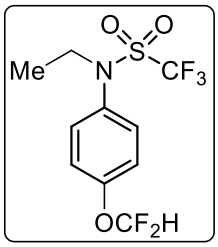
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 3.74 (s, 2H), 1.07 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3 (d, J = 1.8 Hz), 134.9, 130.9, 120.3 (dt, J = 321.6, 96.5 Hz), 48.8, 14.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_9F_6NO_3S$ $(M+H)^+$ 338.0286 found 338.0280.

N-(4-(difluoro methoxy) phenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-(difluoromethoxy) phenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-(difluoro methoxy)aniline as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

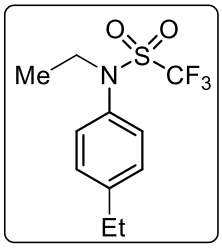
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 6.55 (t, J = 73.2 Hz, 1H), 3.83 (d, J = 4.4 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3 (t, J = 2.8 Hz), 133.4, 130.9, 120.2 (q, J = 321.8 Hz), 120.3, 115.4 (q, J = 259.8 Hz), 48.8, 14.2.

HRMS (ESI) *m/z* calcd for $C_{10}H_{10}F_5NO_3S$ $(M+H)^+$ 320.0380 found 320.0382.

N-ethyl-N-(4-ethylphenyl)-1,1,1-trifluoromethanesulfonamide:

N-ethyl-*N*-(4-ethylphenyl)-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1.** Here, we used 4-ethylaniline as a starting material



Reaction time: 24 h; 70% isolated yield, (eluent: 1% ethyl acetate in hexane)

Properties: Colorless Liquid

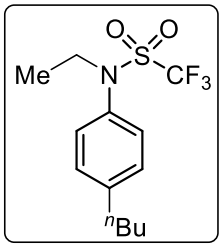
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.30 (m, 4H), 3.86 (s, 2H), 2.71 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 133.9, 129.1, 128.9, 120.3 (q, J = 321.9 Hz), 48.7, 28.4, 15.2, 14.2.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}F_3NO_3S$ $(M+Na)^+$ 297.0646 found 297.0640.

N-(4-butylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-butylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1**. Here, we used 4-butylaniline as a starting material.



Reaction time: 24 h; 86% isolated yield, (eluent: 1% ethyl acetate in hexane)

Properties: Colorless Liquid

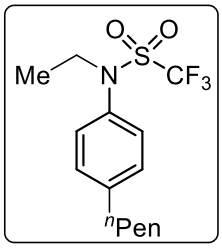
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.26 (m, 4H), 3.82-3.84 (m, 2H), 2.62-2.65 (m, 2H), 1.57-1.65 (m, 2H), 1.33 – 1.42 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 133.9, 129.5, 129.0, 120.4 (q, J = 322.2 Hz), 48.7, 35.2, 33.3, 22.3, 14.2, 13.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{18}F_3NO_2S$ $(M+Na)^+$ 332.0908 found 332.0902.

N-ethyl-1,1,1-trifluoro-N-(4-pentylphenyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-pentylphenyl) methane sulfonamide was prepared by using general procedure **3.5.1**. Here, we used 4-pentylaniline as a starting material.



Reaction time: 24 h; 86% isolated yield, (eluent: 1% ethyl acetate in hexane)

Properties: Colorless Liquid

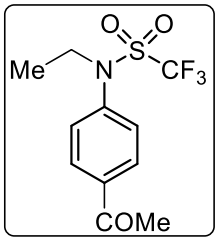
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.24 (m, 4H), 3.81-3.83 (m, 2H), 2.59-2.63 (m, 2H), 1.58 – 1.65 (m, 2H), 1.32-1.37 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 133.9, 129.4, 129.0, 120.3 (q, J = 322.1 Hz), 48.7, 35.5, 31.4, 30.9, 22.4, 14.2, 13.9.

HRMS (ESI) *m/z* calcd for $C_{14}H_{20}F_3NO_2S$ $(M+H)^+$ 346.1065 found 346.1062.

N-(4-acetylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-acetylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1**. Here, we used 1-(4-aminophenyl) ethan-1-one as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: 5% ethyl acetate in hexane)

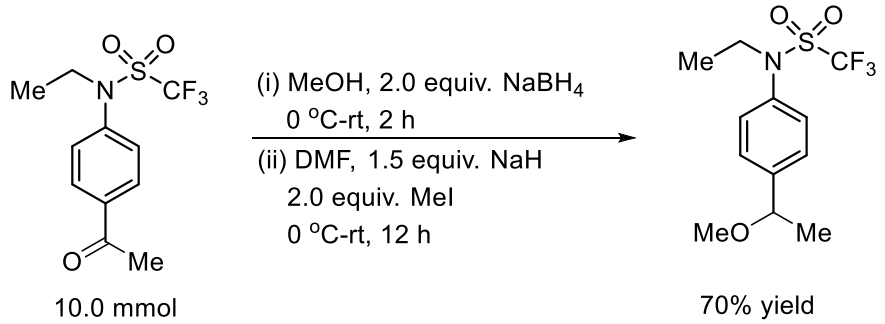
Properties: Colorless Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 3.89-3.91 (m, 2H), 2.62 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 140.6, 137.3, 129.6, 129.2, 120.2 (q, J = 321.8 Hz), 48.5, 26.7, 14.2.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}F_3NO_3S$ $[M+H]^+$ 296.0568, found 296.0560.

Synthesis of N-ethyl-1,1,1-trifluoro-N-(4-(1-methoxyethyl) phenyl) methane sulfonamide:



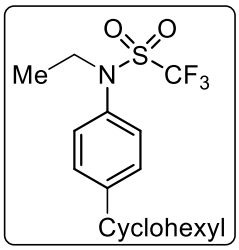
Step-I: In a 100 mL round-bottom flask *N*-(4-acetylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide (2.9 g, 10 mmol) and MeOH (15.0 mL) was added. The reaction mixture was cooled to 0 °C and stirred for 15 minutes. Then, $NaBH_4$ (756 mg, 2.0

equiv.) was added portion wise to the reaction mixture and stirred at room temperature for 2 h. After completion (judged by TLC), methanol was evaporated and the resulting reaction mixture was extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding alcohol quantitatively which was used directly without further purification for the next step.

Step-II: In a 100 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and NaH (360 mg, 1.5 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 30 minutes at room temperature. Then MeI (1.2 mL, 2.0 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and stirred for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane as eluent) gave 2.2 g (70%) of *N*-ethyl-1,1,1-trifluoro-*N*-(4-(1-methoxyethyl)phenyl)methanesulfonamide as colorless liquid.

N-(4-cyclohexylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(4-cyclohexylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by using general procedure **3.5.1**. Here, we used 4-cyclohexylaniline as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: hexane)

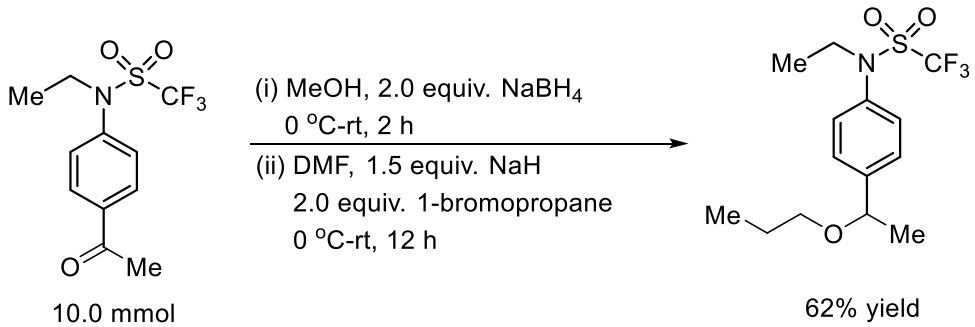
Properties: White solid

^1H NMR (400 MHz, $CDCl_3$): δ 7.20-7.26 (m, 4H), 3.82 (d, J = 6.4 Hz, 2H), 2.53 (m, 1H), 1.87 (m, 4H), 1.74-1.78 (m, 1H), 1.34 – 1.45 (m, 4H), 1.23-1.30 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 134.0, 129.1, 127.9, 120.4 (q, J = 322.1 Hz), 48.8, 44.1, 34.2, 26.7, 26.0, 14.3.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}F_3NO_2S$ $(M+H)^+$ 358.1065 found 358.1064

Synthesis of N-ethyl-1,1,1-trifluoro-N-(4-(1-propoxyethyl) phenyl) methane sulfonamide:



10.0 mmol

62% yield

Step-I: In a 100 mL round-bottom flask, *N*-(4-acetylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide (2.9 g, 10 mmol) and MeOH (15.0 mL) was added. The reaction mixture was cooled to 0 ^{o}C and stirred for 15 minutes. Then, $NaBH_4$ (756 mg, 2.0 equiv.) was added portion wise to the reaction mixture and stirred at room temperature for 2 h. After completion (judged by TLC), methanol was evaporated and the resulting reaction mixture was extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding alcohol quantitatively which was used directly without further purification for the next step.

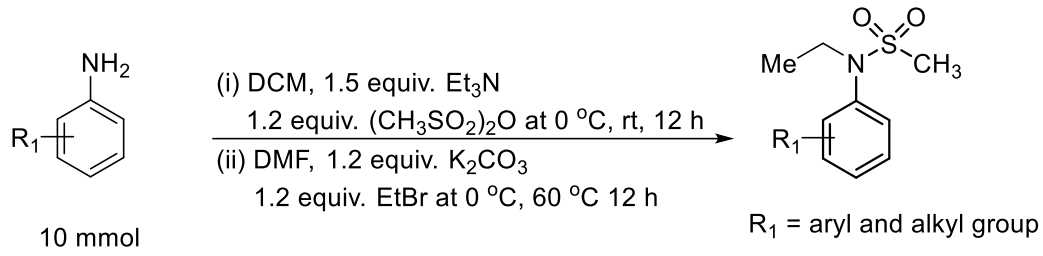
Step-II: In a 100 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and NaH (360 mg, 1.5 equiv.) was added. The reaction mixture was cooled to 0 ^{o}C and stirred for 30 minutes at room temperature. Then, MeI (1.2 mL, 2.0 equiv.) was added at 0 ^{o}C. After that reaction mixture was warmed to room temperature and stirred for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane as eluent) gave 2.1 g (62%) of *N*-ethyl-1,1,1-trifluoro-*N*-(4-(1-propoxyethyl) phenyl) methane sulfonamide as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.41 (q, J = 6.4 Hz, 1H), 3.83-3.84 (m, 2H), 3.22 – 3.31 (m, 2H), 1.54-1.63 (m, 2H), 1.42 (d, J = 6.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 135.3, 129.2, 127.1, 120.3 (q, J = 321.8 Hz), 77.1, 48.8, 24.1, 23.0, 14.3, 10.6.

HRMS (ESI) *m/z* calcd for $C_{14}H_{20}F_3NO_3S$ $(M+Na)^+$ 378.0753 found 378.0754.

3.5.2 General Procedure for the Synthesis of Substituted N-ethyl-N-phenylmethanesulfonamide:

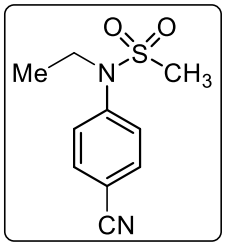


Step-I: In a 100 mL round-bottom flask, corresponding amine (1.18 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture cooled to 0 ^oC and stirred for 15 minutes. Then, $(CH_3SO_2)_2O$ (2.10 g, 1.2 equiv.) dissolved in 10.mL dry DCM was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure extract concentrated under reduced pressure to afford corresponding *N*-SO_2CH_3 protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and heated at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel afforded corresponding substituted *N*-ethyl-*N*-phenylmethanesulfonamide.

N-(4-cyanophenyl)-N-ethylmethanesulfonamide:

N-(4-cyanophenyl)-*N*-ethylmethanesulfonamide was prepared by using general procedure **3.5.2**. Here, we used 4-aminobenzonitrile as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 40% ethyl acetate in hexane)

Properties: White solid

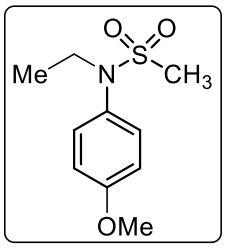
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 3.81 (q, *J* = 6.8 Hz, 2H), 2.90 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 133.3, 127.9, 118.0, 111.1, 45.2, 37.9, 14.3.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_2O_2S$ $[M+Na]^+$ 247.0517, found 247.0509.

N-ethyl-N-(4-methoxyphenyl)methanesulfonamide:

N-ethyl-*N*-(4-methoxyphenyl) methane sulfonamide was prepared by using general procedure **3.5.2**. Here, we used 4-methoxyaniline as a starting material.



Reaction time: 24 h; 89% isolated yield, (eluent: 35% ethyl acetate in hexane)

Properties: White solid

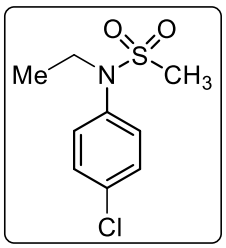
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.68 (q, *J* = 7.2 Hz, 2H), 2.87 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 131.3, 130.1, 114.6, 55.5, 45.9, 37.2, 14.4.

HRMS (ESI) *m/z* calcd for $C_{10}H_{15}NO_3S$ $[M+H]^+$ 230.0851, found 230.0844.

N-(4-chlorophenyl)-N-ethylmethanesulfonamide:

N-(4-chlorophenyl)-*N*-ethylmethanesulfonamide was prepared by using general procedure **3.5.2**. Here, we used 4-chloroaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 35% ethyl acetate in hexane)

Properties: White solid

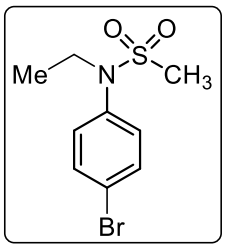
^{1}H NMR (400 MHz, $CDCl_3$): δ7.29 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 2.78 (s, 3H), 1.04 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 133.9, 129.8, 129.6, 45.6, 37.3, 14.3.

HRMS (ESI) *m/z*calcd for $C_9H_{12}ClNO_2S$ $[M+Na]^+$ 256.0175, found 256.0167.

N-(4-bromophenyl)-N-ethylmethanesulfonamide:

N-(4-bromophenyl)-*N*-ethylmethanesulfonamide was prepared by using general procedure **3.5.2**. Here, we used 4-bromoaniline as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 35% ethyl acetate in hexane)

Properties: White solid

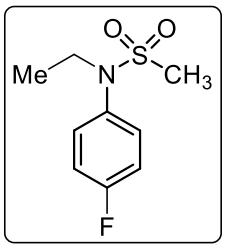
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.87 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 132.6, 130.1, 121.9, 45.6, 37.3, 14.3.

HRMS (ESI) *m/z* calcd for $C_9H_{12}BrNO_2S$ $[M+H]^+$ 277.9850, found 277.9840.

N-ethyl-N-(4-fluorophenyl) methane sulfonamide:

N-ethyl-*N*-(4-fluorophenyl) methane sulfonamide was prepared by using general procedure **3.5.2**. Here, we used 4-fluoroaniline as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 35% ethyl acetate in hexane)

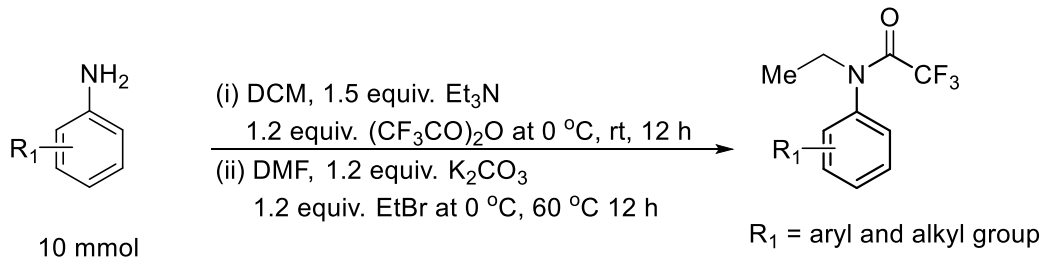
Properties: colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.8, 4.8 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 2.88 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 160.7, 134.8 (d, *J* = 3.3 Hz), 130.6 (d, *J* = 8.7 Hz), 116.3 (d, *J* = 22.5 Hz), 45.9, 37.3, 14.3.

HRMS (ESI) *m/z* calcd for $C_9H_{12}FNO_2S$ $[M+H]^+$ 218.0651, found 218.0643.

3.5.3 General Procedure for the Synthesis of Substituted N-ethyl-2,2,2-trifluoro-N-phenylacetamide:

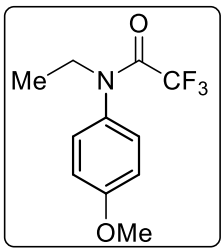


Step-I: In a 100 mL round-bottom flask, corresponding aniline (1.23 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was taken. The reaction mixture was cooled to 0 ^oC and stirred for 15 minutes. Then, $(CF_3CO)_2O$ (1.67 mL, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-$COCF_3$ protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC via a syringe. After that, reaction mixture was warmed to room temperature and heated it at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel afforded corresponding *N*-ethyl-2,2,2-trifluoro-*N*-phenylacetamide.

N-ethyl-N-(4-methoxyphenyl) methane sulfonamide:

N-ethyl-*N*-(4-methoxyphenyl) methane sulfonamide was prepared by using general procedure **3.5.3**. Here, we used 4-methoxyaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: White solid

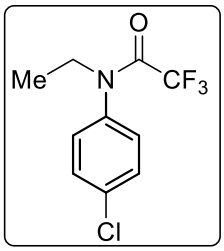
^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 156.6 (q, J = 34.9 Hz), 131.3, 129.5, 1116.4 (q, J = 286.6 Hz), 114.3, 55.4, 46.8, 12.0.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}F_3NO_2$ $[M+H]^+$ 248.0898, found 248.0893.

N-(4-chlorophenyl)-N-ethyl-2,2,2-trifluoroacetamide:

N-(4-chlorophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was prepared by using general procedure **3.5.3**. Here, we used 4-chloroaniline as a starting material.



Reaction time: 24 h; 91% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: White solid

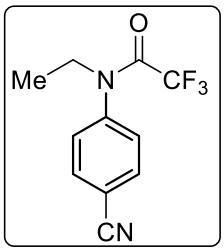
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2 (q, J = 36.7 Hz), 137.3, 135.0, 129.7, 129.6, 116.2 (q, J = 286.6 Hz), 46.8, 12.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_9ClF_3NO$ $[M+H]^+$ 252.0403, found 252.0400.

N-(4-cyanophenyl)-N-ethyl-2,2,2-trifluoroacetamide

N-(4-cyanophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was prepared by using general procedure **3.5.3**. Here, we used 4-aminobenzonitrile as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: White solid

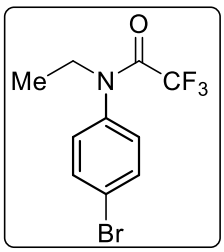
^{1}H NMR (400 MHz, DMSO): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 3.76 (d, *J* = 6.8 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO): δ 154.7 (q, *J* = 39 Hz), 142.6, 133.6, 129.8, 118.0, 116.2 (q, *J* = 366.3 Hz), 112.0 46.4, 11.7.

HRMS (ESI) *m/z* calcd for $C_{11}H_9F_3N_2O$ $[M+H]^+$ 243.0745, found 243.0741.

N-(4-bromophenyl)-N-ethyl-2,2,2-trifluoroacetamide:

N-(4-bromophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was prepared by using general procedure **3.5.3**. Here, we used 4-bromoaniline as a starting material.



Reaction time: 24 h; 86% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: White solid

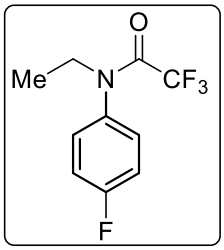
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.76 (q, *J* = 6.8 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (q, *J* = 35.3 Hz), 137.8, 132.6, 130.0, 123.1, 116.2 (q, *J* = 287.0 Hz), 46.8, 12.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_9BrF_3NO$ $[M+H]^+$ 295.9898, found 295.9894.

N-ethyl-2,2,2-trifluoro-N-(4-fluorophenyl)acetamide

N-ethyl-2,2,2-trifluoro-*N*-(4-fluorophenyl) acetamide was prepared by following the general procedure **3.5.3**. Here, we used 4-fluoroaniline as a starting material.



Reaction time: 24 h; 88% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: White solid

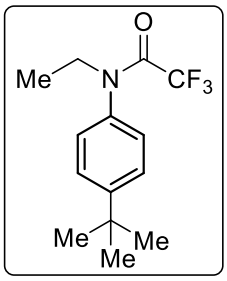
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.20 (m, 2H), 7.02-7.11 (m, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, J = 248 Hz), 156.3 (q, J = 35.2 Hz), 134.7 (q, J = 2.9 Hz), 130.3 (d, *J* = 8.3 Hz), 116.3 (q, J = 286.7 Hz), 116.4, 116.2, 46.8, 12.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_9F_4NO$ $[M+H]^+$ 236.0699, found 236.0692.

N-(4-(tert-butyl)phenyl)-N-ethyl-2,2,2-trifluoroacetamide:

N-(4-(tert-butyl) phenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was prepared by following the general procedure **3.5.3**. Here, we used 4-tertbutylaniline as a starting material.



Reaction time: 24 h; 78% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: White solid

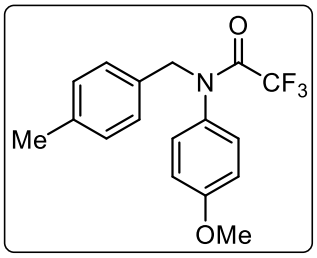
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.76 (q, *J* = 7.2 Hz, 2H), 1.33 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (q, *J* = 35.2 Hz), 152.1, 136.0, 127.8, 126.1, 116.4 (q, *J* = 286.5 Hz), 46.9, 34.7, 31.2, 12.2.

HRMS (ESI) *m/z* calcd for $C_{14}H_{18}F_3NO$ $[M+H]^+$ 274.1419, found 274.1412.

2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(4-methylbenzyl) acetamide:

2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(4-methylbenzyl) acetamide was prepared by following the general procedure **3.5.3**. Here, we used 4-methoxyaniline as a starting material. In this case, we used 4-methylbenzyl bromide (1.2 equiv.) as a protecting group.



Reaction time: 24 h; 81% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Colorless Liquid

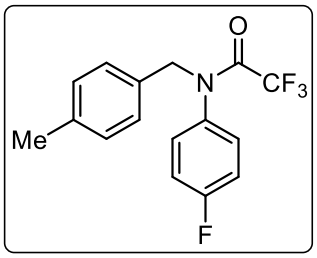
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 – 7.11 (m, 4H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.84 (s, 2H), 3.77 (d, *J* = 1.6 Hz, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 156.9 (q, *J* = 34.9 Hz), 137.6, 132.3, 131.1, 129.6, 129.1 (d, *J* = 1.6 Hz), 116.5 (q, *J* = 286.8 Hz), 114.0, 55.1, 21.0.

HRMS (ESI) *m/z* calcd for $C_{17}H_{16}F_3NO_2$ $[M+H]^+$ 324.1217, found 324.1211.

2,2,2-trifluoro-N-(4-fluorophenyl)-N-(4-methylbenzyl)acetamide:

2,2,2-trifluoro-*N*-(4-fluorophenyl)-*N*-(4-methylbenzyl) acetamide was prepared by following the general procedure **3.5.3**. Here, we used 4-fluoroaniline as a starting material. In this case, we used 4-methylbenzyl bromide (1.2 equiv.) as a protecting group.



Reaction time: 24 h; 84% isolated yield, (eluent: 15% ethyl acetate in hexane)

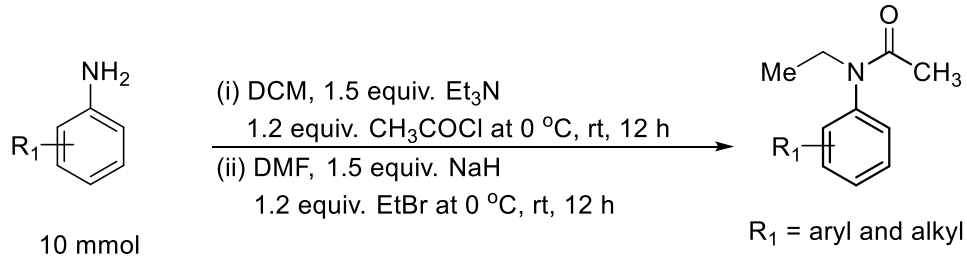
Properties: Colorless Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.0 Hz, 2H), 6.94 – 7.05 (m, 6H), 4.84 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, *J* = 248.1 Hz), 156.9 (q, *J* = 35.1 Hz), 138.1, 134.5, 132.0, 130.6 (d, *J* = 8.9 Hz), 129.4, 129.2, 116.4 (q, *J* = 286.9 Hz), 116.1 (d, *J* = 22.8 Hz), 55.2, 21.1.

HRMS (ESI) *m/z*calcd for $C_{16}H_{13}F_4NO$ $[M+H]^+$ 312.1012, found 312.1010.

3.5.4 General Procedure for the Synthesis of Substituted N-ethyl-N-phenylacetamide:



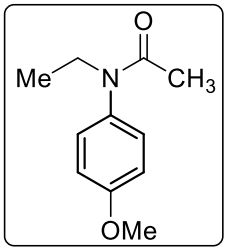
Step-I: In a 100 mL round-bottom flask, corresponding aniline (1.23 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 °C and stirred for 15 minutes. Then, CH_3COCl (856.25 μL, 1.2 equiv.) was added

dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding *N*-$COCH_3$ protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and NaH (360 mg, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC after that reaction mixture warmed to room temperature and stirred for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel afforded corresponding substituted N-ethyl-N-phenylacetamide.

N-ethyl-N-(4-methoxyphenyl)acetamide:

N-ethyl-N-(4-methoxyphenyl) acetamide was prepared following the general procedure **3.5.4**. Here, we used 4-methoxyaniline as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: White Solid

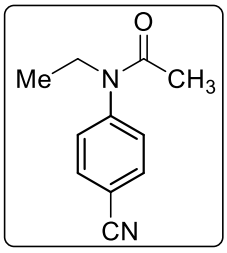
^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.69 (d, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.08 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 158.9, 135.6, 129.2, 114.7, 55.4, 43.8, 22.7, 13.0.

HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO_2$ $[M+Na]^+$ 216.1000, found 216.0995.

N-(4-cyanophenyl)-N-ethylacetamide:

N-(4-cyanophenyl)-*N*-ethylacetamide was prepared by the following general procedure **3.5.4**. Here, we used 4-aminobenzonitrile as a starting material.



Reaction time: 24 h; 83% isolated yield, (eluent: 50% ethyl acetate in hexane)

Properties: White Solid.

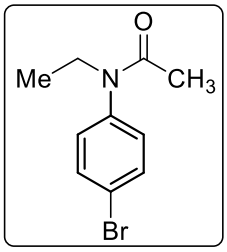
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.89 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 146.9, 133.6, 128.9, 117.9, 111.6, 44.2, 22.8, 13.2.

HRMS (ESI) *m/z*calcd for $C_{11}H_{12}N_2O$ $[M+Na]^+$ 211.0847, found 211.0849.

N-(4-bromophenyl)-N-ethylacetamide:

*N-(*4-bromophenyl)-*N*-ethylacetamide was prepared following the general procedure **3.5.4**. Here, we used 4-bromoaniline as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: White Solid

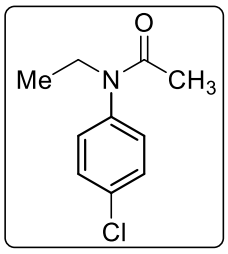
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 3.70 (q, J = 6.8 Hz, 2H), 1.80 (s, 3H), 1.07 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 141.9, 132.8, 129.9, 121.6, 43.7, 22.8, 13.0.

HRMS (ESI) m/z calcd for $C_{10}H_{12}BrNO$ $[M+H]^+$ 242.0181, found 242.0175.

N-(4-chlorophenyl)-N-ethylacetamide:

N-(4-chlorophenyl)-*N*-ethylacetamide was prepared following the general procedure **3.5.4**. Here, we used 4-chloroaniline as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: White Solid

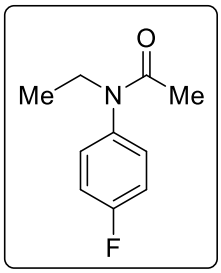
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.68 (q, *J* = 7.2 Hz, 2H), 1.78 (s, 3H), 1.05 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 141.3, 133.6, 129.8, 129.5, 43.7, 29.6, 22.7, 12.9.

HRMS (ESI) *m/z*calcd for $C_{10}H_{12}ClNO$ $[M+H]^+$ 198.0686, found 198.0685.

N-ethyl-N-(4-fluorophenyl)acetamide:

N-ethyl-*N*-(4-fluorophenyl) acetamide was prepared by the following general procedure **3.5.4**. Here, we used 4-fluoroaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 50% ethyl acetate in hexane)

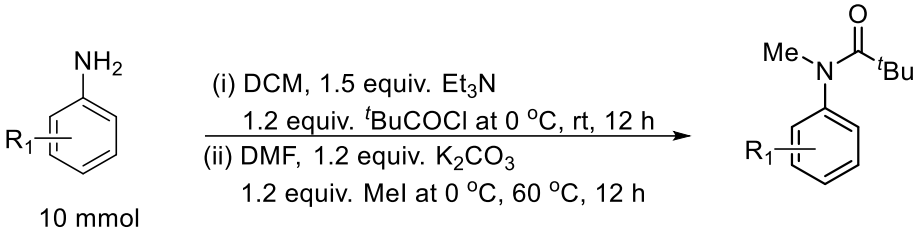
Properties: White Solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 –7.08 (m, 4H), 3.62 (q, *J* = 7.2 Hz, 2H), 1.71 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 161.5 (d, *J* = 246.3 Hz), 138.7 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 8.6 Hz), 116.3 (d, *J* = 22.5 Hz), 43.6, 22.5, 12.7.

HRMS (ESI) *m/z*calcd for $C_{10}H_{12}FNO$ $[M+H]^+$ 182.0981, found 182.0978

3.5.5 General Procedure for the Synthesis of Substituted N-ethyl-N-phenylpivalamide



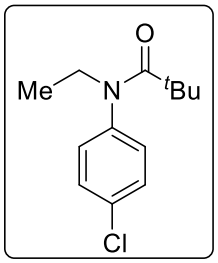
Step-I: In a 100 mL round-bottom flask, the corresponding aniline (10 mmol), 20 mL dry DCM and Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^{o}C and stir for 15 minute. Then, ^{t}BuCOCl (1.47 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-CO^{t}Bu protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture cooled to 0 ^{o}C and stir for 5 minute. Then MeI (747.0 µL, 1.2 equiv.) was added at 0 ^{o}C after that reaction mixture warmed to room temperature and reflux it at 60 ^{o}C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated

under reduced pressure and chromatographic separation with silica gel afforded corresponding substituted N-ethyl-N-phenylpivalamide.

N-(4-chlorophenyl)-N-methylpivalamide :

N-(4-chlorophenyl)-*N*-methylpivalamide was prepared by following general procedure **3.5.5**. Here, we used 4-chloroaniline as a starting material.



Reaction time: 24 h; 83% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: Colourless liquid.

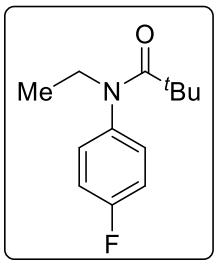
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 3.18 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 143.9, 133.5, 130.1, 129.5, 41.3, 40.8, 29.4.

HRMS (ESI) *m/*zcalcd for $C_{12}H_{16}ClNO$ $[M+Na]^+$ 248.0818, found 248.0822.

N-ethyl-N-(4-fluorophenyl)pivalamide:

N-ethyl-*N*-(4-fluorophenyl)pivalamide was prepared by the following general procedure **3.5.5**. Here, we used 4-fluoroaniline as a starting material.



Reaction time: 24 h; 83% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: Colourless liquid.

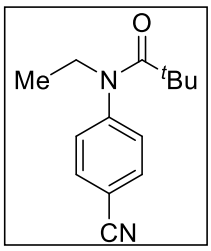
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.16 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 2H), 3.13 (s, 3H), 0.99 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 161.5 (d, *J* = 246.5 Hz), 141.1 (d, *J* = 3.4 Hz), 130.3 (d, *J* = 8.5 Hz), 116.0 (d, *J* = 22.5 Hz), 41.2, 40.6, 29.3.

HRMS (ESI) *m/*zcalcd for $C_{12}H_{16}FNO$ $[M+Na]^+$ 232.1114, found 232.1114.

N-(4-cyanophenyl)-N-methylpivalamide:

N-(4-cyanophenyl)-*N*-methylpivalamide was prepared by the following general procedure **3.5.5**. Here, we used 4-aminobenzonitrile as a starting material.



Reaction time: 24 h; 90% isolated yield, (eluent: 5% ethyl acetate in hexane)

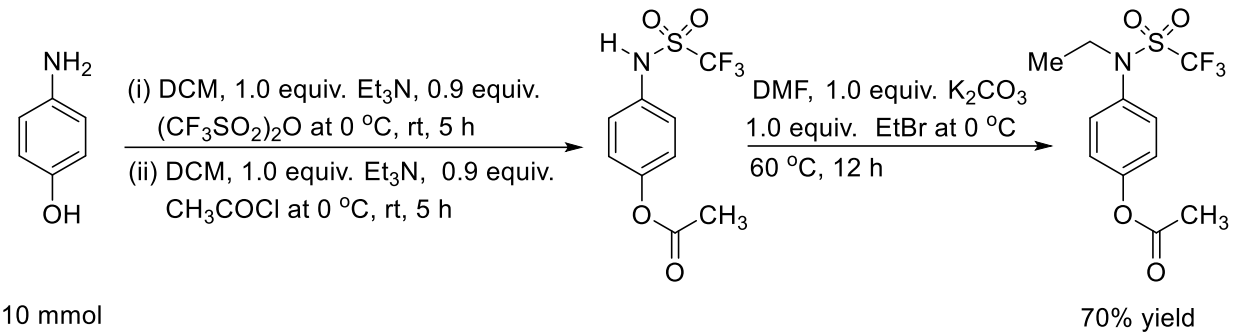
Properties: Colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 3.65 (s, 3H), 1.08 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 152.8, 132.8, 120.7, 119.7, 104.3, 54.1, 40.6, 29.3.

HRMS (ESI) *m/z*calcd for $C_{13}H_{16}N_2O$ $[M+H]^+$ 217.1341, found 217.1339.

Synthesis of 4-((N-ethyl-1,1,1-trifluoromethyl)sulfonamido)phenyl acetate:



10 mmol

70% yield

Step-I: In a 100 mL round-bottom flask, 4-aminophenol (1.10 g, 10 mmol), 20 mL dry DCM and dry Et_3N (1.40 mL, 1.0 equiv.) added. The reaction mixture cooled to 0 °C and stirred for 15 minutes. Then, $(CF_3SO_2)_2O$ (1.5 mL, 0.9 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 5 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected aniline quantitatively which was used directly without further purification for the next step.

Step-II: In a 100 mL round-bottom flask charge with crude reaction mixture (10 mmol), 20 mL dry DCM and dry Et_3N (1.4 mL, 1.0 equiv.) added. The reaction mixture cooled to 0 °C and stirred for 15 minutes. Then, CH_3COCl (642.2 µL, 0.9 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 5 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-$COCH_3$ protected aniline quantitatively which was used directly without further purification for the next step.

Step-III: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.38 g, 1.0 equiv.) added. The reaction mixture cooled to 0 °C and stirred for 5 minutes. Then EtBr (741.5 µL, 1.0 equiv.) was added at 0 °C. After that reaction mixture warmed to room temperature and reflux it at 60 °C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and

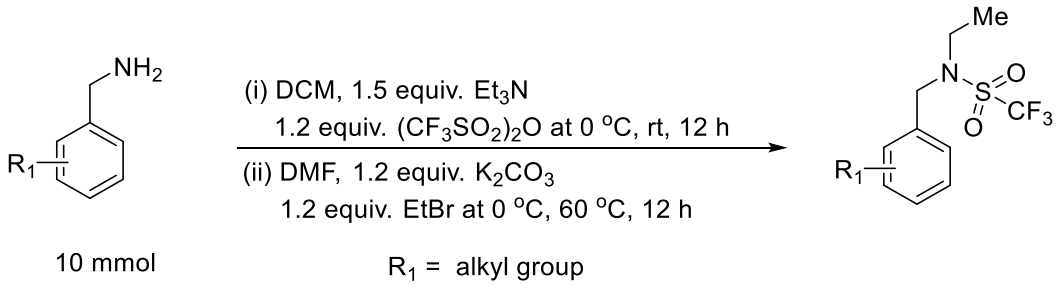
extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (10% ethyl acetate in hexane as eluent) gave 2.20 g (70%) of 4-((*N*-ethyl-1,1,1-trifluoromethyl)sulfonamido)phenyl acetate as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 3.83 (d, *J* = 6.8 Hz, 2H), 2.32 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 133.9, 130.4, 122.7, 48.9, 21.1, 14.3.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}F_3NO_4S$ $[M+Na]^+$ 334.337, found 334.336.

3.5.6 General Procedure for the Synthesis of Substituted N-ethyl-N-((ethyl(phenyl)amino) methyl)-1,1,1-trifluoromethanesulfonamide:



10 mmol

R_1 = alkyl group

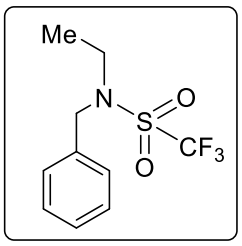
Step-I: In a 100 mL round-bottom flask corresponding benzyl amine (10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 °C and stirred for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected benzyl amine quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) added. The reaction mixture cooled to 0 °C and stirred for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 °C. After that reaction mixture warmed to room temperature and heated it at 60 °C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract

was concentrated under reduced pressure and chromatographic separation with silica gel gave of substituted *N*-ethyl-*N*-((ethyl(phenyl)amino)methyl)-1,1,1-trifluoromethanesulfonamide.

N-benzyl-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-ethyl-N N-benzyl-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by the following procedure **3.5.5**. Here, we used benzyl amine as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

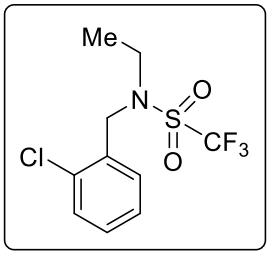
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.42 (m, 5H), 4.56 (bs, 2H), 3.38 (s, 2H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.3, 128.9, 128.5, 128.3, 120.1 (q, *J* = 320.5 Hz), 51.0, 42.7, 13.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}F_3NO_2S$ $[M+H]^+$ 268.0619, found 268.0615.

N-(2-chlorobenzyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(2-chlorobenzyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.6**. Here, we used 2-chloro benzyl amine as a starting material.



Reaction time: 24 h; 81% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

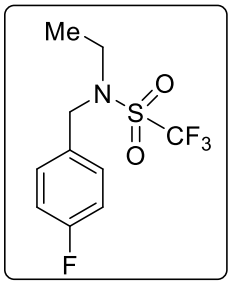
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.0, 2.0 Hz, 1H), 7.39 (dd, J = 7.6, 1.6 Hz, 1H), 7.27 – 7.41 (m, 2H), 4.71 (s, 2H), 3.43 (s, 2H), 1.16 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 132.2, 129.7, 129.7, 129.6, 127.5, 120.0 (q, J = 321.1 Hz), 48.0, 43.6, 13.4.

HRMS (ESI) *m/z* calcd for $C_{10}H_{11}ClF_3NO_2S$ $(M+H)^+$ 302.0223 found 302.0229.

N-ethyl-1,1,1-trifluoro-N-(4-fluorobenzyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-fluorobenzyl) methane sulfonamide was prepared by following the general procedure **3.5.6**. Here, we used 4-fluoro benzyl amine as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

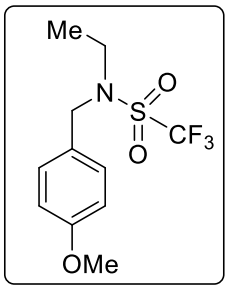
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.36 (m, 2H), 7.05-7.09 (m, 2H), 4.47 (bs, 2H), 3.36 (s, 2H), 1.12 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, J = 246 Hz), 130.2 (d, J = 5.9 Hz), 130.2 (d, J = 8.3 Hz), 120.0 (q, J = 321.1 Hz), 115.9 (d, J = 21.6 Hz), 67.9, 50.4, 42.7, 25.6, 13.1.

HRMS (ESI) *m/z* calcd for $C_{10}H_{11}F_4NO_2S$ $(M+H)^+$ 286.0525 found 286.0520.

N-ethyl-1,1,1-trifluoro-N-(4-methoxybenzyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(4-methoxybenzyl)methanesulfonamide was prepared by following the general procedure **3.5.6**. Here, we used 4-methoxybenzyl amine as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

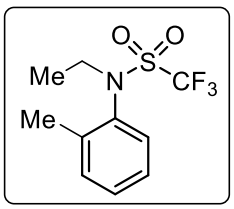
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.50 (s, 2H), 3.80 (s, 3H), 3.33 (s, 2H), 1.10 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 129.8, 126.1, 120.0 (q, J = 320.9 Hz), 114.2, 55.2, 50.5, 42.3, 13.1.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}F_3NO_3S$ $(M+K)^+$ 336.0284 found 336.0282.

N-ethyl-1,1,1-trifluoro-N-(o-tolyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(o-tolyl)methanesulfonamide was prepared following the using general procedure **3.5.1**. Here, we used *o*-toluidine as a starting material.



Reaction time: 24 h; 85% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

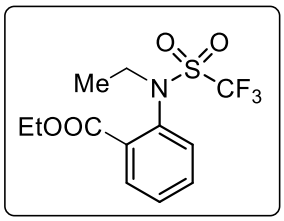
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.33 (m, 2H), 7.23 – 7.28 (m, 2H), 3.76-3.87 (m, 2H), 2.42 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.6, 135.5, 131.7, 129.6, 129.4, 126.9, 123.4 (q, J = 322.1 Hz), 48.6, 18.1, 13.7.

HRMS (ESI) *m/z*calcd for $C_{10}H_{12}F_3NO_2S$ $[M+H]^+$ 268.0619, found 268.0614.

ethyl 2-((N-ethyl-1,1,1-trifluoromethyl)sulfonamido)benzoate:

ethyl 2-((N-ethyl-1,1,1-trifluoromethyl)sulfonamide)benzoate was prepared by following general procedure **3.5.1**. Here, we used ethyl 2-aminobenzoate as a starting material.



Reaction time: 24 h; 89% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

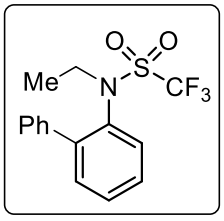
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.37 – 4.43 (m, 2H), 3.98 – 4.05 (m, 1H), 3.80 – 3.87 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 136.0, 132.8, 132.2, 131.4, 129.4, 123.2 (q, *J* = 321.2 Hz), 61.8, 49.0, 14.0, 13.8.

HRMS (ESI) *m/z*calcd for $C_{12}H_{14}F_3NO_4S$ $[M+Na]^+$ 348.0493, found 348.0493.

N-([1,1'-biphenyl]-2-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-([1,1'-biphenyl]-2-yl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the using general procedure **3.5.1**. Here, we used ethyl 2-phenylaniline as a starting material.



Reaction time: 24 h; 87% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

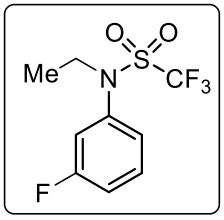
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.49 (m, 8H), 7.34 (d, *J* = 7.6 Hz, 1H), 3.59 (s, 1H), 3.01 (s, 1H), 0.96 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 138.3, 134.1, 132.1, 130.3, 129.4, 129.0, 128.5, 128.4, 128.0, 119.9 (d, *J* = 321.5 Hz), 47.2, 13.2.

HRMS (ESI) *m/z*calcd for $C_{15}H_{14}F_3NO_2S$ $[M+H]^+$ 330.0776, found 330.0775.

N-ethyl-1,1,1-trifluoro-N-(3-fluorophenyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(3-fluorophenyl)methane sulfonamide was prepared by following the using general procedure **3.5.1**. Here, we used ethyl 2-fluoroaniline as a starting material.



Reaction time: 24 h; 82% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

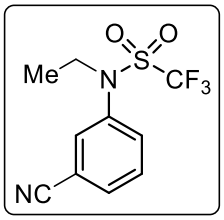
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 14.8, 8.0 Hz, 1H), 7.11-7.15 (m, 2H), 7.07 (d, *J* = 9.2 Hz, 1H), 3.85-7.86 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, J = 247.9 Hz), 137.89 (d, *J* = 9.5 Hz), 130.63 (d, *J* = 8.9 Hz), 125.0 (d, *J* = 3.2 Hz), 123.5 (q, *J* = 321.9 Hz), 116.8 (d, *J* = 22.8 Hz), 116.5 (d, *J* = 20.7 Hz), 48.7, 14.2.

HRMS (ESI) *m/z*calcd for $C_9H_9F_4NO_2S$ $[M+H]^+$ 272.0368, found 272.0365.

N-(3-cyanophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(3-cyanophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide was prepared following the using general procedure **3.5.1**. Here, we used 3-aminobenzonitrile as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: White Solid

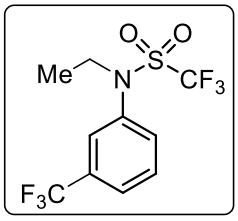
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.72 (m, 1H), 7.63 (s, 1H), 7.58-7.59 (m, 2H), 3.87-3.89 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 133.8, 132.7, 132.6, 130.7, 120.1 (q, *J* = 321.6 Hz), 117.2, 114.0, 48.7, 14.2.

HRMS (ESI) *m/z* calcd for $C_{10}H_9F_3N_2O_2S$ $[M+H]^+$ 279.0415, found 279.0409.

N-ethyl-1,1,1-trifluoro-N-(3-(trifluoromethyl)phenyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(3-(trifluoromethyl) phenyl) methanesulfonamide was prepared by following the using general procedure **3.5.1**. Here, we used 3-(trifluoromethyl)aniline as a starting material.



Reaction time: 24 h; 84% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: White Solid

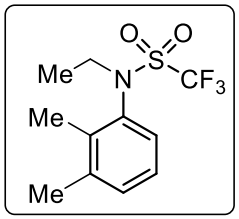
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.61 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 3.89 (d, *J* = 5.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 132.8, 132.3 (d, *J* = 33 Hz), 130.3, 130.3, 126.1(q, *J* = 3.6 Hz), 122.1 (d, *J* = 591.7 Hz), 121.5 (d, *J* = 270.9 Hz), 48.8, 14.2.

HRMS (ESI) *m/z*calcd for C10H9F6NO2S $[M+H]^+$ 322.0336, found 322.0331.

N-(2,3-dimethylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(2,3-dimethylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 2,3-dimethylaniline as a starting material.



Reaction time: 24 h; 93% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: White Solid

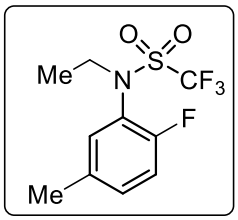
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.33 (m, 3H), 3.86-3.97 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 137.2, 135.3, 130.8, 127.0, 126.1, 120.2 (q, *J* = 322.1 Hz), 48.8, 20.4, 14.9, 13.6.

HRMS (ESI) *m/*zcalcd for $C_{11}H_{14}F_3NO_2S$ $[M+NH_4]^+$ 299.1041, found 299.1045

N-ethyl-1,1,1-trifluoro-N-(2-fluoro-5-methylphenyl)methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(2-fluoro-5-methylphenyl)methanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 2-fluoro-5-methylaniline as a starting material.



Reaction time: 24 h; 89% isolated yield, (eluent: 5% ethyl acetate in hexane)

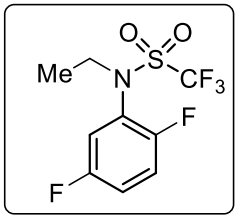
Properties: White Solid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.21 (m, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.06 (t, *J* = 9.6 Hz, 1H), 3.82 (q, *J* = 6.0 Hz, 2H), 2.34 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4 (d, J = 248.6 Hz), 156.12, 134.7 (d, *J* = 3.9 Hz), 132.4, 131.8 (d, *J* = 5.6 Hz), 123.4 (d, *J* = 12.7 Hz), 123.3 (q, *J* = 321.4 Hz), 116.4 (d, *J* = 20.0 Hz), 48.2, 20.4, 14.1

N-(2,5-difluorophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(2,5-difluorophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 2,5-difluoroaniline as a starting material.



Reaction time: 24 h; 71% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Colorless Liquid

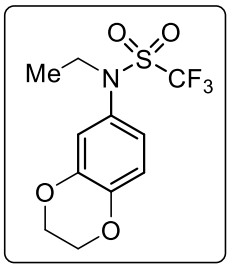
^{1}H NMR (400 MHz, $CDCl_3$): δ .21 – 7.14 (m, 2H), 7.12 – 7.08 (m, 1H), 3.83 (d, J = 5.6 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0 (dd, J = 2.6, 244.6 Hz), 155.7 (dd, J = 3.2, 247.5 Hz), 124.6 (dd, J = 10.3, 14.8 Hz), 119.9 (q, J = 320.8 Hz), 119.1 (d, J = 24.4 Hz), 118.2 (dd, J = 8.3, 23.7 Hz), 117.6 (dd, J = 9.2, 22.9 Hz), 48.2 (d, J = 2.2 Hz), 14.1.

HRMS (ESI) *m/z*calcd for $C_9H_8F_5NO_2S$ $(M+H)^+$ 290.0274 found 290.0276.

N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine as a starting material.



Reaction time: 24 h; 86% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: White Solid

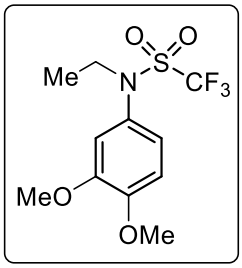
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.27 (s, 4H), 3.75-3.80 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 143.7, 129.4, 123.6 (q, *J* = 322.0 Hz), 122.4, 118.4, 117.7, 64.3, 64.2, 48.8, 14.2.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}F_3NO_4S$ $[M+Na]^+$ 334.0337, found 334.0328.

N-(3,4-dimethoxyphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(3,4-dimethoxyphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 3,4-dimethoxyaniline as a starting material.



Reaction time: 24 h; 82% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: White Solid

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 – 6.90 (m, 2H), 6.77-6.78 (m, 1H), 3.85-3.90 (m, 6H), 3.79 – 3.82 (m, 2H), 1.13-1.21 (m, 3H).

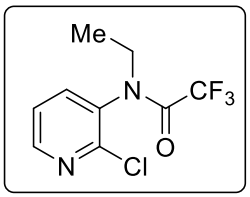
^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 149.4, 129.1, 121.7, 120.4 (q, *J* = 322.3 Hz), 112.7, 111.1, 56.1, 56.0, 48.8, 14.3.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}F_3NO_4S$ $[M+H]^+$ 314.0674, found 314.0670.

N-(2-chloropyridin-3-yl)-N-ethyl-2,2,2-trifluoroacetamide:

N-(2-chloropyridin-3-yl)-*N*-ethyl-2,2,2-trifluoroacetamide was prepared by following the general procedure **3.5.1**. Here, we used 2-chloropyridin-3-amine as a starting material.

Reaction time: 24 h; 76% isolated yield, (eluent: 35% ethyl acetate in hexane)



Properties: colourless liquid

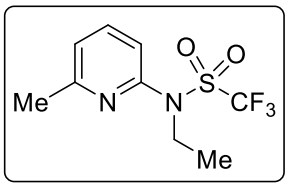
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.33-7.36 (m, 1H), 4.20 – 4.30 (m, 1H), 3.24-3.32 (m, 1H), 1.13-1.17 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.11 (q, *J* = 36.7 Hz), 150.0, 139.5, 138.8, 132.9, 122.8, 115.8 (q, *J* = 286.7 Hz), 45.1, 11.9.

HRMS (ESI) *m/z*calcd for $C_9H_8ClF_3N_2O$ $[M+H]^+$ 253.0356, found 253.0350.

N-ethyl-1,1,1-trifluoro-N-(6-methylpyridin-2-yl) methanesulfonamide

N-ethyl-1,1,1-trifluoro-*N*-(6-methylpyridin-2-yl) methane sulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 6-methylpyridin-2-amine as a starting material.



Reaction time: 24 h; 72% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: colourless liquid

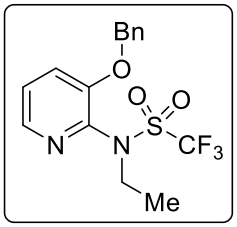
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.52 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 149.0, 138.3, 122.7, 120.1 (q, *J* = 322.4 Hz), 119.6, 45.9, 24.1, 14.3.

HRMS (ESI) *m/z*calcd for $C_9H_{11}F_3N_2O_2S$ $[M+H]^+$ 269.0572, found 269.0565.

N-(3-(benzyloxy) pyridin-2-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

N-(3-(benzyloxy) pyridin-2-yl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 3-(benzyloxy) pyridin-2-amine as a starting material.



Reaction time: 24 h; 68% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: colourless liquid

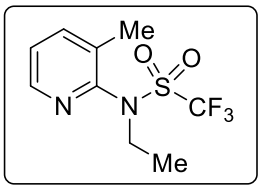
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 4.4 Hz, 1H), 7.28 – 7.46 (m, 7H), 5.17 (s, 2H), 3.91 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 140.6, 139.5, 135.4, 128.7, 128.3, 127.1, 121.7, 120.2 (q, *J* = 402.3 Hz), 70.7, 46.9, 14.0.

HRMS (ESI) *m/z*calcd for $C_{15}H_{15}F_3N_2O_3S$ $[M+H]^+$ 361.0834, found 361.0840.

N-ethyl-1,1,1-trifluoro-N-(3-methylpyridin-2-yl) methanesulfonamide:

N-ethyl-1,1,1-trifluoro-*N*-(3-methylpyridin-2-yl) methanesulfonamide was prepared by following the general procedure **3.5.1**. Here, we used 3-methylpyridin-2-amine as a starting material.



Reaction time: 24 h; 79% isolated yield, (eluent: 40% ethyl acetate in hexane)

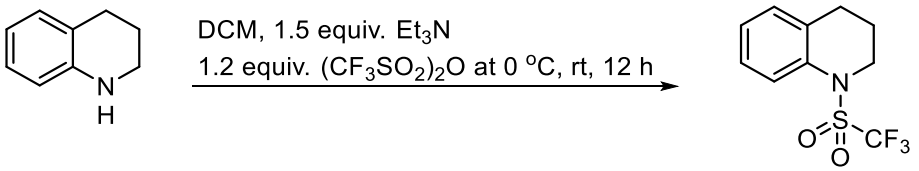
Properties: colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 4.1 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 147.2, 140.3, 134.4, 124.4, 120.1 (q, *J* = 322.8 Hz), 47.3, 18.0, 13.6.

HRMS (ESI) *m/z*calcd for $C_9H_{11}F_3N_2O_2S$ $[M+H]^+$ 269.0572, found 269.0566

Synthesis of 1-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroquinoline:



10 mmol

83% yield

In a 100 mL round-bottom flask 1,2,3,4-tetrahydroquinoline (1.33 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minute. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4.

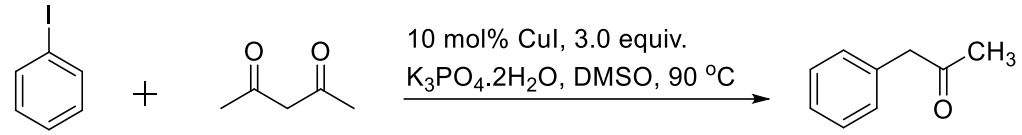
Solvent evaporated under reduced pressure and chromatographic separation with silica gel (10% ethyl acetate in hexane as eluent) gave 2.20 g (83%) of 1-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroquinoline (**6a-IX**) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.23 (m, 3H), 3.88 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 2.09 – 2.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 130.9, 129.5, 126.7, 126.1, 123.3 (d, *J* = 1.2 Hz), 120.0 (q, *J* = 322.1 Hz), 47.9, 26.1, 23.3.

HRMS (ESI) *m/z*calcd for $C_{10}H_{10}F_3NO_2S$ $[M+H]^+$ 266.0463, found 266.0459.

Synthesis of 1-phenylpropan-2-one:



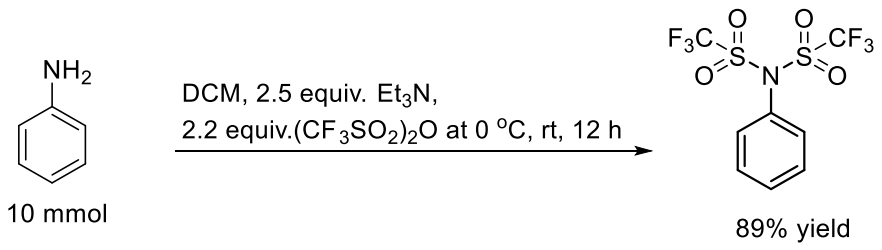
A mixture of iodobenzene (1.0 mmol), acetylacetone (3.0 mmol), CuI (10 mol %), and K_3PO_4. $3H_2O$ (3.0 mmol) in DMSO (3 mL) was stirred in N_2 at 90 °C. After completion (check by TLC), the reaction mixture was quenched with diluted hydrochloride (2 mL, 2M), the solution was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane as eluent) gave 98.0 mg (73%) of 1-phenylpropan-2-one as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 2H), 3.70 (s, 2H), 2.16 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$: δ 206.4, 134.1, 129.3, 128.6, 126.9, 50.9, 29.1.

HRMS (ESI) *m/z* calcd for $C_9H_{10}O$ $[M+H]^+$ 135.0810, found 135.0805.

Synthesis of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl) methane sulfonamide:



In a 100 mL round-bottom flask aniline (930 mg, 10 mmol), 20 mL dry DCM and Et_3N (3.50 mL, 2.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minute. Then, $(CF_3SO_2)_2O$ (3.70 mL, 2.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure extract concentrated under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as eluent) gave 3.2 g (89%) of 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide as white solid.

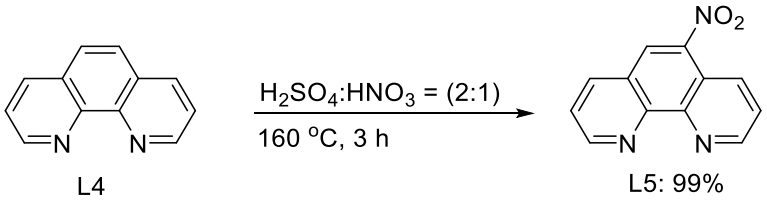
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$: δ 132.1, 132.0, 131.0, 129.9, 119.4 (q, *J* = 323.2 Hz).

HRMS (ESI) *m/z* calcd for $C_8H_5F_6NO_4S_2$ $[M+H]^+$ 357.9642, found 357.9645.

3.5.7 Synthesis of Ligands (L5 and L7):

3.5.7.1 Synthesis of 5-nitro-1, 10-phenanthroline (L5):



L4 L5: 99%

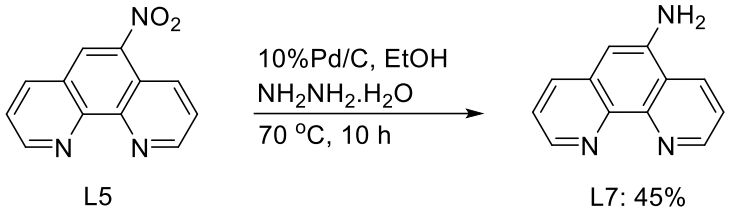
To a stirred solution of 1,10-Phenanthroline (5 g, 27.8 mmol) in concentrated sulfuric acid (30 mL), fuming nitric acid (15 mL) was added dropwise at 160 °C. The reaction mixture was kept at 160 °C for three hours, and subsequently poured into ice water. Then the saturated aqueous NaOH was added to this solution to adjust the pH = 3, and yellow solid precipitated. The precipitate of 5-nitro-1, 10-phenanthroline was filtered off, washed with water and dried in vacuum gave 6.2 g (99 %) of 5-nitro-1, 10-phenanthroline (**L5**) as yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.35 (d, *J* = 4.0 Hz, 1H), 9.30 (d, *J* = 4.0 Hz, 1H), 9.03 (d, *J* = 8.8 Hz, 1H), 8.69 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.77-7.84 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$: δ 153.6, 151.5, 147.7, 146.2, 144.3, 137.9, 132.5, 125.5, 125.5, 124.4, 124.3, 121.0.

HRMS (ESI) *m/z* calcd for $C_{12}H_7N_3O_2$ $[M+Na]^+$ 248.0436, found 248.0443.

3.5.7.2 Synthesis of 5-amino-1, 10-phenanthroline (L7):



5-Nitro-1,10-phenanthroline (5 g, 22.2 mmol) was dissolved in 100 mL of absolute ethanol, then 10% Pd/C (1.0 g) catalyst was added. The reaction mixture was purged with argon, and hydrazine monohydrate (13 mL, 26.7 mmol) was added dropwise over a period of 30 minutes. After the addition was complete, the mixture was stirred at 70 °C for 10 h. At the end of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. Then the precipitate was filtered and dried under vacuum gave 1.95 g (45%) of 5-amino-1, 10-phenanthroline (**L7**) as a yellow solid.

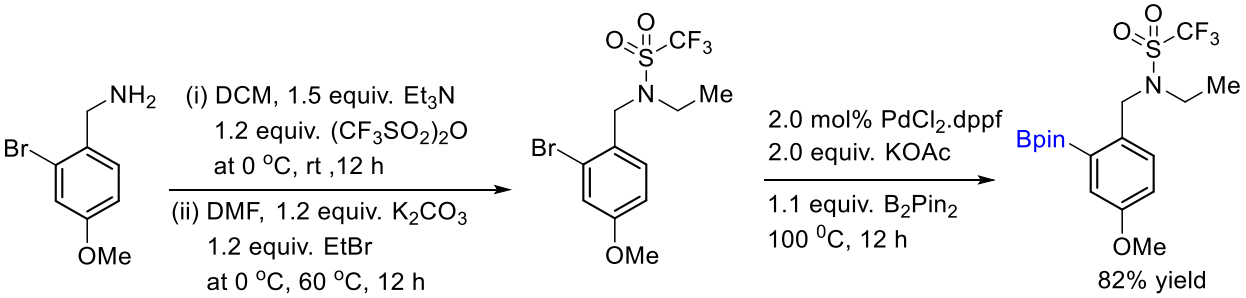
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.16 (d, *J* = 4.0 Hz, 1H), 8.91 (d, *J* = 4.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.46 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.88 (s, 1H), 4.04 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$: δ 150.0, 147.0, 146.7, 142.3, 139.9, 133.4, 129.8, 129.4, 123.2, 122.2, 122.1, 105.5.

HRMS (ESI) *m/z* calcd for $C_{12}H_9N_3$ $[M+Na]^+$ 218.0694, found 218.0699.

3.5.8 Preparation of Authentic Borylated Compound:

Preparation of ortho-borylated product of N-ethyl-1,1,1-trifluoro-N-phenylmethanesulfonamide



Step-I: In a 100 mL round-bottom flask (2-bromo-4-methoxyphenyl)methanamine (2.16 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 °C and stirred for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with

DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford corresponding *N*-SO_2CF_3 protected benzylamine quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 5 minutes. Then EtBr (889.6 µL, 1.2 equiv.) was added at 0 ^oC. After that reaction mixture was warmed to room temperature and heated it at 60 ^oC temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and passes through a short pad of silica gel (15% EtOAc in hexane as eluent) gave crude metarial of *N*-(2-bromo-4-methoxybenzyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide as a colorless liquid.

Step-III: In an argon-filled glovebox, a 15 mL pressure tube was charged with $PdCl_2$•dppf (29.3 mg, 2.0 mol%), KOAc (392 mg, 2.0 equiv.), B_2pin_2 (558.8 mg, 1.1 equiv.), crude *N*-(2-bromo-4-methoxybenzyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide (752 mg, 2.0 mmol) and dry THF (5.0 mL). The pressure tube was placed into a preheated silicon oil bath and heated at 100 °C for 12 h. After completion (monitored by GC/MS), the reaction mixture was cooled to room temperature and filtered through a short pad of celite and evaporated under reduced pressure to afford the crude product. Chromatographic separation with silica gel (20% ethyl acetate in hexane as eluent) gave 693.7 mg (82%) 2-borylated- *N*-(2-bromo-4-methoxybenzyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide as gummy liquid.

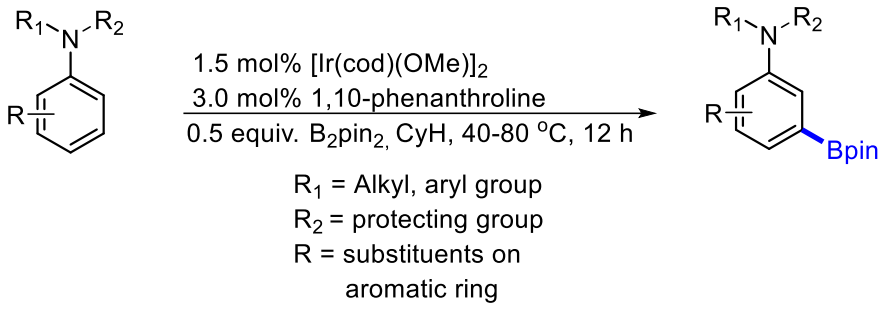
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.85 (s, 2H), 3.84 (s, 3H), 3.33 (s, 2H), 1.35 (s, 12H), 1.07 (t, *J* = 7.2 Hz,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 133.2, 130.3, 120.3, 117.9, 84.1, 55.3, 49.0, 42.8, 24.8,13.7.

^{11}BNMR(128MHz,$CDCl_3$):δ31.3.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_5S$ [M+H]+ 424.1577, found 424.1565.

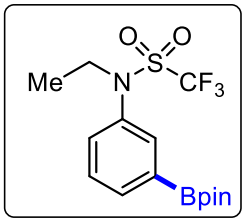
3.5.9 General Procedure for Meta Borylation of N-protected Aniline



In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected aniline (0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40-80 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure and chromatographic separation with silica gel gave corresponding *meta*-borylated product.

Meta Borylation of N-ethyl-1,1,1-trifluoro-N-phenylmethanesulfonamide:

Meta borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12h; 96% isolated yield, (eluent:10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 4.8 Hz, 1H), 7.59 (s, 1H), 7.26 (s, 2H), 3.71 (s, 2H), 1.20 (s, 12H), 1.02 (s, 3H).

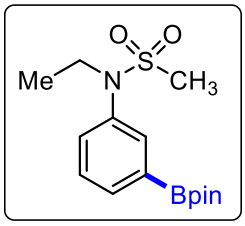
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 135.5, 135.0, 132.0, 128.9, 120.3 (q, *J* = 322.1 Hz), 84.2, 48.6, 24.7, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BF_3NO_4S$ $[M+H]^+$ 380.1315, found 380.1309.

Meta-borylation of N-ethyl-N-phenylmethanesulfonamide:

Meta borylated product of *N*-ethyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 94% isolated yield, (eluent: 25% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.2 Hz, 1H), 7.70 (s, 1H), 7.39 – 7.47 (m, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 2.90 (s, 3H), 1.34 (s, 12H), 1.13 (t, *J* = 7.2 Hz, 3H).

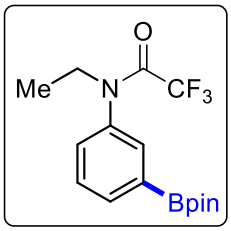
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 134.5, 133.7, 132.6, 128.9, 84.1, 45.8, 37.5, 24.9, 14.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{15}H_{24}BNO_4S$ $[M+H]^+$ 326.1597, found 326.1591.

Meta-borylation of N-ethyl-2,2,2-trifluoro-N-phenylacetamide:

Meta borylated product of *N*-ethyl-2,2,2-trifluoro-*N*-phenylacetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 10.0 Hz, 1H), 3.79 (s, 2H), 1.35 (s, 12H), 1.18 (t, *J* = 7.2 Hz, 3H).

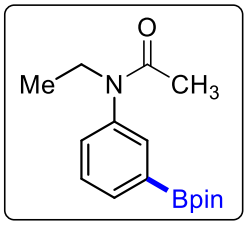
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (q, *J* = 35.1 Hz), 138.5, 135.3, 134.2, 131.1, 128.7, 116.4 (d, *J* = 286.7 Hz), 84.2, 46.9, 24.9, 12.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.1.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}BF_3NO_3$ $[M+H]^+$ 344.1645, found 344.1637.

Meta-borylation of N-ethyl-N-phenylacetamide:

Meta borylated product of *N-ethyl-N-phenylacetamide* was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 90% isolated yield, (eluent: 40% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.55 (s, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 3.71 (q, *J* = 6.8 Hz, 2H), 1.78 (s, 3H), 1.32 (s, 12H), 1.07 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 142.2, 134.0, 133.8, 130.9, 129.0, 84.0, 43.7, 24.7, 22.7, 12.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.0.

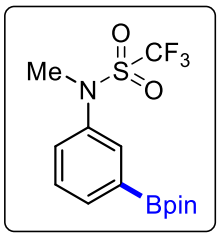
HRMS (ESI) *m/z* calcd for $C_{16}H_{24}BNO_3$ $[M+H]^+$ 290.1927, found 290.1924.

Meta-borylation of 1,1,1-trifluoro-N-methyl-N-phenylmethanesulfonamide:

Meta borylated product of 1,1,1-trifluoro-*N*-methyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.

Reaction time: 12 h; 97% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6.8 Hz, 1H), 7.64 (s, 1H), 7.26 – 7.30 (m, 2H), 3.32 (s, 3H), 1.21 (s, 12H).

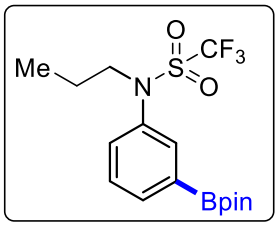
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 135.2, 133.3, 130.3, 129.01 (s), 125.25 (s), 122.0, 120.4 (q, *J* = 322.2 Hz), 84.2, 40.5, 24.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.3.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BF_3NO_4S$ $[M+Na]^+$ 388.0978, found 388.0985.

Meta-borylation of 1,1,1-trifluoro-N-phenyl-N-propylmethanesulfonamide:

Meta-borylated product of 1,1,1-trifluoro-*N*-phenyl-*N*-propylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 98% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.84 (m, 1H), 7.72 (s, 1H), 7.39 – 7.44 (m, 2H), 3.76 (t, *J* = 6.8 Hz, 2H), 1.52 (m, 2H), 1.35 (s, 12H), 0.91 (t, *J* = 7.6 Hz, 3H).

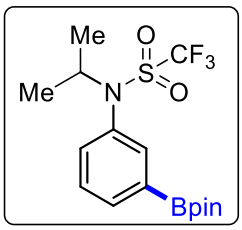
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.4, 134.7, 131.9, 128.9, 120.4 (q, *J* = 322.3 Hz), 84.2, 54.9, 24.8, 21.5, 10.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_4S$ $[M+H]^+$ 394.1471, found 394.1469.

Meta-borylation of 1,1,1-trifluoro-N-isopropyl-N-phenylmethanesulfonamide:

Meta-borylated product of 1,1,1-trifluoro-*N*-isopropyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 96% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.65 (s, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 4.49 – 4.59 (m, 1H), 1.35 (s, 12H), 1.23 (s, 3H), 1.21 (s, 3H).

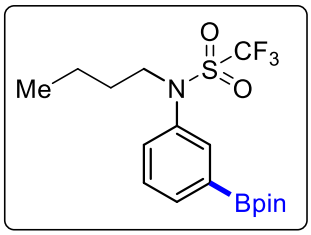
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.0, 134.5, 132.1, 128.5, 120.2 (q, *J* = 321.0 Hz), 84.1, 54.2, 24.8, 22.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.7.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_4S$ $[M+H]^+$ 394.1471, found 394.1465.

Meta-borylation of N-butyl-1,1,1-trifluoro-N-phenylmethanesulfonamide:

Meta-borylated product of *N*-butyl-1,1,1-trifluoro-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 97% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 6.4 Hz, 1H), 7.72 (s, 1H), 7.39-7.45 (m, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 1.43 – 1.51 (m, 2H), 1.35 (s, 12H), 1.26 – 1.33 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H).

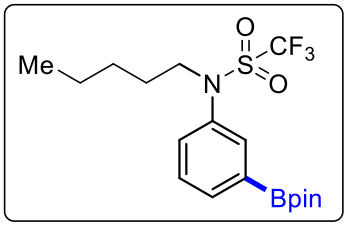
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.4, 134.6, 131.9, 128.9, 120.4 (q, *J* = 322.3 Hz), 84.2, 53.1, 30.3, 24.8, 19.3, 13.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_4S$ $[M+Na]^+$ 430.1447, found 430.1452.

Meta-borylation of 1,1,1-trifluoro-N-pentyl-N-phenylmethanesulfonamide:

Meta-borylated product of 1,1,1-trifluoro-*N*-pentyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 91% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 5.6, 1.2 Hz, 1H), 7.72 (s, 1H), 7.39 – 7.44 (m, 2H), 3.78 (t, *J* = 6.8 Hz, 2H), 1.45-1.52 (m, 2H), 1.35 (s, 12H), 1.26-1.30 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H).

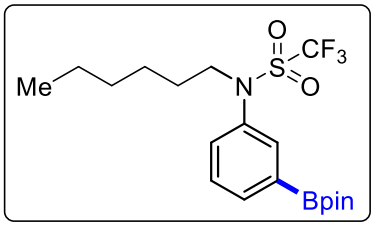
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.4, 134.7, 131.9, 128.9, 120.4 (q, *J* = 323.4 Hz), 84.2, 53.4, 28.1, 27.9, 24.9, 22.1, 13.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.2.

HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BF_3NO_4S$ $[M+H]^+$ 422.1784, found 422.1778.

Meta-borylation of 1,1,1-trifluoro-N-hexyl-N-phenylmethanesulfonamide:

Meta-borylated product of 1,1,1-trifluoro-*N*-hexyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 95% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (t, J = 3.6 Hz, 1H), 7.58 (s, 1H), 7.23 (d, *J* = 4.4 Hz, 2H), 3.62 (s, 2H), 1.27 – 1.35 (m, 2H), 1.16 (s, 12H), 1.06 – 1.13 (m, 6H), 0.68 (t, *J* = 6.4 Hz, 3H).

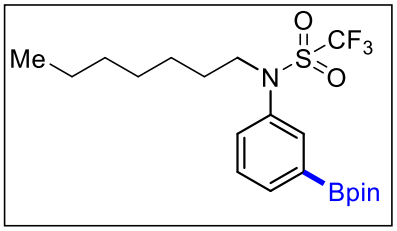
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.3, 134.7, 131.7, 128.8, 120.4 (q, *J* = 322.3 Hz), 84.1, 53.2, 31.0, 28.1, 25.5, 24.7, 22.3, 13.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{19}H_{29}BF_3NO_4S$ $[M+H]^+$ 436.1941, found 436.1940.

Meta-borylation of 1,1,1-trifluoro-N-heptyl-N-phenylmethanesulfonamide:

Meta-borylated product of 1,1,1-trifluoro-*N*-hexyl-*N*-phenylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 92% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 6.4 Hz, 1H), 7.72 (s, 1H), 7.38 – 7.44 (m, 2H), 3.78 (s, 2H), 1.44-1.50 (m, 2H), 1.35 (s, 12H), 1.22-1.28 (m, 8H), 0.85 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.4, 134.7, 131.9, 128.9, 120.5 (q, *J* = 322.6 Hz), 84.2, 53.4, 31.6, 28.6, 28.3, 26.0, 24.8, 22.5, 14.0.

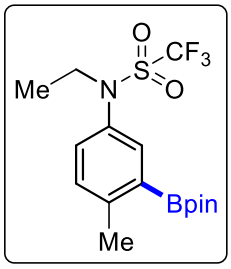
^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{20}H_{31}BF_3NO_4S$ $[M+H]^+$ 450.2097, found 450.2093.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(p-tolyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(p-tolyl)methane sulfonamide was synthesized by following the general procedure **3.5.9**.

Reaction time: 12 h; 89% isolated yield, (eluent: 10% ethyl acetate in hexane)



Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.19 – 7.25 (m, 2H), 3.83 (q, *J* = 6.8 Hz, 2H), 2.55 (s, 3H), 1.34 (s, 12H), 1.17 (t, *J* = 6.8 Hz, 3H).

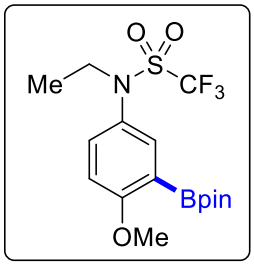
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 136.1, 133.3, 131.4, 131.0, 125.2, 120.3 (q, *J* = 322.0 Hz), 83.8, 48.7, 24.8, 21.9, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.6.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_4S$ $(M+NH_4)^+$ 411.1737, found 411.1736.

Meta-borylation of N-ethy l-1,1,1-trifluoro-N-(4-methoxyphenyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl l-1,1,1-trifluoro-N-(4-methoxyphenyl)methanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 91% isolated yield, (eluent: 10% ethyl acetate in hexane

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 77.56 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.77 – 3.83 (m, 2H), 1.34 (s, 12H), 1.16 (t, *J* = 7.2 Hz, 3H).

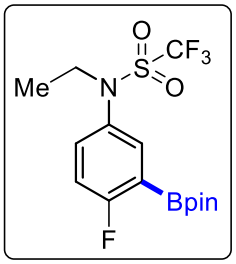
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 137.0, 133.4, 128.5, 120.3 (q, *J* = 322.0 Hz), 111.0, 83.8, 56.0, 48.7, 24.7, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_5S$ $[M+K]^+$ 448.0979, found 448.0968.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-fluorophenyl)methanesulfonamide:

Meta borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-fluorophenyl)methanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.66 (m, 1H), 7.34 – 7.38 (m, 1H), 7.08 (t, *J* = 8.4 Hz, 1H), 3.82 (q, *J* = 6.0 Hz, 2H), 1.35 (s, 12H), 1.17 (t, *J* = 7.2 Hz, 3H).

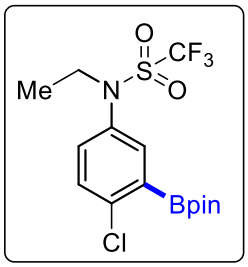
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (d, *J* = 254 Hz), 137.5 (d, *J* = 9.2 Hz), 134.3 (d, *J* = 9.8 Hz), 132.2 (d, *J* = 3.3 Hz), 123.5 (d, *J* = 322 Hz), 116.7 (d, *J* = 25.9 Hz), 84.4, 48.8, 24.8, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.5.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}BF_4NO_4S$ [M+H]+ 398.1220, found 398.1227.

Meta borylation of N-(4-chlorophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta borylated product of *N*-(4-chlorophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 88% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.70 (q, *J* = 6.8 Hz, 2H), 1.24 (s, 12H), 1.03 (t, *J* = 7.2 Hz, 3H).

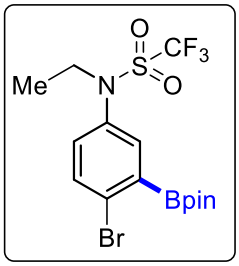
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 136.8, 134.6, 132.4, 130.7, 120.3 (q, *J* = 321.8 Hz), 84.55, 48.7, 24.7, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.6.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}BClF_3NO_4S$ $[M+H]^+$ 414.0926, found 414.0925.

Meta-borylation of N-(4-bromophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-(4-bromophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 90% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.83 (q, *J* = 6.8 Hz, 2H), 1.37 (s, 12H), 1.16 (t, *J* = 6.8 Hz, 3H).

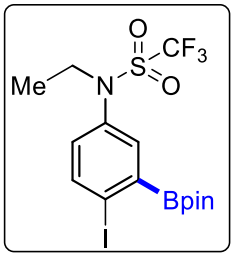
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 135.1, 134.0, 132.4, 128.9, 125.05 (s), 120.2 (q, *J* = 321.7 Hz), 84.7, 48.6, 24.7, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.5.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}BBrF_3NO_4S$ $[M+Na]^+$ 480.0237, found 480.0239.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-iodophenyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-iodophenyl)methanesulfonamide was synthesized by following the general procedure **3.5.9**.



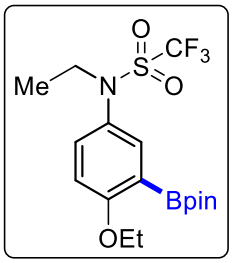
Reaction time: 12 h; Crude NMR was taken which showed 26% conversion of corresponding meta borylated product.

Crude ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (bs, 1H for -OH group), 7.50 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.76 – 3.86 (m, 2H of product CH_2 group merge with starting CH_2 proton), 1.37 (s, 12H), 1.23-1.26 (3H of product CH_3 group merge with boron junk).

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}BF_3INO_4S$ $[M+H]^+$ 506.0281, found 506.0272.

Meta-borylation of N-(4-ethoxyphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-(4-ethoxyphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 80% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 2.8 Hz, 1H), 7.27 (dd, J = 8.8, 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.03 (q, J = 6.8 Hz, 2H), 3.79 (q, J = 6.8 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.34 (s, 12H), 1.15 (t, J = 6.8 Hz, 3H).

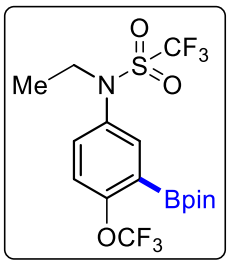
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 136.3, 133.1, 128.5, 120.3 (q, J = 322.1 Hz), 112.2, 83.8, 64.4, 48.7, 24.7, 14.6, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.4.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_5S$ $(M+Na)^+$ 446.1396 found 446.1390.

***Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-(trifluoromethoxy) phenyl) methane sulfonamide**:*

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-(trifluoromethoxy)phenyl) methanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 75% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 3.86 (d, J = 5.6 Hz, 2H), 1.35 (s, 12H), 1.18 (t, J = 7.2 Hz, 3H).

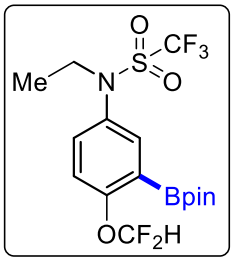
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (d, J = 1.8 Hz), 137.1, 134.9, 133.3, 122.6, 120.2 (dq, J = 104, 321.8 Hz), 84.5, 48.8, 24.7, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.0.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BF_6NO_5S$ $(M+H)^+$ 464.1138 found 464.1130.

Meta-borylation of N-(4-(difluoromethoxy)phenyl)-N-ethyl-1,1,1 trifluoromethanesulfonamide

Meta-borylated product of *N*-(4-(difluoromethoxy)phenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 82% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 2.8 Hz, 1H), 7.38 (dd, J = 8.8, 2.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.54 (t, J = 74.8 Hz, 1H), 3.84 (q, J = 6.8 Hz, 2H), 1.35 (s, 12H), 1.18 (t, J = 7.2 Hz, 3H).

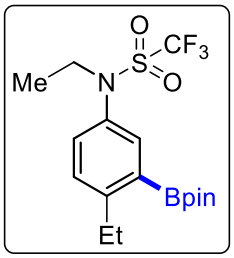
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (t, J = 3.1 Hz), 137.1, 133.9, 133.4, 122.5, 118.74 (d, J = 321.7 Hz), 116.2 (t, J = 259.3 Hz), 84.5, 48.8, 24.7, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}BF_5NO_5S$ $(M+Na)^+$ 468.1056 found 468.1051.

Meta-borylation of N-ethyl-N-(4-ethylphenyl)-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-ethyl-*N*-(4-ethylphenyl)-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 86% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 1.6 Hz, 1H), 7.20-7.26 (m, 2H), 3.81 (q, J = 6.8 Hz, 2H), 2.91 (q, J = 7.2 Hz, 2H), 1.33 (s, 12H), 1.14-1.20 (m, 6H).

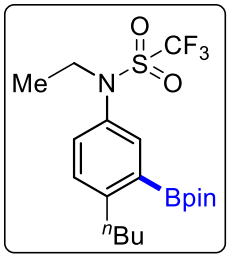
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 136.3, 133.5, 131.6, 129.6, 120.4 (d, J = 322.1 Hz), 83.8, 48.7, 28.4, 24.8, 16.8, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.5.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_4S$ $(M+H)^+$ 408.1628 found 408.1631.

Meta-borylation of N-(4-butylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta borylated product of *N*-(4-butylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 74% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 2.0 Hz, 1H), 7.19-7.26 (m, 2H), 3.83 (q, J = 6.8 Hz, 2H), 2.86 – 2.90 (m, 2H), 1.49-1.54 (m, 2H), 1.34 (s, 12H), 1.23-1.28 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H).

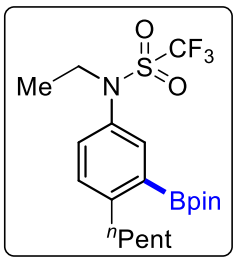
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 136.2, 133.4, 131.4, 130.4, 83.7, 48.7, 35.4, 35.2, 24.8, 22.8, 14.3, 14.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.3.

HRMS (ESI) *m/z* calcd for $C_{19}H_{29}BF_3NO_4S$ (M+H)+ 436.1941 found 436.1945.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-pentylphenyl)methanesulfonamide:

Meta borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-pentylphenyl)methanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 69% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.18 – 7.26 (m, 2H), 3.83 (q, J = 6.4 Hz, 2H), 2.85 – 2.89 (m, 2H), 1.50 – 1.58 (m, 2H), 1.34 (s, 12H), 1.34 (m, 2H), 1.23-1.26 (m, 2H), 1.17 (t, J = 6.8 Hz, 3H), 0.90 (t, J = 6.4 Hz, 3H).

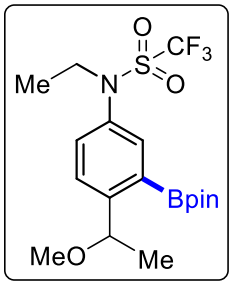
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 136.2, 133.4, 131.4, 130.3, 120.4 (d, J = 322.1 Hz), 83.7, 48.7, 35.5, 32.9, 31.9, 24.8, 22.5, 14.3, 14.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.4.

HRMS (ESI) *m/z* calcd for $C_{20}H_{31}BF_3NO_4S$ $(M+H)^+$ 450.2097 found 450.2100.

Meta Borylation of N-ethyl-1,1,1-trifluoro-N-(4-(1-methoxyethyl)phenyl)methanesulfonamide:

Meta borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-(1-methoxyethyl) phenyl)methanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 91% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 1.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.8, 1.6 Hz, 1H), 4.99 (q, J = 6.8 Hz, 1H), 3.84 (q, J = 5.6 Hz, 2H), 3.24 (s, 3H), 1.39 (d, J = 6.4 Hz, 3H), 1.35 (s, 12H), 1.18 (t, J = 6.8 Hz, 3H).

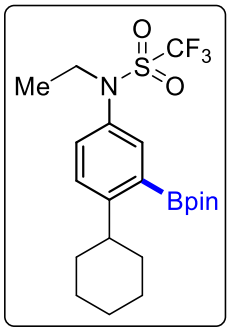
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 135.7, 134.7, 131.8, 126.1, 84.0, 56.7, 48.8, 24.9, 24.8, 24.3, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.9.

HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BF_3NO_5S$ $(M+K)^+$ 476.1292 found 476.1289.

Meta-borylation of N-(4-cyclohexylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta borylated product of *N*-(4-cyclohexylphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 59% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.26-7.31 (m, 2H), 3.82-3.83 (m, 2H), 3.24-3.29 (m, 1H), 1.73-1.85 (m, 6H), 1.37-1.43 (m, 2H), 1.35 (s, 12H), 1.22-1.28 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H).

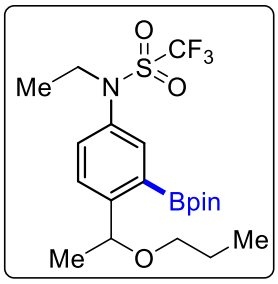
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 135.8, 133.2, 131.5, 126.2, 120.3 (q, J = 322.1 Hz), 83.8, 48.8, 42.0, 34.8, 27.0, 26.2, 24.8, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.5.

HRMS (ESI) *m/z* calcd for $C_{21}H_{31}BF_3NO_4S$ $(M+H)^+$ 462.2097 found 462.2099.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-(1-propoxyethyl)phenyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-(1-propoxyethyl) phenyl)methanesulfonamide was synthesized following the general procedure **3.5.9**.



Reaction time: 12 h; 58% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

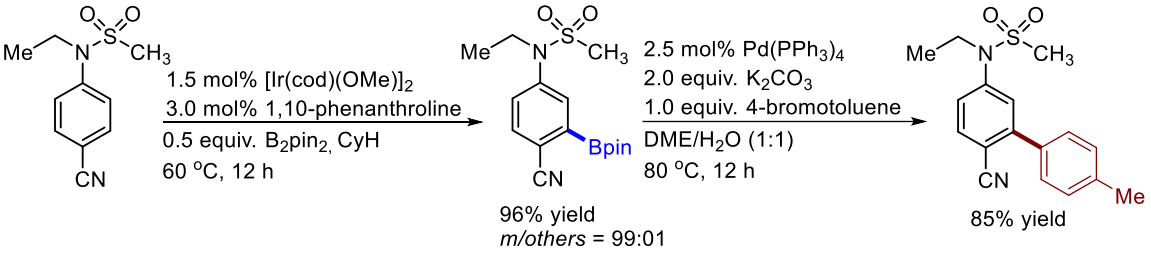
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 1.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.0, 1.6 Hz, 1H), 5.11 (q, J = 6.0 Hz, 1H), 3.84 (q, J = 6.0 Hz, 2H), 3.26 (t, J = 6.8 Hz, 2H), 1.57 – 1.63 (m, 2H), 1.38 (d, J = 6.4 Hz, 3H), 1.35 (s, 12H), 1.18 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 135.8, 134.5, 131.9, 126.1, 84.0, 75.4, 70.6, 48.8, 24.9, 24.7, 23.1, 14.4, 10.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.8.

HRMS (ESI) *m/z* calcd for $C_{20}H_{31}BF_3NO_5S$ $(M+NH4)^+$ 483.2312 found 483.2310.

Meta-borylation of N-(4-cyanophenyl)-N-ethylmethanesulfonamide :



Step-I: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-(4-cyanophenyl)-*N*-ethylmethanesulfonamide (112.2 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 60 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure and crude borylated product directly used for the next step.

Step-II: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $Pd(PPh_3)_4$ (14.44 mg, 2.5 mol%), K_2CO_3 (138.0 mg, 2.0 equiv.) and 4-bromotolulene

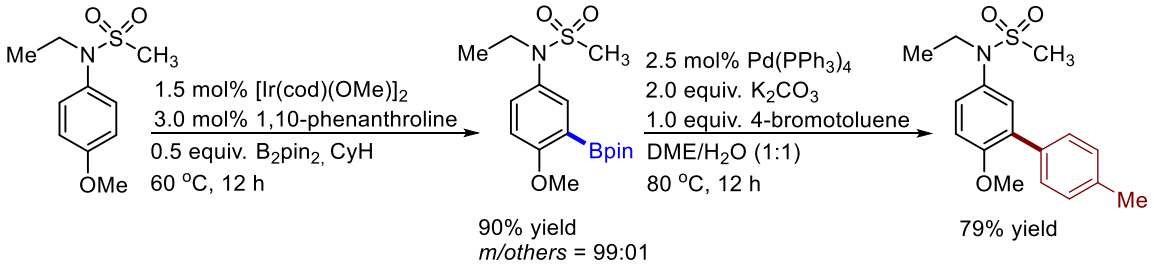
(85.52, 0.5 mmol). To this mixture, borylated crude product (0.5 mmol), DME (1.5 mL) and water (1.5 mL) was added outside the glove box. Then the reaction mixture was heated for 12 h at 80 °C. After the completion of the reaction, it was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (30% ethyl acetate in hexane) gave 133.6 mg of 85% of *meta*- arylated product as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.49 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.83 (q, *J* = 7.2 Hz, 2H), 2.93 (s, 3H), 2.43 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 143.1, 139.3, 134.7, 134.3, 129.6, 128.7, 128.6, 125.8, 118.2, 109.8, 45.3, 38.0, 21.2, 14.4.

HRMS (ESI) *m/z* calcd for $C_{17}H_{18}N_2O_2S$ $[M+H]^+$ 315.1167, found 315.1161.

Meta-borylation of N-ethyl-N-(4-methoxyphenyl)methanesulfonamide :



Step-I: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-ethyl-*N*-(4-methoxyphenyl)methanesulfonamide (114.7 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 60 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure crude borylated product directly used for the next step.

Step-II: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $Pd(PPh_3)_4$ (14.44 mg, 2.5 mol%), K_2CO_3 (138.0 mg, 2.0 equiv.), and 4-bromotolulene (85.52, 0.5 mmol). To this mixture, borylated crude product (0.5 mmol), DME (1.5 mL) and water (1.5 mL) was added outside the glove box. Then the reaction mixture was heated for 12 h at 80 °C. After the completion of the reaction, it was cooled to room temperature

and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (25% ethyl acetate in hexane) gave 126.2 mg of 79% of *meta*- arylated product as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22-7.25 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.91 (s, 3H), 2.40 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

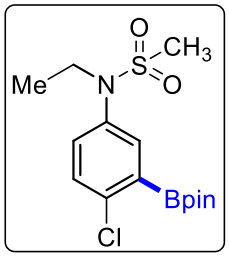
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 137.2, 134.5, 131.6, 131.4, 130.6, 130.1, 129.3, 128.8, 111.7, 55.8, 45.9, 37.3, 21.2, 14.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{16}H_{26}BNO_5S$ $[M+H]^+$ 320.1320, found 320.1315.

Meta-borylation of N-(4-chlorophenyl)-N-ethylmethanesulfonamide:

Meta-borylated product of N-(4-chlorophenyl)-*N*-ethylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 97% isolated yield, (eluent:90% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.88 (s, 3H), 1.36 (s, 12H), 1.12 (t, *J* = 7.2 Hz, 3H).

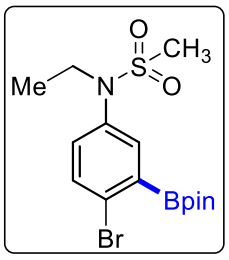
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 136.8, 135.6, 132.5, 130.5, 84.4, 45.7, 37.5, 24.8, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{15}H_{23}BClNO_4S$ $[M+Na]^+$ 360.1208, found 360.1205.

Meta-borylation of N-(4-bromophenyl)-N-ethylmethanesulfonamide:

Meta-borylated product *of* *N*-(4-bromophenyl)-*N*-ethylmethanesulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 90% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.87 (s, 3H), 1.37 (s, 12H), 1.12 (t, *J* = 7.2 Hz, 3H).

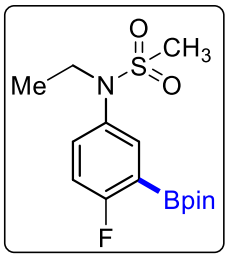
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 135.6, 133.9, 132.5, 127.5, 84.6, 45.7, 37.5, 24.8, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{15}H_{23}BBrNO_4S$ $[M+H]^+$ 404.0702, found 404.0706.

Meta-borylation of N-ethyl-N-(4-fluorophenyl)methanesulfonamide:

Meta-borylation of N-ethyl-N-(4-fluorophenyl)methane sulfonamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 91% isolated yield, (eluent: 95% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.33 – 7.37 (m, 1H), 7.00 (t, *J* = 8.8 Hz, 1H), 3.64 (q, *J* = 7.2 Hz, 2H), 2.84 (s, 3H), 1.29 (s, 12H), 1.06 (t, *J* = 7.2 Hz, 3H).

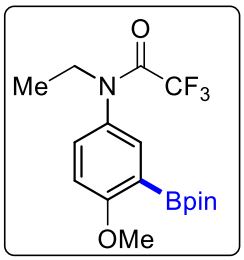
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (d, J = 252 Hz), 136.15 (d, *J* = 9.0 Hz), 134.5 (d, *J* = 9.7 Hz), 134.4 (d, *J* = 3.2 Hz), 116.4 (d, *J* = 25.6 Hz), 84.2, 45.9, 37.4, 24.7, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.6.

HRMS (ESI) *m/z* calcd for $C_{15}H_{23}BFNO_4S$ $[M+Na]^+$ 344.1503, found 344.1500.

Meta-borylation of N-ethyl-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide:

Meta-borylated product of *N*-ethyl-2,2,2-trifluoro-*N*-(4-methoxyphenyl) acetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 83% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.20 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.77 (bs, 2H), 1.35 (s, 12H), 1.16 (t, *J* = 6.8 Hz, 3H).

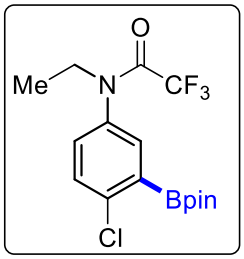
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.12 (s), 156.48, 136.18, 132.28, 131.01, 110.6, 83.8, 77.32, 77.00, 76.68, 56.0, 46.8, 24.8, 12.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.9.

HRMS (ESI) *m/z* calcd for $C_{17}H_{23}BF_3NO_4$ $[M+H]^+$ 374.1750, found 374.1748.

Meta-borylation of N-(4-chlorophenyl)-N-ethyl-2,2,2-trifluoroacetamide:

Meta-borylated product of *N*-(4-chlorophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 96% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.17 (m, 1H), 3.76 (s, 2H), 1.35 (s, 12H), 1.15 (t, *J* = 7.2 Hz, 3H).

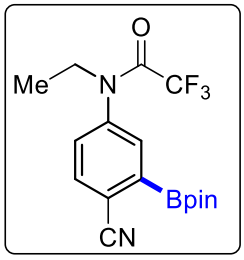
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3 (q, *J* = 35.4 Hz), 140.3, 136.7, 135.9, 131.6, 130.4, 116.2 (q, *J* = 286.6 Hz), 84.6, 46.8, 24.7, 12.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.3.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BClF_3NO_3$ $[M+Na]^+$ 400.1075, found 400.1072.

Meta-borylation of N-(4-cyanophenyl)-N-ethyl-2,2,2-trifluoroacetamide:

Meta-borylation of N-(4-cyanophenyl)-N-ethyl-2,2,2-trifluoroacetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 98% isolated yield, (eluent: 25% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 3.82 (d, *J* = 6.4 Hz, 2H), 1.39 (s, 12H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (q, *J* = 18.2 Hz), 141.8, 135.5, 134.6, 131.1, 117.9, 117.8, 85.3, 47.0, 24.7, 12.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.7.

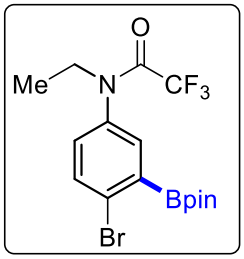
HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BF_3N_2O_3$ $[M+Na]^+$ 391.1417, found 391.1420

Meta-borylation of N-(4-bromophenyl)-N-ethyl-2,2,2-trifluoroacetamide:

Meta-borylated product of *N*-(4-bromophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide acetamide was synthesized by following the general procedure **3.5.9**.

Reaction time: 12 h; 93% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: Gummy Liquid



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.44 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 2H), 1.37 (s, 12H), 1.16 (t, *J* = 7.2 Hz, 3H).

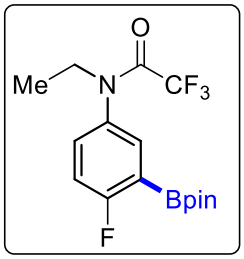
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3 (q, *J* = 35.7 Hz), 137.3, 135.9, 133.8, 131.6, 128.6, 116.3 (q, J = 301.5 Hz), 84.7, 46.8, 24.8, 12.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BBrF_3NO_3$ $[M+Na]^+$ 444.0569, found 444.0570.

Meta-borylation of N-ethyl-2,2,2-trifluoro-N-(4-fluorophenyl)acetamide:

Meta-borylation of N-ethyl-2,2,2-trifluoro-N-(4-fluorophenyl) acetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 94% isolated yield, (eluent: 25% ethyl acetate in hexane)

Properties: Gummy Liquid

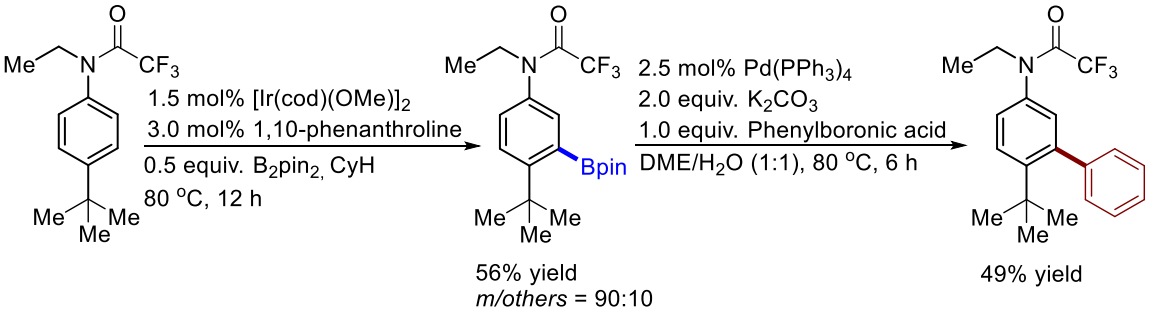
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.27 (s, 1H), 7.09 (t, *J* = 8.4 Hz, 1H), 3.78 (s, 2H), 1.37 (s, 12H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (d, *J* = 253.1 Hz), 156.4 (q, *J* = 35.5 Hz), 136.6 (d, *J* = 9.2 Hz), 134.4 (d, *J* = 2.2 Hz), 133.3 (d, *J* = 9.4 Hz), 116.4 (d, *J* = 25.9 Hz), 116.3 (d, *J* = 286.8 Hz), 84.3, 46.9, 24.8, 12.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.6.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BF_4NO_3$ $[M+Na]^+$ 384.1373, found 384.1370.

Meta-borylation of N-(4-(tert-butyl)phenyl)-N-ethyl-2,2,2-trifluoroacetamide :



Step-I: In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-(4-(tert-butyl)phenyl)-*N*-ethyl-2,2,2-

trifluoroacetamide (136.7 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure and crude borylated product durectly used for the next step.

Step-II: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $Pd(PPh_3)_4$ (14.44 mg, 2.5 mol%), K_2CO_3 (138.0 mg, 2.0 equiv.), and phenyl boronic acid (61.0 mg, 0.5 mmol). To this mixture, borylated crude product (0.5 mmol), DME (1.5 mL) and water (1.5 mL) was added outside the glove box. Then the reaction mixture was heated for 6 h at 80 °C. After the completion of the reaction it was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane) gave 85.6 mg of 49% of *meta*- arylated product as gummy liquid.

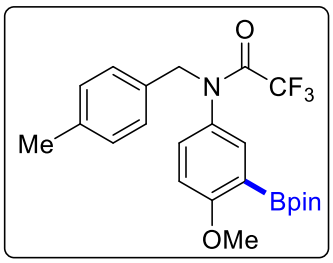
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.34-7.35 (M, 3H), 7.24 – 7.26 (m, 2H), 7.12 (d, *J* = 6.8 Hz, 1H), 6.86 (s, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.17 – 1.20 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 143.7, 143.2, 135.4, 132.0, 130.0, 129.8, 127.7, 127.4, 127.0, 126.6, 46.8, 36.6, 32.5, 12.3.

HRMS (ESI) *m/z* calcd for $C_{20}H_{22}F_3NO$ $[M+Na]^+$ 372.1551, found 372.1546.

Meta-borylation of 2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(4-methylbenzyl)acetamide :

Meta-borylation of 2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(4-methylbenzyl) acetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 94% isolated yield, (eluent: 30% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 2.4 Hz, 1H), 7.03-7.08 (m, 4H), 6.84 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 5.09 (bs, 1H), 4.54 (bs, 1H), 3.81 (s, 3H), 2.31 (s, 3H), 1.33 (s, 12H).

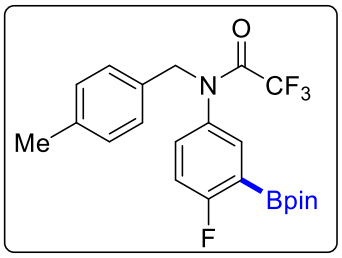
^{13}C NMR (200 MHz, $CDCl_3$): δ 164.0, 157.0 (q, *J* = 35.0 Hz), 137.7, 136.4, 132.7, 132.3, 130.7, 129.4, 129.1, 116.5 (q, *J* = 286.9 Hz), 110.2, 83.7, 55.8, 55.1, 24.7, 21.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.5.

HRMS (ESI) *m/z* calcd for $C_{23}H_{27}BF_3NO_4$ $[M+H]^+$ 450.2063, found 450.2057.

Meta-borylation of 2,2,2-trifluoro-N-(4-fluorophenyl)-N-(4-methylbenzyl)acetamide

Meta-borylation of 2,2,2-trifluoro-N-(4-fluorophenyl)-N-(4-methylbenzyl) acetamide was synthesized by following the general procedure **3.5.9**.



Reaction time: 12 h; 89% isolated yield, (eluent: 35% ethyl acetate in hexane)

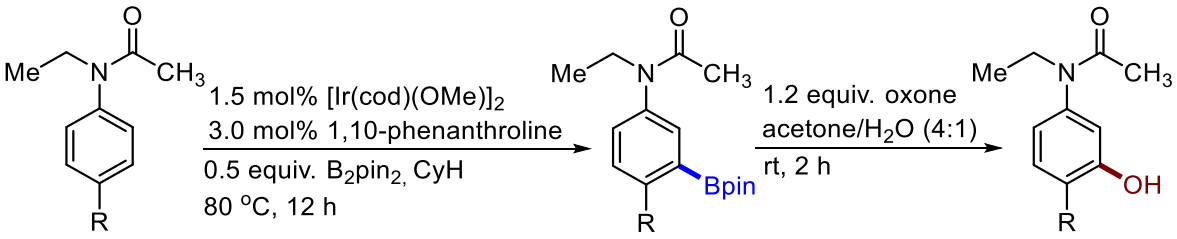
Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.21 (bs, 1H), 3.91 (s, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 1.83 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 146.3, 146.3,136.1, 119.6, 114.5, 110.9, 56.0, 43.8, 22.6, 13.0.

HRMS (ESI) m/z calcd for $C_{11}H_{15}NO_3$ $[M+Na]^+$ 232.0950, found 232.0956.

3.5.10 ***General Procedure for meta-borylation of substituted-N-ethylacetamide:***



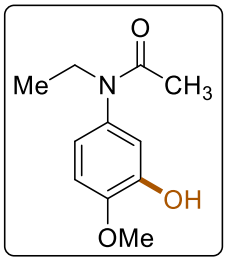
Step- I: In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, substitued-*N*-ethylacetamide (0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure and crude borylated product directly used for the next step.

Step-II: A 25 mL round-bottom flask was charged with crude borylated material (0.5 mmol) in acetone (6 mL) and it was cooled to 0 °C and stirred for 5 minutes. Then a solution of oxone (369.0 mg, 1.2 equiv.) in H_2O (1.5 mL) was added drop wise to the reaction mixture and stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous $NaHSO_3$, and then extracted three times with ethyl acetate. After that, the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass

was purified by silica gel column chromatography to give corresponding oxidized product as white solid.

Meta-borylation of N-ethyl-N-(4-methoxyphenyl)acetamide:

Meta-borylation of N-ethyl-N-(4-methoxyphenyl)acetamide was synthesized following the general procedure **3.5.10**.



Reaction time: 14 h; 75% isolated yield, (eluent: 50% ethyl acetate in hexane)

Properties: Gummy Liquid

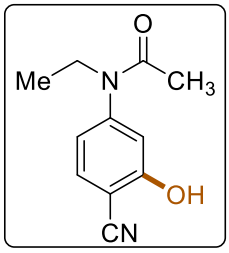
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.21 (bs, 1H), 3.91 (s, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 1.83 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 146.3, 146.3,136.1, 119.6, 114.5, 110.9, 56.0, 43.8, 22.6, 13.0.

HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO_3$ $[M+Na]^+$ 232.0950, found 232.0956.

Meta-borylation of N-(4-cyanophenyl)-N-ethylacetamide:

Meta-borylation of N-(4-cyanophenyl)-N-ethylacetamide was synthesized following the general procedure **3.5.10**.



Reaction time: 14 h; 82% isolated yield, (eluent: 55% ethyl acetate in hexane)

Properties: Gummy Liquid

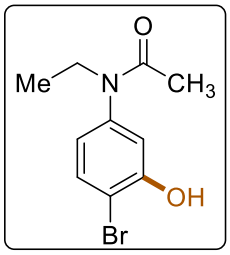
^{1}H NMR (400 MHz, DMSO-d6): δ 11.37 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 6.87-6.88 (m, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 1.82 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 168.3, 161.0, 148.0, 134.2, 119.4, 116.6, 115.4, 98.0, 43.3, 22.5, 13.2.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2O_2$ $[M+H]^+$ 205.0977, found 205.0968

Meta-borylation of N-(4-bromophenyl)-N-ethylacetamide:

Meta-borylation of N-(4-bromophenyl)-N-ethylacetamide was synthesized by following the general procedure **3.5.10**.



Reaction time: 14 h; 82% isolated yield, (eluent: 50% ethyl acetate in hexane)

Properties: Gummy Liquid

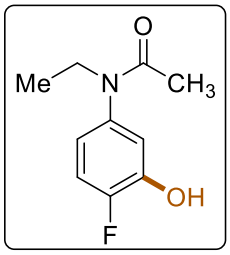
^{1}H NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 3.57 (q, *J* = 6.8 Hz, 2H), 1.73 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 168.3, 154.8, 142.9, 133.5, 120.3, 115.9, 108.6, 42.9, 22.4, 13.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}BrNO_2$ $[M+H]^+$ 258.0130, found 258.0117

Meta-borylation of N-ethyl-N-(4-fluorophenyl)acetamide:

Meta-borylation of N-ethyl-N-(4-fluorophenyl) acetamide was synthesized by following the general procedure **3.5.10**.



Reaction time: 14 h; 86% isolated yield, (eluent: 55% ethyl acetate in hexane)

Properties: Gummy Liquid

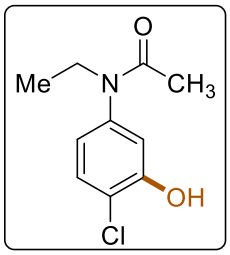
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (bs, 1H), 7.07 (t, *J* = 10.4 Hz, 1H), 6.85 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.58 – 6.62 (m, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.87 (s, 3H), 1.10 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 152.2, 149.8, 145.6 (d, *J* = 14.2 Hz), 138.5, 119.24 (d, *J* = 6.7 Hz), 117.39 (d, *J* = 3.1 Hz), 116.54 (d, *J* = 19.3 Hz), 44.2, 22.4, 12.8.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}FNO_2$ $[M+H]^+$ 198.0930, found 198.0935.

Meta-borylation of N-(4-chlorophenyl)-N-ethylacetamide:

Meta-borylation of N-(4-chlorophenyl)-N-ethylacetamide was synthesized by following the general procedure **3.5.10**.



Reaction time: 14 h; 73% isolated yield, (eluent: 50% ethyl acetate in hexane

Properties: Gummy Liquid

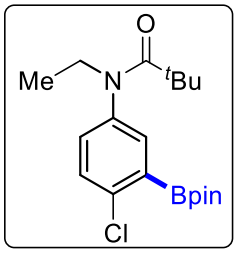
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (bs, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 3.72 (q, *J* = 6.8 Hz, 2H), 1.88 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 153.0, 142.4, 130.2, 120.5, 120.1, 116.1, 44.1, 22.7, 13.0.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}ClNO_2$ $[M+H]^+$ 214.0635, found 214.0640.

Meta-borylation of N-(4-fluorophenyl)-N-methylpivalamide:

Meta-borylated product of *N*-(4-chlorophenyl)-*N*-ethyl-2,2,2-trifluoroacetamide was synthesized following the general procedure **3.5.9**.



Reaction time: 12 h; 80% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.18 (s, 3H), 1.36 (s, 12H), 1.04 (s, 9H).

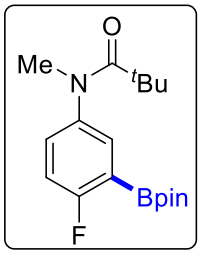
^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 143.3, 138.8, 136.4, 132.0, 130.4, 84.5, 41.3, 40.8, 29.5, 24.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.7.

HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BClNO_3$ $[M+H]^+$ 352.1851, found 352.1849.

Meta-borylation of N-(4-fluorophenyl)-N-methylpivalamide:

Meta-borylation of *N*-(4-fluorophenyl)-N-methylpivalamide was synthesized following the general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.21 – 7.23 (m, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 3.15 (s, 3H), 1.31 (s, 12H), 0.99 (s, 9H).

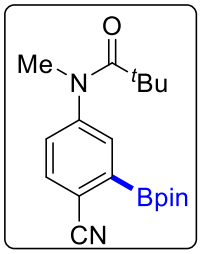
^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 165.8 (d, *J* = 251.4 Hz), 140.8 (d, *J* = 3.5 Hz), 136.7 (d, *J* = 8.8 Hz), 133.4 (d, *J* = 9.5 Hz), 116.23 (d, *J* = 25.6 Hz), 84.1, 40.9 (d, *J* = 68.3 Hz), 29.4, 24.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.6.

HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BFNO_3$ $[M+H]^+$ 336.2146, found 336.2148.

Meta-borylation of N-(4-cyanophenyl)-N-methylpivalamide:

Meta-borylation of *N*-(4-cyanophenyl)-N-methylpivalamide was synthesized following the general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: Gummy Liquid

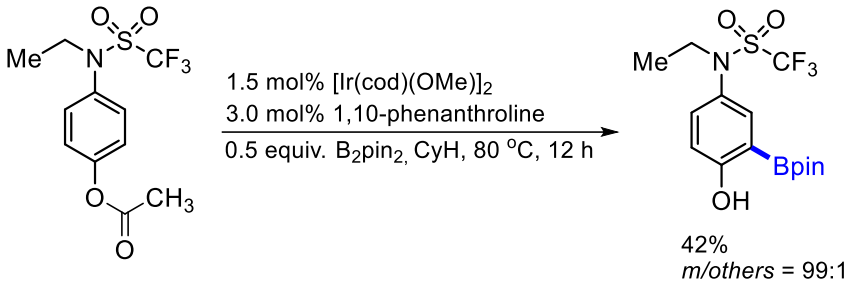
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 1.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.63 (s, 3H), 1.37 (s, 12H), 1.08 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 151.6, 134.1, 127.2, 122.4, 119.8, 109.0, 84.6, 54.0, 40.5, 29.3, 24.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{19}H_{27}BN_2O_3$ $[M+H]^+$ 343.2193, found 343.2186.

Meta-borylation of 4-((N-ethyl-1,1,1-trifluoromethyl)sulfonamido)phenyl acetate :

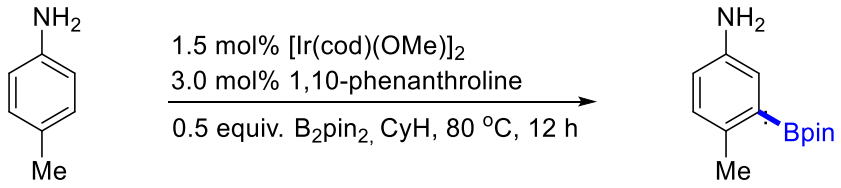


In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 4-((*N*-ethyl-1,1,1-trifluoromethyl)sulfonamido)phenyl acetate (155.7 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure. During borylation reaction deprotection of acetyl group happened. Crude NMR of borylated product was reported.

Crude ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (bs, 1H for -OH group), 7.50 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.76 – 3.86 (m, 2H of product CH_2 group merge with starting CH_2 proton), 1.37 (s, 12H), 1.23-1.26 (3H of product CH_3 group merge with boron junk).

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BF_3NO_5S$ $[M+Na]^+$ 418.1083, found 418.1090.

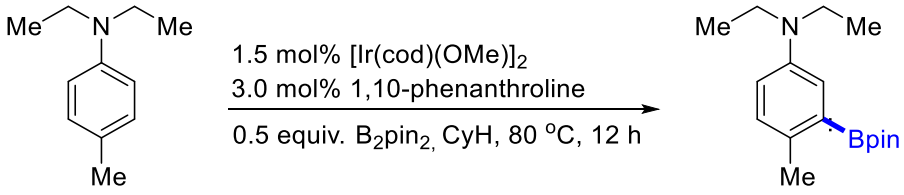
Meta-borylation of 4-methylaniline :



Conv. = 0%

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 4-methylaniline (53.6 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After 12 h, no borylated product observed in GC/MS.

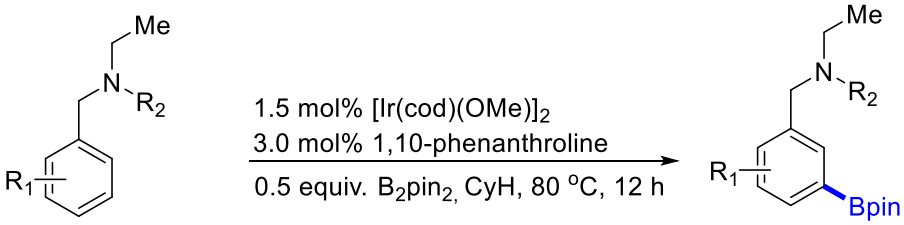
Meta-borylation of N,N-diethyl-4-methylaniline :



Conv.: 0%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*,*N*-diethyl-4-methylaniline (81.6 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After 12 h, no borylated product observed in GC/MS.

3.5.11 General Procedure for Meta Borylation of Substituted N-Protected Benzyl Amine:

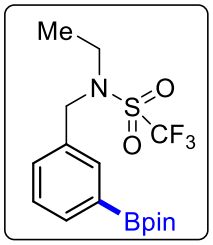


R_1 = alkyl,halogen
R_2 = $-SO_2CF_3$ group

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, corresponding *N*-protected benzyl amine (0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^oC. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), CyH was removed under reduced pressure and chromatographic separation with silica gel afforded desired *meta* borylated product of corresponding benzyl amine.

Meta-borylation of N-benzyl-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-benzyl-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized following general procedure **3.5.11**.



Reaction time: 12 h; 79% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.2 Hz, 1H), 7.65 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 5.43 (br, 2H), 3.27 (s, 2H), 1.26 (s, 12H), 1.02 (t, *J* = 7.2 Hz, 3H).

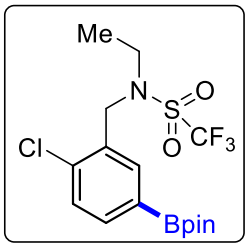
^{13}C NMR (00 MHz, $CDCl_3$): δ 134.9, 134.5, 133.6, 131.0, 128.4, 120.0 (q, *J* = 321.2 Hz), 83.9, 51.0, 42.6, 24.7, 13.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.3.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_4S$ $[M+Na]^+$ 416.1291, found 416.1289.

Meta-borylation of N-(2-chlorobenzyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide

Meta-borylated product of *N*-(2-chlorobenzyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized following general procedure **3.5.11**.



Reaction time: 12 h; GC-MS conversion was 61%.

After 12 h, GC-MS was checked which showed isomer ratio 60:40. From the crude NMR analysis, it was found that isomeric ratio is 59/41 (meta/others). The crude reaction mixture passes through a short pad of silica to remove starting material. Then, 2D-NOESY NMR was performed which further confirmed the *meta* and *para* isomer. After removing the substrate from the crude ^1H NMR of *meta* product (400 MHz, CDCl3): δ 7.87 (s,1H),

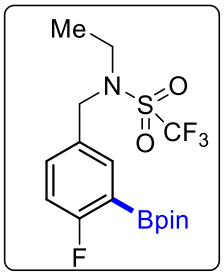
7.69-7.73 (m, 1H of meta isomer doublet merge with 1H of para isomer doublet), 7.39(d, J = 7.6 Hz, 1H), 4.71 (s, merge with para isomer singlet, 2H), 3.42 (s, merge with para isomer singlet, 2H), 1.35 (s, merge with para isomer singlet, 12H), 1.35 (m, merge with para isomer triplet, 3H)

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-fluorobenzyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-fluorobenzyl) methane sulfonamide was synthesized following general procedure **3.5.11**

Reaction time: 12 h; 75% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 3.6 Hz, 1H), 7.46 – 7.48 (m, 1H), 7.06 (t, J = 8.4 Hz, 1H), 4.49 (bs, 2H), 3.34 (s, 2H), 2.16 (s, 1H), 1.35 (s, 12H), 1.11 (t, J = 7.2 Hz, 3H).

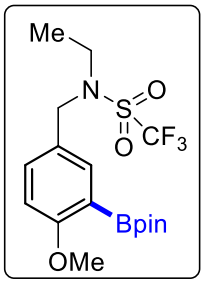
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (d, J = 251.2 Hz), 136.7 (d, J = 8.5 Hz), 133.3 (d, J = 9.3 Hz), 129.6 (d, J = 3.2 Hz), 120.0 (q, J = 321.1 Hz), 116.1 (d, J = 24.7 Hz), 84.1, 50.3, 42.7, 24.7, 13.2.

^{11}B NMR (128 MHz, CDCl3): δ 29.6.

HRMS (ESI) m/z calcd for $C_{16}H_{22}BF_4NO_4S$ $(M+Na)^+$ 434.1196 found 434.1195.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(4-methoxybenzyl)methanesulfonamide:

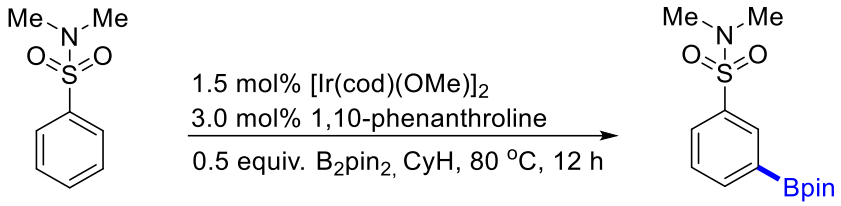
Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(4-methoxybenzyl)methanesulfonamide was synthesized following general procedure **3.5.11**.



Reaction time: 12 h; GC-MS conversion is 70%.

After 12 h, GC-MS was checked which showed isomer ratio 69:31. From the crude ^{1}H-NMR analysis we identified ortho isomer peak thus, assigned corresponding peaks to meta and calculated GCMS ratio which was in accordance with ^{1}HNMR ratio. (Note: We noticed some deborylation while taking ^{1}H-NMR thus GCMS ratio is given).

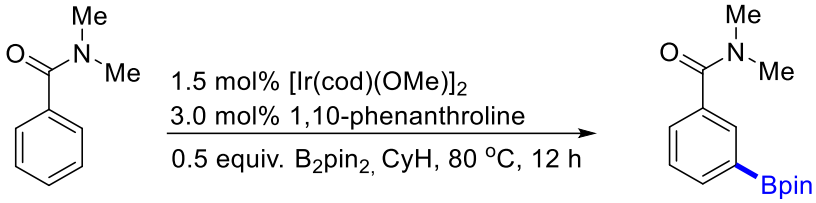
Meta-borylation of N,N-dimethylbenzenesulfonamide :



GC-MS conv. = 55%
(m/others) = 72:28

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*,*N*-dimethylbenzenesulfonamide (92.6 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After 12 h, GC-MS was checked which showed isomer ratio (*m*/others) 72:28.

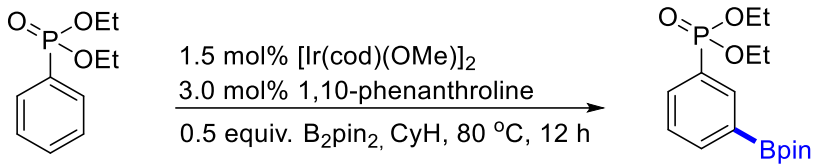
Meta-borylation of N,N-dimethylbenzenesulfonamide *:*



GC/Ms Conv.: <10%

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*,*N*-dimethylbenzamide (74.6 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 60 °C. The reaction mixture was stirred for 12 h. After 12 h, GC-MS was checked which showed trace amount of product conversion.

Meta-borylation of diethyl phenylphosphonate :



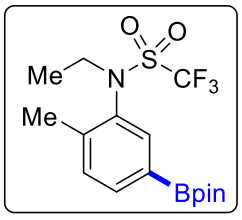
GC/Ms Conv.: 0%

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.97 mg, 1.5 mol%), 1,10-phenanthroline (2.70 mg, 3.0 mol%), B_2pin_2 (63.50 mg, 0.5 equiv.) and dry CyH (1.5 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, diethyl phenylphosphonate (107.1 mg, 0.5 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 12 h. After 12 h, GC-MS was checked which showed no product conversion.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(o-tolyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(o-tolyl)methanesulfonamide was synthesized using general procedure **3.5.9.**

Reaction time: 12 h; 84% isolated yield, (eluent: 5% ethyl acetate in hexane)



Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.34 (s, 12H), 1.17 (t, *J* = 7.2 Hz, 3H).

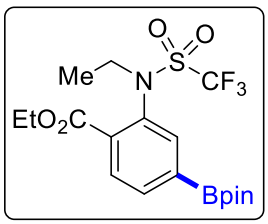
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 135.7, 135.5, 135.3, 131.2, 120.2 (q, *J* = 322.1 Hz), 84.0, 48.9, 24.9, 24.7, 18.5, 13.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BF_3NO_4S$ $[M+H]^+$ 394.1471, found 394.1471.

Meta-borylation of ethyl 2-((N-ethyl-1,1,1-trifluoromethyl)sulfonamido)benzoate:

Meta borylated product of ethyl 2-((N-ethyl-1,1,1-trifluoromethyl)sulfonamido)benzoate was synthesized using general procedure **3.5.9**.



Reaction time: 12 h; 89% isolated yield, (eluent: 15% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.69 (s, 1H), 4.26-4.44 (m, 2H), 3.97 – 4.06 (m, 1H), 3.82-3.91 (m, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 12H), 1.23 (t, *J* = 5.6 Hz, 3H).

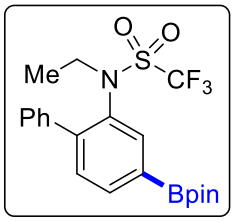
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 138.6, 135.6, 135.3, 133.5, 131.2, 120.0 (q, *J* = 321.6 Hz), 84.5, 61.9, 49.1, 24.9, 24.8, 24.8, 14.0, 13.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.9.

HRMS (ESI) *m/z* calcd for $C_{18}H_{25}BF_3NO_6S$ $[M+Na]^+$ 474.1345, found 474.1340.

Meta-borylation of N-([1,1'-biphenyl]-2-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-([1,1'-biphenyl]-2-yl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 79% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.39 – 7.48 (m, 6H), 3.56 – 3.65 (m, 1H), 3.00 – 3.09 (m, 1H), 1.36 (s, 12H), 0.96 (t, *J* = 7.2 Hz, 3H)

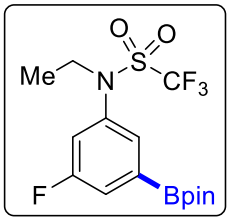
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 138.4, 136.2 (d, *J* = 2.1 Hz), 135.7, 133.8, 131.5, 128.9, 128.4, 128.1, 119.9 (q, *J* = 321.7 Hz), 84.2, 47.4, 24.9 (d, *J* = 18.9 Hz), 13.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.4.

HRMS (ESI) *m/z* calcd for $C_{21}H_{25}BF_3NO_4S$ $[M+Na]^+$ 478.1447, found 478.1446.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(3-fluorophenyl)methanesulfonamide:

Meta-borylated product of *N*-ethyl-1,1,1-trifluoro-*N*-(3-fluorophenyl)methane sulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 71% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.55 (m, 2H), 7.11-7.14 (m, 1H), 3.86 (q, *J* = 6.4 Hz, 2H), 1.35 (s, 12H), 1.18 (t, *J* = 7.2 Hz, 3H).

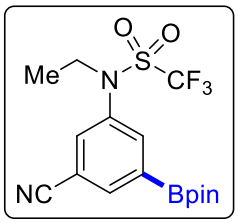
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d, *J* = 248.9 Hz), 137.49 (d, *J* = 8.7 Hz), 130.6 (d, *J* = 2.9 Hz), 122.1 (d, *J* = 19 Hz), 120.3 (q, *J* = 321.7 Hz), 119.4 (d, *J* = 22.8 Hz), 84.6, 48.7, 24.8, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.6.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}BF_4NO_4S$ $[M+Na]^+$ 420.1040, found 420.1046.

Meta-borylation of N-(3-cyanophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-(3-cyanophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 71% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.92 (s, 1H), 7.67 (s, 1H), 3.88 (d, *J* = 6.4 Hz, 2H), 1.35 (s, 12H), 1.18 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.8, 137.2, 134.9, 120.2 (q, *J* = 321.6 Hz), 117.3, 113.6, 85.0, 48.7, 24.8, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.5.

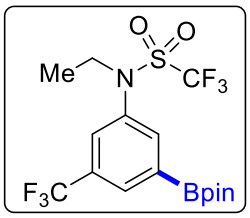
HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BF_3N_2O_4S$ $[M+Na]^+$ 427.1087, found 427.1085.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(3-(trifluoromethyl)phenyl)methanesulfonamide

Meta-borylation of *N*-ethyl-1,1,1-trifluoro-N-(3-(trifluoromethyl) phenyl)methanesulfonamide was synthesized by using general procedure **3.5.9**.

Reaction time: 12 h; 91% isolated yield, (eluent: 10% ethyl acetate in hexane)

Properties: Gummy Liquid



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.91 (s, 1H), 7.64 (s, 1H), 3.89 (d, *J* = 6.4 Hz, 2H), 1.36 (s, 12H), 1.18 (t, *J* = 7.2 Hz, 3H).

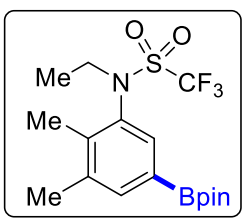
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6 (d, *J* = 145.7 Hz), 132.1 – 131.2 (m), 131.7 (d, *J* = 32.8 Hz), 129.3 (d, *J* = 379.5 Hz), 128.6-128.7 (m), 123.3 (d, *J* = 281.8 Hz),120.3 (q, *J* = 310.7 Hz), 84.8, 48.8, 24.8, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.7.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}BF_6NO_4S$ $[M+NH_4]^+$ 465.1454, found 465.1453.

Meta-borylation of N-(2,3-dimethylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylation of N-(2,3-dimethylphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 96% isolated yield, (eluent: 5% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.49 (s, 1H), 3.81 (q, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 1.34 (s, 12H), 1.16 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 138.4, 137.0, 135.3, 133.0, 120.2 (d, *J* = 322.1 Hz), 84.0, 48.9, 24.9, 24.7, 20.3, 15.6, 13.8.

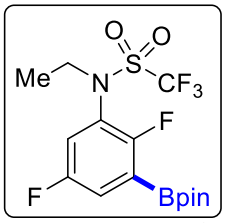
^{11}B NMR (128 MHz, $CDCl_3$): δ 30.7.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_4S$ $[M+NH_4]^+$ 425.1893, found 425.1894.

Meta-borylation of N-(2,5-difluorophenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

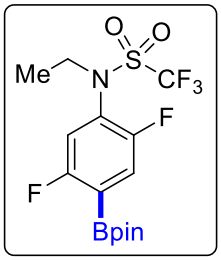
Meta-borylated product of *N*-(2,5-difluorophenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.

Reaction time: 12 h; (eluent: 5% ethyl acetate in hexane)



After completion (judged by GC/MS), CyH was removed under reduced pressure and chromatographic separation with silica gel (5% EtOAc in hexane as eluent) gave the mixture of desire borylated product (*m/p*: 80/20) as a gummy liquid.

***Meta*- isomer:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.53 (m, 1H), 7.15-7.19 (m, 1H), 3.83 (s, 2H merge with another isomer), 1.36 (s, 12H merge with another isomer), 1.18 (t, J = 7.2 Hz, 4H merge with another isomer).



***Para*- isomer:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.57 (m, 1H), 7.05 – 7.09 (m, 1H), 3.83 (s, 2H merge with another isomer), 1.36 (s, 12H merge with another isomer), 1.18 (t, J = 7.2 Hz, 4H merge with another isomer).

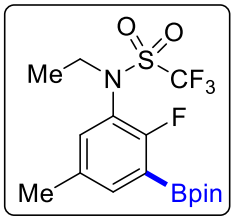
^{11}B NMR (128 MHz, $CDCl_3$): δ 29.8.

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}BF_5NO_4S$ $[M+NH_4]^+$ 416.1126, found 416.1129.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(2-fluoro-5-methylphenyl)methanesulfonamide:

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(2-fluoro-5-methylphenyl)methanesulfonamide was synthesized by using general procedure **3.5.9**.

Reaction time: 12 h; 98% isolated yield, (eluent: 10% ethyl acetate in hexane)



Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 6.0 Hz, 1H), 3.82 (d, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 1.36 (s, 12H), 1.16 (t, *J* = 7.2 Hz, 3H).

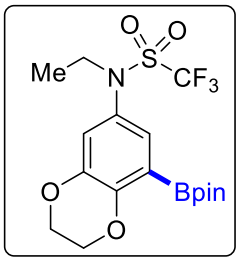
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (d, *J* = 253.7 Hz), 138.5 (d, *J* = 8.1 Hz), 135.7, 134.0 (d, *J* = 4.1 Hz), 123.2 (d, *J* = 14.8 Hz), 120.1 (q, *J* = 321.2 Hz), 84.2, 47.9, 24.8, 20.3, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.5.

HRMS (ESI) *m/z* calcd for $C_{16}H_{22}BF_4NO_4S$ $[M+NH_4]^+$ 429.1642, found 429.1646.

Meta-borylation of N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized using general procedure **3.5.9**.



Reaction time: 12 h; 95% isolated yield, (eluent: 10% ethyl acetate in hexane).

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 4.30-4.31 (m, 2H), 4.23-4.24 (m, 2H), 3.77 (d, *J* = 6.8 Hz, 2H), 1.33 (s, 12H), 1.16 (t, *J* = 7.2 Hz, 3H).

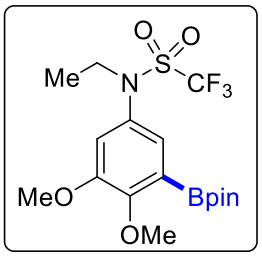
^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 143.3, 128.9, 128.8, 120.9, 120.3 (q, *J* = 322.1 Hz), 83.8, 64.3, 63.8, 48.7, 24.7, 14.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.8.

HRMS (ESI) *m/z* calcd for $C_{17}H_{23}BF_3NO_6S$ $[M+NH_4]^+$ 455.1635, found 455.1636.

Meta-borylation of N-(3,4-dimethoxyphenyl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylated product of *N*-(3,4-dimethoxyphenyl)-*N*-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 87% isolated yield, (eluent: 10% ethyl acetate in hexane).

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 3.78-3.84 (m, 8H), 1.34 (s, 12H), 1.17 (t, *J* = 7.2 Hz, 3H).

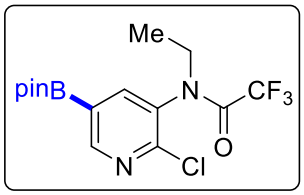
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 152.9, 131.9, 127.5, 120.3 (q, *J* = 322.1 Hz), 116.5, 83.9, 61.6, 56.1, 48.8, 24.7, 14.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.2.

HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BF_3NO_6S$ $[M+NH_4]^+$ 457.1791, found 457.1791.

Meta-borylation of N-(2-chloropyridin-3-yl)-N-ethyl-2,2,2-trifluoroacetamide:

Meta-borylation of N-(2-chloropyridin-3-yl)-N-ethyl-2,2,2-trifluoroacetamide was synthesized using general procedure **3.5.9**.



Reaction time: 12 h; 91% isolated yield, (eluent: 45% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.91 (s, 1H), 4.21-4.29 (m, 1H), 3.27-3.36 (m, 1H), 1.35 (s, 12H), 1.20 (t, *J* = 7.2 Hz, 3H).

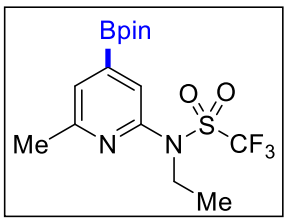
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 153.2, 145.0, 144.4, 132.7, 115.8 (q, *J* = 286.7 Hz), 84.9, 45.5, 24.7 – 24.9 (m), 12.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 29.9.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BClF_3N_2O_4S$ $[M+H]^+$ 379.1208, found 379.1213.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(6-methylpyridin-2-yl)methanesulfonamide:

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(6-methylpyridin-2-yl)methanesulfonamide was synthesized using general procedure **3.5.9**.



Reaction time: 12 h; 88% isolated yield, (eluent: 50% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.78 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.33 – 7.37 (m, 1H), 5.18 (s, 2H), 3.89 (q, *J* = 7.2 Hz, 2H), 1.36 (s, 12H), 1.11 (t, *J* = 7.2 Hz, 3H).

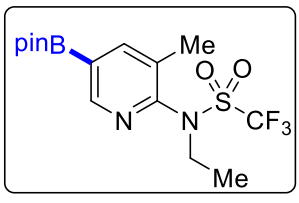
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 146.5, 141.5, 135.5, 128.6, 128.3, 127.4, 127.0, 120.0 (q, *J* = 321.8 Hz), 84.6, 70.7, 46.8, 24.8, 14.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{21}H_{26}BF_3N_2O_5S$ $[M+H]^+$ 487.1686, found 487.1695.

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(3-methylpyridin-2-yl)methanesulfonamide:

Meta-borylation of N-ethyl-1,1,1-trifluoro-N-(3-methylpyridin-2-yl)methanesulfonamide was synthesized using general procedure **3.5.9**.



Reaction time: 12 h; 93% isolated yield, (eluent: 50% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.04 (s, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.35 (s, 12H), 1.09 (t, *J* = 6.8 Hz, 3H).

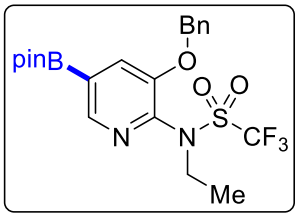
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 150.9, 146.8, 133.4, 120.1 (q, *J* = 323.0 Hz), 84.5, 47.3, 24.8, 17.8, 13.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.9.

HRMS (ESI) *m/z* calcd for $C_{15}H_{22}BF_3N_2O_4S$ $[M+H]^+$ 395.1424, found 395.1427.

Meta-borylation of N-(3-(benzyloxy)pyridin-2-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide:

Meta-borylation of N-(3-(benzyloxy)pyridin-2-yl)-N-ethyl-1,1,1-trifluoromethanesulfonamide was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 89% isolated yield, (eluent: 55% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.78 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.33 – 7.37 (m, 1H), 5.18 (s, 2H), 3.89 (q, *J* = 7.2 Hz, 2H), 1.36 (s, 12H), 1.11 (t, *J* = 7.2 Hz, 3H).

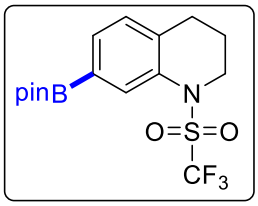
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 146.5, 141.5, 135.5, 128.6, 128.3, 127.4, 127.0, 120.0 (q, *J* = 321.8 Hz), 84.6, 70.7, 46.8, 24.8, 14.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.1.

HRMS (ESI) *m/z* calcd for $C_{21}H_{26}BF_3N_2O_5S$ $[M+H]^+$ 487.1686, found 487.1695.

Meta-borylation of 1-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroquinoline :

Meta-borylation of 1-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroquinoline was synthesized by using general procedure **3.5.9**.



Reaction time: 12 h; 78% isolated yield, (eluent: 20% ethyl acetate in hexane)

Properties: Gummy Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.08 – 2.143 (m, 2H), 1.33 (s, 12H).

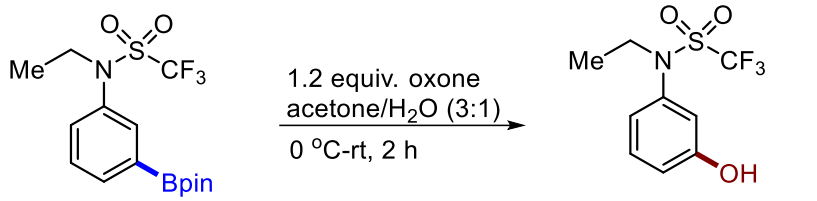
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 134.7, 132.5, 129.9, 128.8, 84.0, 47.8, 26.2, 24.8, 23.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.0.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}BF_3NO_4S$ $[M+H]^+$ 392.1315, found 392.1310.

3.6 *Useful Synthetic Transformations*

Bpin to Hydroxylation:



isolated yield: 79%

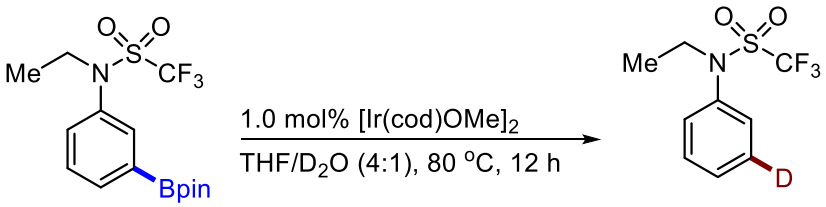
A 25 mL round-bottom flask was charged with **2a** (189.6 mg, 0.5 mmol) in acetone (6 mL) and it was cooled to 0 °C and stirred for 5 minutes. Then a solution of oxone (369.30 mg, 1.2 equiv.) in water (1.5 mL) was added drop wise to the reaction mixture and stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous $NaHSO_3$ and extracted with ethyl acetate (20 mL x 3). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification with silica gel (10% ethyl acetate in hexane as eluent) gave 106.3 mg (79%) of the product (**5a-XI)** as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.0 Hz, 1H), 6.81-6.88 (m, 3H), 6.11 (s, 1H), 3.81 (q, *J* = 6.8 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 137.3, 130.4, 121.1, 120.3 (q, *J* = 322.0 Hz), 116.6, 116.5, 48.7, 14.0.

HRMS (ESI) *m/z* calcd. for $C_9H_{10}F_3NO_3S$ $[M+Na]^+$ 292.0231, found 292.0236.

Bpin to deuteration:



isolated yield: 70%

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (3.31 mg, 1.0 mol%), **2a** (189.6 mg, 0.5 mmol) and dry THF (2.0 mL). The reaction vial was sealed and brought out of the glove box and charged with D_2O (0.5 mL). The reaction vial was resealed and heated at 80 °C for 12 h. The reaction mixture was then cooled to room temperature and extracted with Et_2O (20 mL x 3). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated

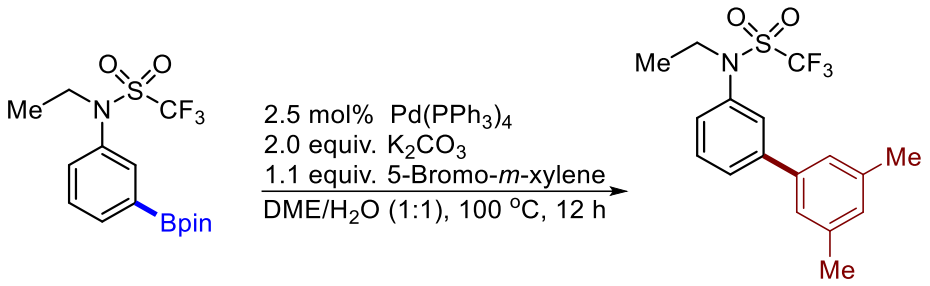
under reduced pressure. Chromatographic purification with silica gel (5% ethyl acetate in hexane as eluent) gave 89.0 mg (70%) of the product (**5a-XII)** as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.35 (m, 2H), 7.22-7.23 (m, 2H), 3.76 (q, *J* = 6.8 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 129.5, 129.2, 129.1, 129.0, 128.9, 120.4 (q, *J* = 321.9 Hz), 48.7, 14.1.

HRMS (ESI) *m/z* calcd. for $C_9H_9DF_3NO_2S$ $[M+H]^+$ 255.0525, found 255.0519.

***Bpin to aryl via Suzuki cross coupling**:*



2a isolated yield: 85%

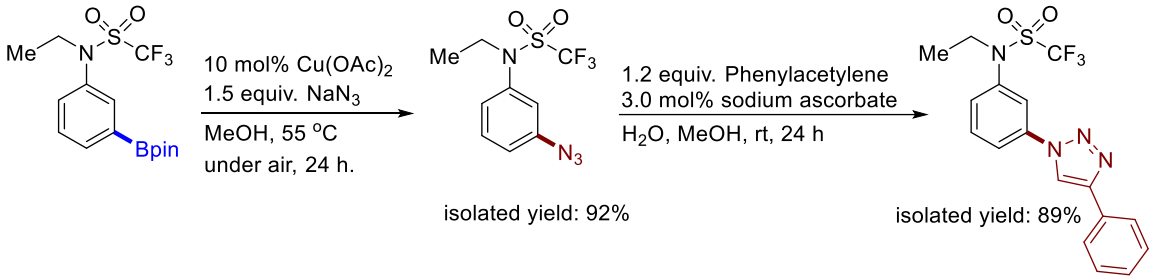
In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with **2a** (189.6 mg, 0.5 mmol), $Pd(PPh_3)_4$ (14.44 mg, 2.5 mol%), K_2CO_3 (138.0 mg, 2.0 equiv.) and 5-Bromo-*m*-xylene (101.8 mg, 1.1 equiv.). The reaction vial was taken out from glove box, DME (1.5 mL) and water (1.5 mL) was added. The reaction vial was placed in a preheated aluminium block at 100 °C and heated for 12 h. After 12 h, the reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3).The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of crude mass with silica gel (2% ethyl acetate in hexane as eluent) gave 151.90 mg (85%) of the corresponding product as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 2H), 7.02 (s, 1H), 3.87 (dd, *J* = 6.0 Hz, 2H), 2.37 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 139.6, 138.5, 136.9, 129.7, 129.6, 128.1, 127.9, 127.6, 125.0, 120.4 (q, *J* = 322.1 Hz), 48.8, 21.3, 14.3.

HRMS (ESI) *m/z* calcd. for $C_{17}H_{18}F_3NO_2S$ $[M+H]^+$ 358.1089, found 358.1094.

Bpin to azidation followed by cycloaddition:



Step I: In a 25 mL round bottom flask was charged with $Cu(OAc)_2$ (18.2 mg, 10 mol%), NaN_3 (97.6 mg, 1.5 mmol), **2a** (379.1 mg, 1.0 mmol) and MeOH (4 mL) were stirred at 55 °C under air condition (monitored by TLC). After the completion of the reaction, add 10 ml H_2O and extracted with EtOAc. The combined organic layers were washed with saturated brines, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Chromatographic purification of crude mass with silica gel (10% ethyl acetate in hexane as eluent) gave 270.7 mg (92%) of the product as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (t, *J* = 8.4 Hz, 1H), 7.09 – 7.11 (m, 2H), 6.96 (s, 1H), 3.82 – 3.86 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 138.0, 130.6, 125.4, 120.1, 120.2 (q, *J* = 321.8 Hz), 119.7, 48.7, 14.2.

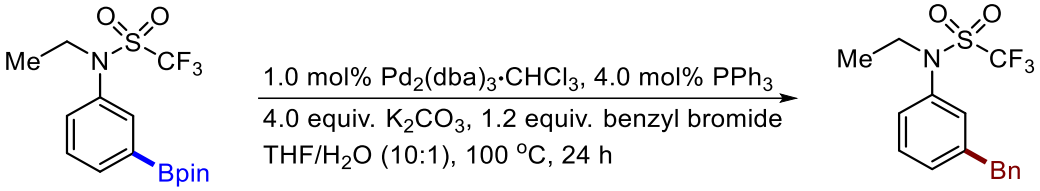
Step II: In a 5.0 mL Wheaton microreactor was charged with the corresponding azide product (147.2 mg, 0.5 mmol), phenylacetylene (61.3 mg, 1.2 equiv.), sodium ascorbate (3.0 mg, 3.0 mol%), 0.5 mL of H_2O, 3.0 mL MeOH were added and continued stirring at rt for 24 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was washed with saturated $NaHCO_3$, extracted with EtOAc. The combined organic layers were washed with saturated brines, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Chromatographic purification of crude mass with silica gel (5% ethyl acetate in hexane as eluent) gave 176.4 mg (89%) of the product as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.88 – 7.81 (m, 2H), 7.63 (t, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.40 (dd, *J* = 17.2, 8.5 Hz, 2H), 3.95 (d, *J* = 6.7 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 138.0, 137.9, 130.9, 129.8, 129.1, 128.9, 128.6, 125.8, 121.2, 120.8, 120.2 (q, *J* = 321.8 Hz), 117.5, 48.8, 14.3.

HRMS (ESI) *m/z* calcd. for $C_{17}H_{15}F_3N_4O_2S$ $[M+H]^+$ 397.0946, found 397.0939.

***Bpin to benzylation**:*



isolated yield: 90%

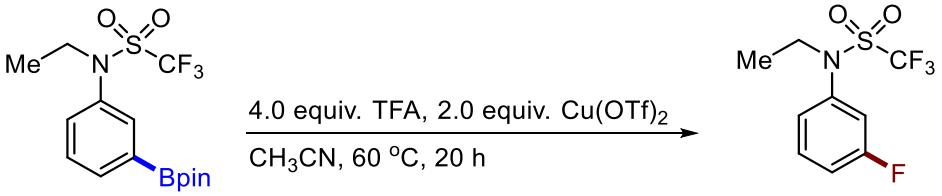
In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with **2a** (189.6 mg, 0.5 mmol), $Pd_2(dba)_3$•$CHCl_3$ (5.18 mg, 1.0 mol%), PPh_3 (5.25 mg, 4.0 mol%), K_2CO_3 (276.0 mg, 4.0 equiv.) and benzyl bromide (102.6 mg, 1.2 equiv.) and THF (2.5 mL). The reaction vial was taken out from glove box and water (50 µL) was added. The pressure tubewas placed in a preheated aluminium block at 100 °C and heated for 24 h. After 24 h, the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3).The combine organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of crude mass with silica gel (5% ethyl acetate in hexane as eluent) gave 154.5 mg (90%) of the corresponding product as gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, *J* = 8.4 Hz, 3H), 7.13 (t, *J* = 8.0 Hz, 2H), 7.06 – 7.09 (m, 4H), 3.92 (s, 2H), 3.72 (d, *J* = 6.8 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 140.0, 136.6, 129.8, 129.7, 129.5, 128.8, 128.6, 126.9, 126.4, 120.3 (q, *J* = 311.2 Hz), 48.7, 41.4, 14.2.

HRMS (ESI) *m/z* calcd. for $C_{16}H_{16}F_3NO_2S$ $[M+NH_4]^+$ 361.1198, found 361.1191.

***Bpin to Fluorination**:*

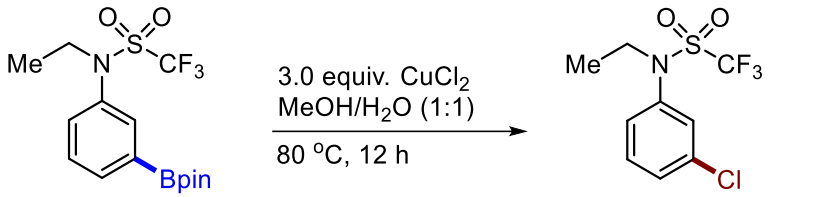


isolated yield: 70%

In a 5.0 mL Wheaton microreactor was charged with **2a** (189.6 mg, 0.5 mmol), $Cu(OTf)_2$ (361.7 mg, 2.0 equiv.), trifluoroacetic acid (153.2 µL, 4.0 equiv.) and acetonitrile (2.0 mL). The reaction mixture was stirred at 60 °C for 20 h. After 20 h, the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate

(10 mL x 3). The combine organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of crude mass with silica gel (7% ethyl acetate in hexane as eluent) gave 94.9 mg (75%) of the corresponding product as colourless liquid. Spectral data is match with starting metarial.

***Bpin to Chlorination**:*



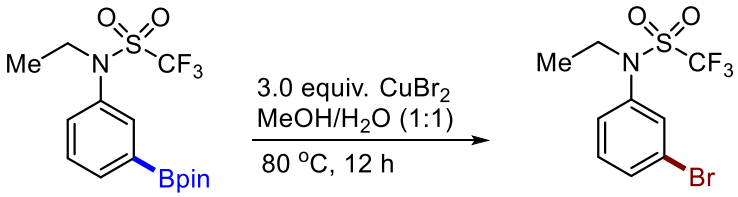
In a 5.0 mL Wheaton microreactor was charged with **2a** (189.6 mg, 1.0 mmol), $CuCl_2$ (201.7 mg, 3.0 equiv.), MeOH (2.0 mL) and water (2.0 mL). The reaction vial was capped with a teflon pressure cap and the reaction mixture was stirred at 80 °C for 12 h. After 12 h, the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combine organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of crude mass with silica gel (5% ethyl acetate in hexane as eluent) gave 107.8 mg (75%) of the corresponding product as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 16.9, 8.3 Hz, 3H), 7.23 (d, *J* = 7.3 Hz, 1H), 3.85 (d, *J* = 6.8 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 135.0, 130.4, 129.5, 129.5, 127.5, 120.2 (q, *J* = 321.8 Hz), 48.7, 14.1.

HRMS (ESI) *m/z* calcd. for $C_9H_9ClF_3NO_2S$ $[M+H]^+$ 288.0073, found 288.0070.

***Bpin to Bromination**:*



In a 5.0 mL Wheaton microreactor was charged with **2a** (189.6 mg, 0.5 mmol), $CuBr_2$ (335.05 mg, 3.0 equiv.), MeOH (2.0 mL) and water (2.0 mL). The pressure tube was

capped with a teflon pressure cap and the reaction mixture was stirred at 80 °C for 12 h. After 12 h, the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combine organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of crude mass with silica gel (5% ethyl acetate in hexane as eluent) gave 141.14 mg (85%) of the correspomding product as colourless liquid.

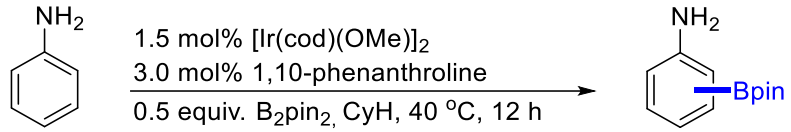
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.72 (m, 1H), 7.63 (s, 1H), 7.561 – 7.59 (m, 2H), 3.88 (d, *J* = 6.4 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 133.8, 132.7, 132.6, 130.7, 120.2 (q, *J* = 321.7 Hz), 117.24, 114.1, 48.7, 14.2.

HRMS (ESI) *m/z* calcd. for $C_9H_9BrF_3NO_2S$ $[M+H]^+$ 331.9568, found 331.9559.

3.7 Validation of Proposed Electrostatic Model:

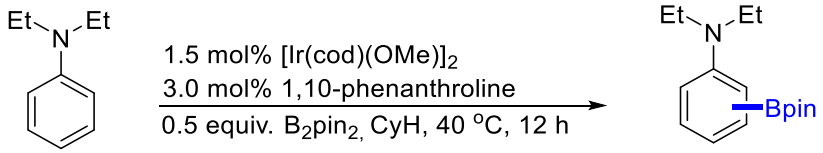
***Meta-borylation of aniline**:*



Conv.: 0%

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, aniline (18.6 mg, 0.2 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h, no borylated product is observed (judged by GC/MS).

***Meta-borylation of N,N-diethylaniline**:*

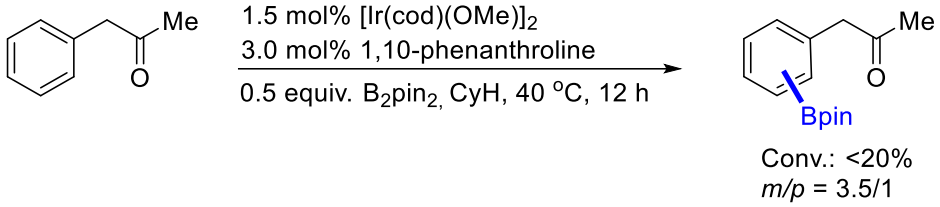


Conv.: <40%
m/p = 2.7/1

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at

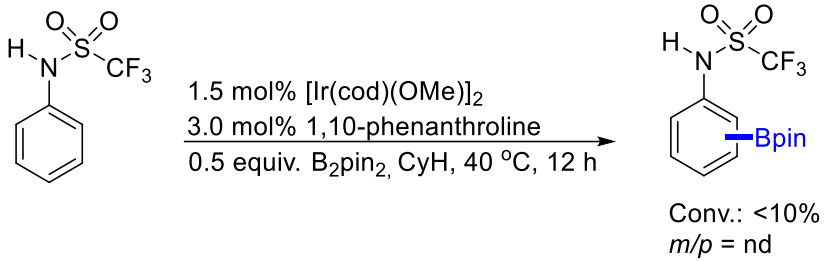
room temperature. To this mixture, *N*,*N*-diethylaniline (29.8 mg, 0.2 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h, <40% conversion of corresponding borylated product **10'** with 2.7/1 (*m/p*) selectivity (judged by GC/MS).

Meta-borylation of 1-phenylpropan-2-one:



In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 1-phenylpropan-2-one (26.8 mg, 0.2 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h, we observed <20% conversion of corresponding borylated product **11'** with 3.5/1 (*m/p*) selectivity (judged by GC/MS).

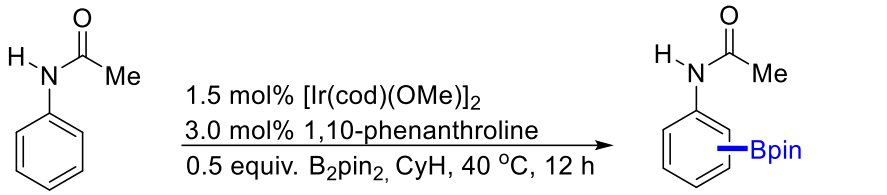
Meta-borylation of 1,1,1-trifluoro-N-phenylmethanesulfonamide :



In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (26.8 mg, 0.2 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12

h. After 12 h, we observed <10% conversion of corresponding borylated product **12'** (judged by GC/MS).

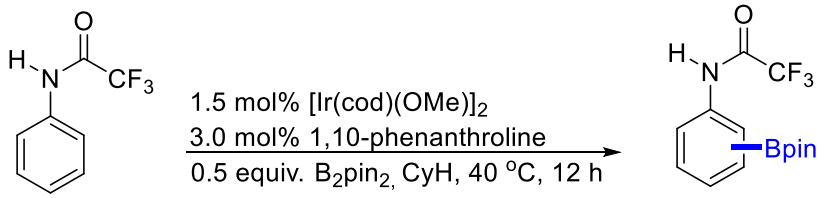
Meta-borylation of 1,1,1-trifluoro-N-phenylmethanesulfonamide :



Conv.: no reaction

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-phenylacetamide (67.6 mg, 0.2 mmol) was added. The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h, we observed no product conversion.

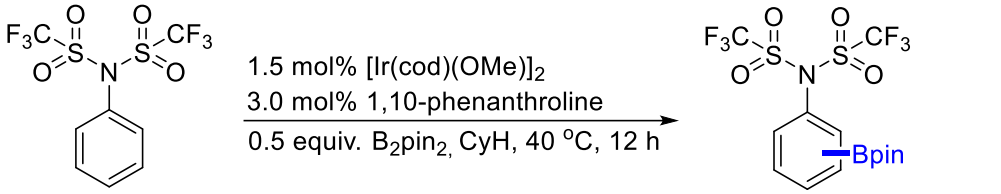
Meta-borylation of 1,1,1-trifluoro-N-phenylmethanesulfonamide :



Conv.: trace

In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 2,2,2-trifluoro-*N*-phenylacetamide (94.5 mg, 0.2 mmol) was added. The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h, we observed trace conversion.

Meta-borylation of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide

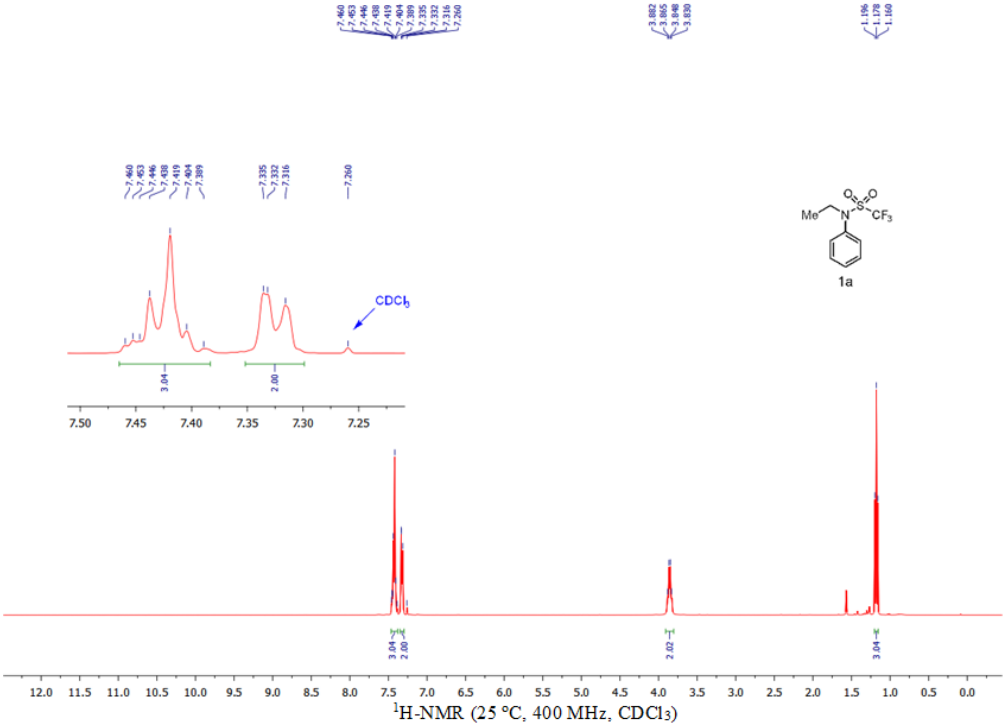


GC/Ms Conv.= 45%
(m/p) = 4/1

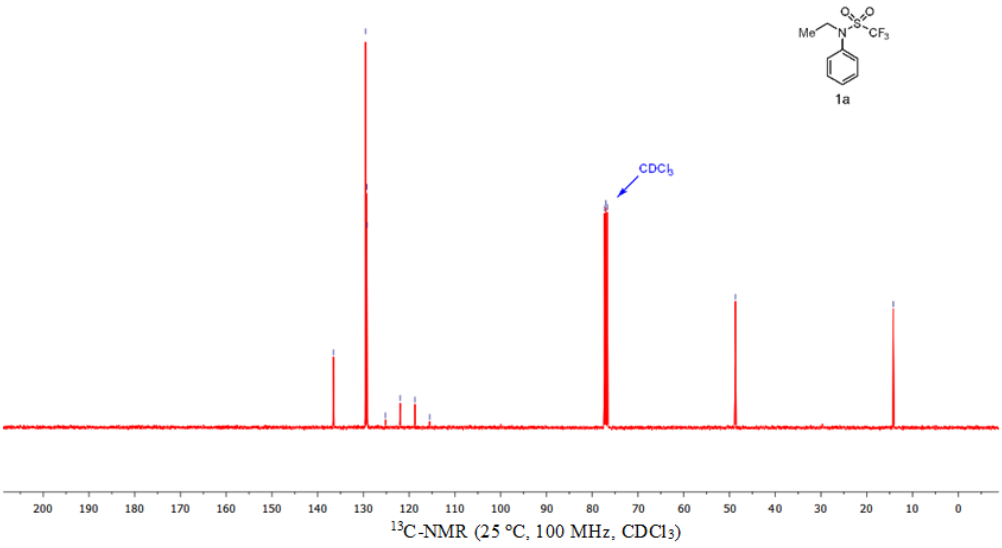
In an argon filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (2.0 mg, 1.5 mol%), 1,10-phenanthroline (1.1 mg, 3.0 mol%), B_2pin_2 (25.4 mg, 0.5 equiv.) and dry CyH (0.7 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide (71.4 mg, 0.2 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 40 °C. The reaction mixture was stirred for 12 h. After 12 h,we observed 45% conversion of corresponding borylated product **13'** with 4/1 (*m/p*) selectivity (judged by GC/MS).

3.8 Spectral Copies

^{1}H and ^{13}C NMR Spectra of **1a:**

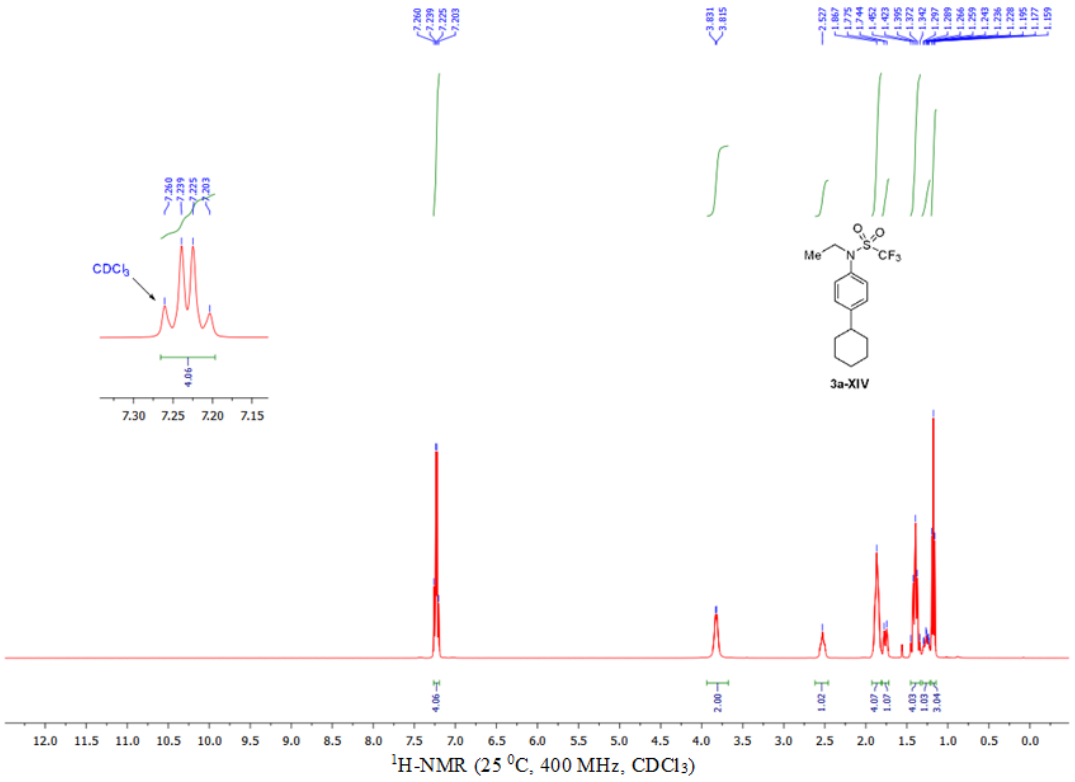


^{1}H-NMR (25 °C, 400 MHz, $CDCl_3$)



^{13}C-NMR (25 °C, 100 MHz, $CDCl_3$)

^{1}H and ^{13}C-NMR Spectra of **3a-XIV:**



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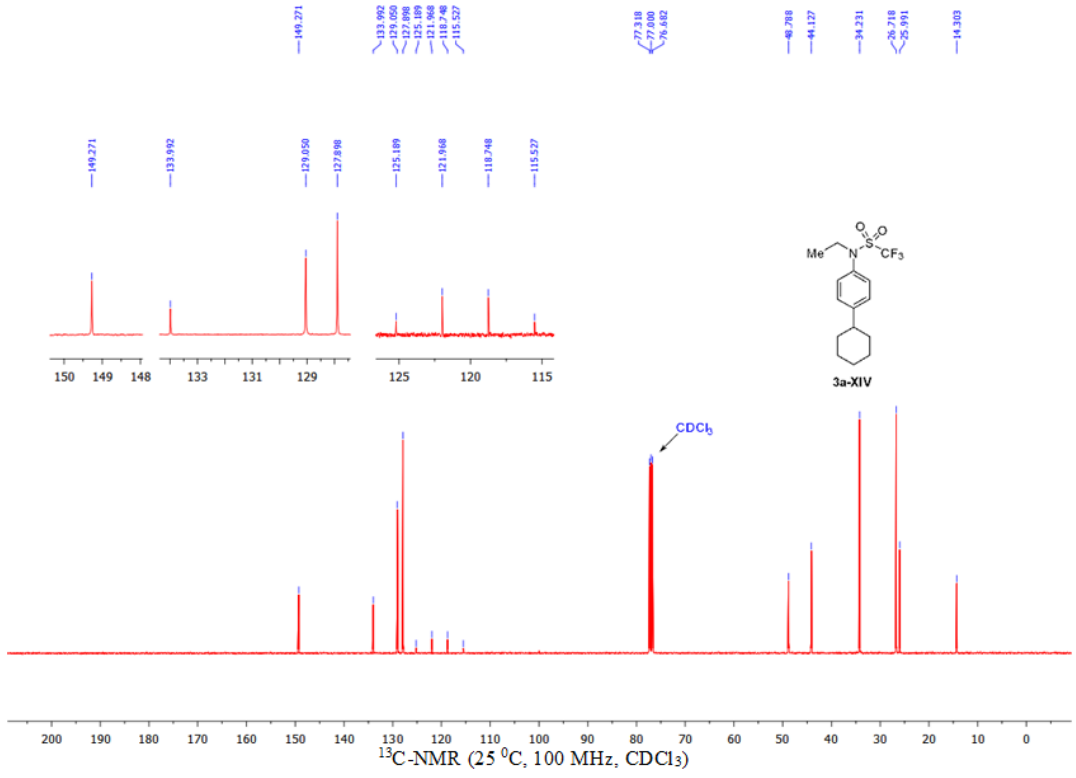
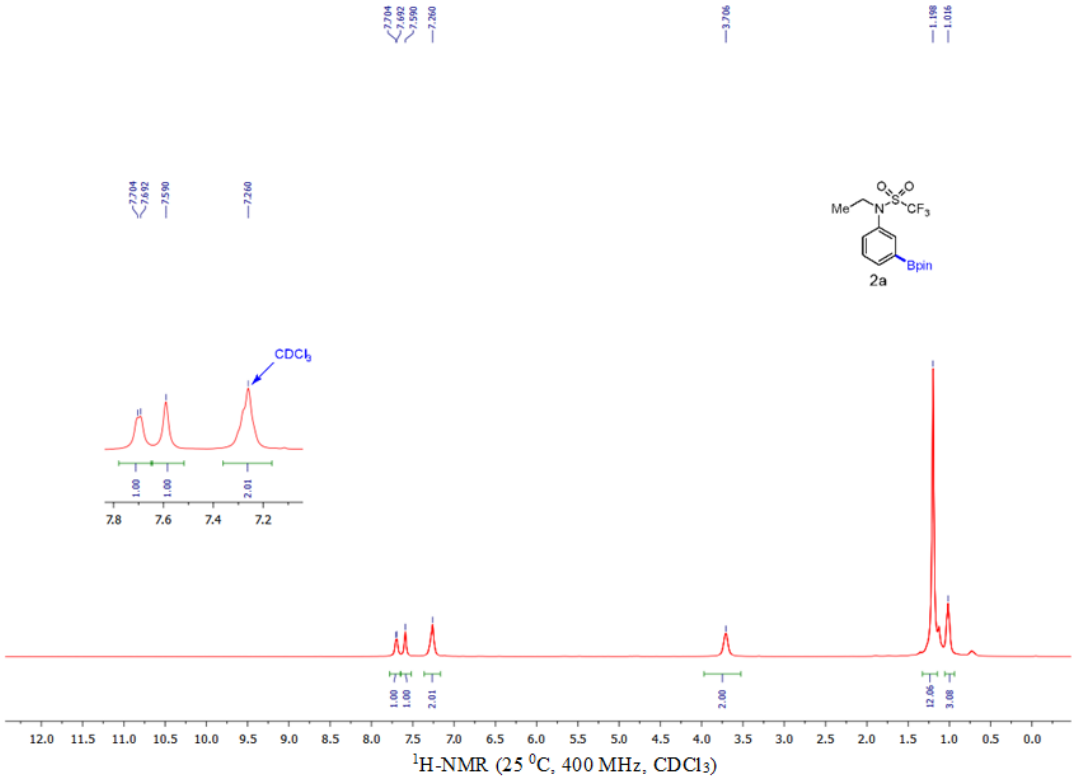
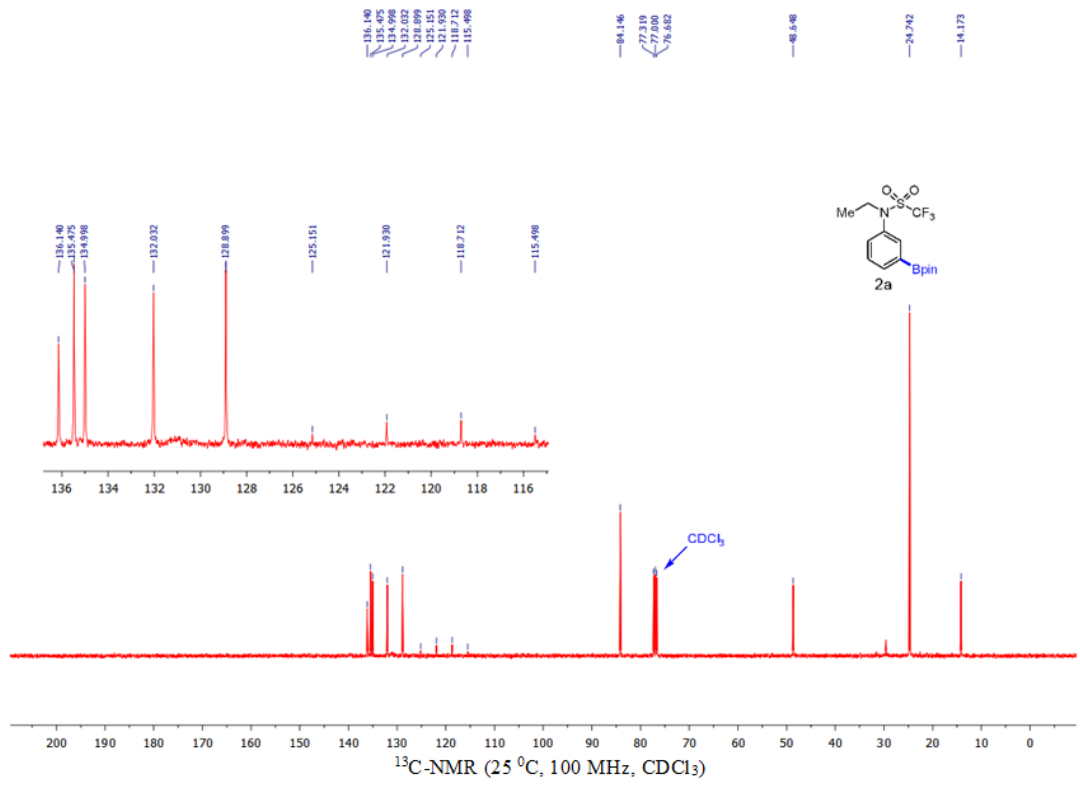


^{13}C-NMR (25 ^{0}C, 100 MHz, $CDCl_3$)

^{1}H and ^{13}C-NMR Spectra of **2a:**

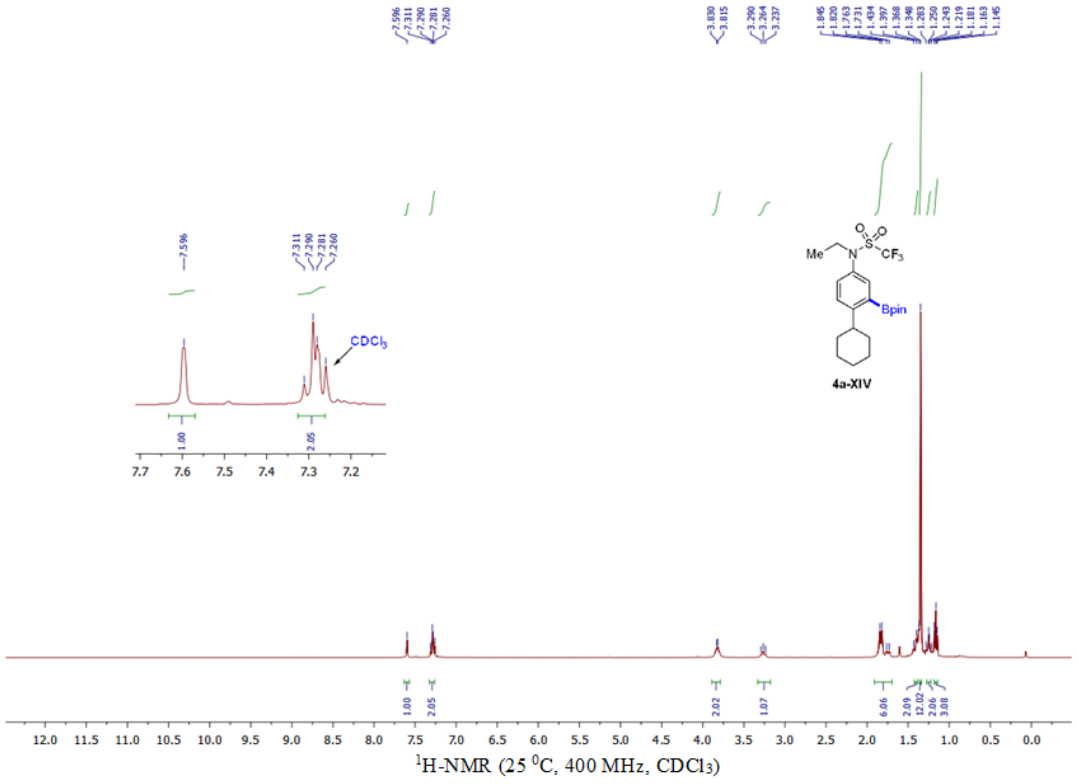


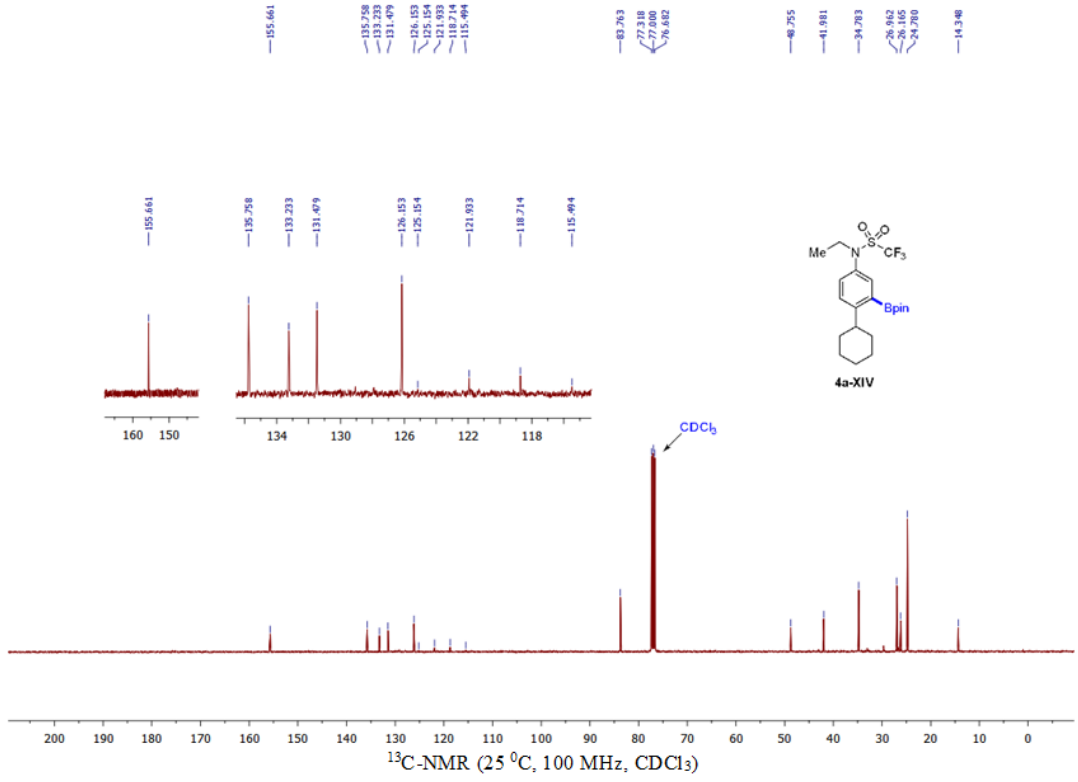
^{1}H-NMR (25 ^{0}C, 400 MHz, $CDCl_3$)



^{13}C-NMR (25 ^{0}C, 100 MHz, $CDCl_3$)

^{1}H and ^{13}C-NMR Spectra of **4a-XIV:**





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48. Notably, in case of the substrates (**2a**-**2d** and **2a-I** to **2a-III**) we observed a minor amount of *m,m*-diborylated products under the reaction conditions. However, during the column chromatography isolation, the diborylated products perhaps decomposed and became only monoborylated products, which were isolated, and the yields are reported accordingly.

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55. However, we cannot completely exclude the possibility of an intrinsic electronic directing effect of the sulphonamide group for the origin of the meta selectivity, which is a matter for future studies. Moreover, literature reports have revealed that the NH-R group might be considered as an activating group and that +M effect groups are found to be meta-activating. For details, see: Tajuddin,H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A.S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.;Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505.

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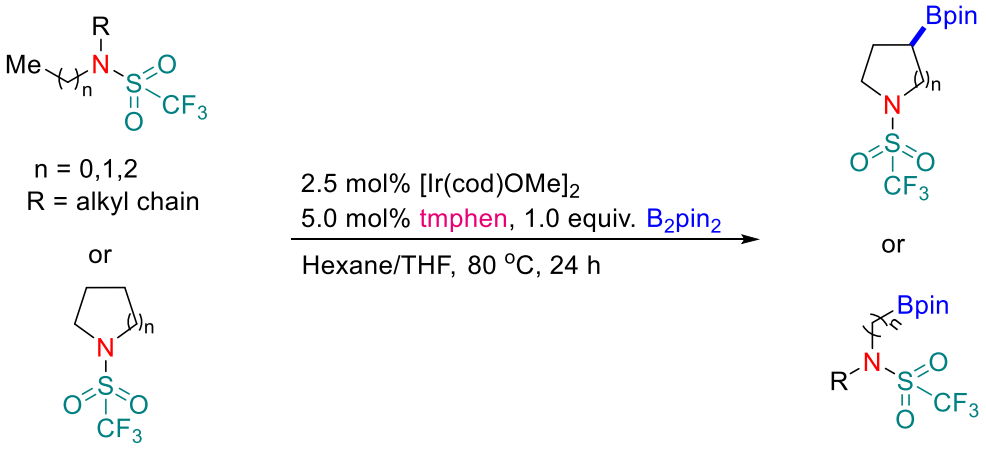
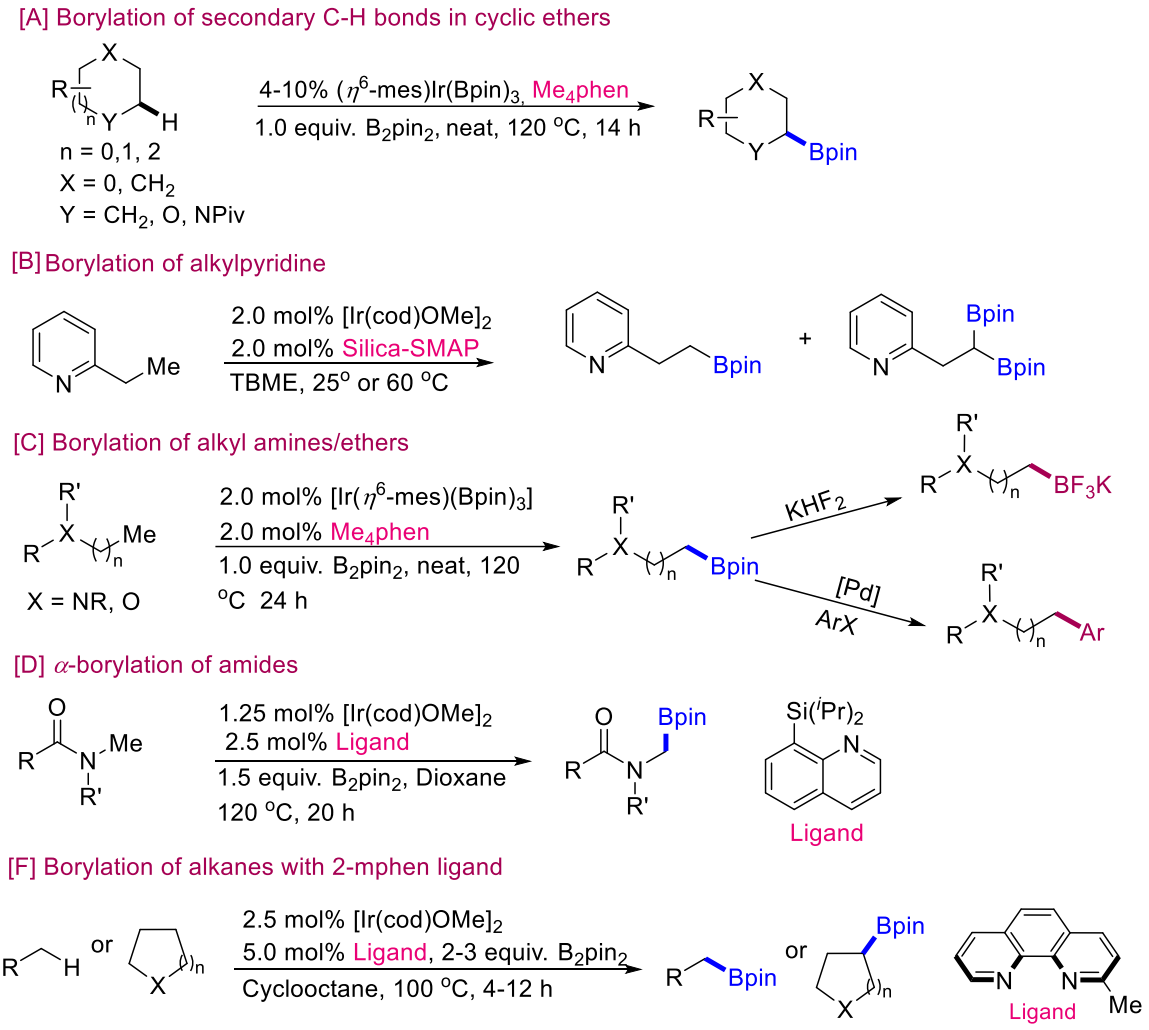
CHAPTER 4

Iridium-catalyzed C(sp^3)-H activation and borylation of N-protected alkylamines



4.1 Introduction

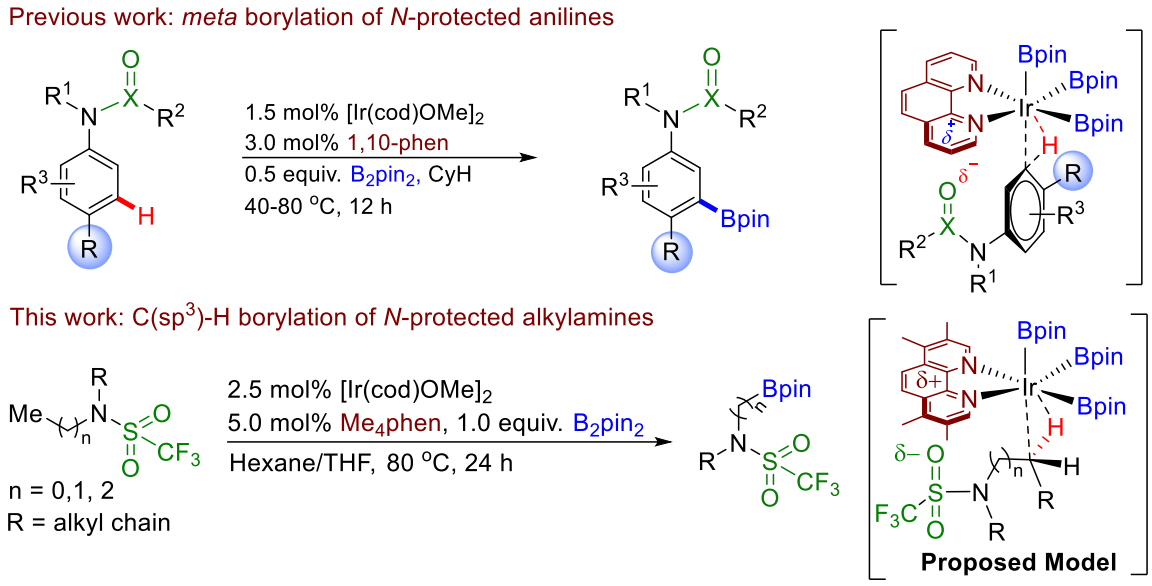
Alkylboron reagents are widely used in many synthetic transformations because it can be transformed into a variety of functional groups.[1] The cross-coupling reactions, amination and oxidation reactions are some common synthetic transformations that are extremely important in synthetic organic chemistry.[2]



Scheme 4.1: Previous Reports of C(sp^3)-H Borylation

The most common and traditional protocol for the preparation of alkyl organoboron precursors is the addition of sensitive alkyl lithium reagents and alkyl Grignard reagents to an electrophilic boron compound.[3] Apart from these traditional methods, another unique approach for the synthesis of alkyl boron reagents is the activation of aliphatic C-H bond via transition metals. Pioneering work reported by Hartwig group reveals that the transition metal catalysts like Re,[4] Rh[5] and Ru[6] form metal-boryl complex and activate the primary aliphatic C-H bond of the terminal alkane. At first, Hartwig *et al.* in 2012 utilized the

phenanthroline-Ir system for C(sp^3)-H borylation of cyclic ethers.[7] This borylation reaction preferred to borylate at the β to the oxygen atom rather than the weak α C-H bond (**Scheme 4.1 A**). In 2013, Sawamura group reported[8] a silica-supported monophosphate Ir-complex for primary and secondary borylation of 2-alkylpyridines under lenient reaction conditions (**Scheme 4.1 B**). Hartwig group explored various possibilities for the activation of aliphatic C-H bonds of many useful substrates. In 2013, Hartwig group discovered the terminal borylation reaction of alkylamines and alkylethers.[9] This borylation reaction mainly preferred β to the nitrogen and O atoms. However, the borylated products were directly transformed into the coupling products and highly stable trifluoroborate salts (**Scheme 4.1 C**).



Scheme 4.2: Previous Work and This Work

In 2019, Clark and his co-worker discovered C(sp^3)-H borylation of amide substrates with N-Si monoanionic bidentate ligand (**Scheme 4.1 D**).[10] These groups demonstrated a new idea for activation of C(sp^3)-H bond which are highly useful to get access of alkyl boron reagents. In the literature some useful protocols for activation of aliphatic carbon hydrogen bonds are reported which are highly useful in organic chemistry.[11] Selective functionalization of strong and inert carbon hydrogen bond is desirable and challenging task, so with this respect Schley and co-workers reported[12] a useful method for borylation of various alkanes utilizing the dipyridylarylmethane ligand. In 2020, Hartwig group[13] utilized 2-methylphenanthroline ligated Ir-catalyst to borylate the inert carbon hydrogen bond of undirected substrates and extend their utility in the form of various synthetic

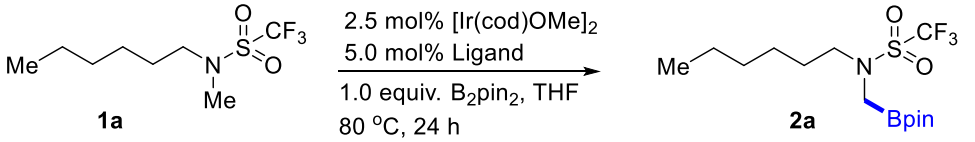
transformations (**Scheme 4.1E**). The major limitation in case of borylation of directed and undirected substrates is the requirement of high temperature and use of excess substrates, which limits their application.

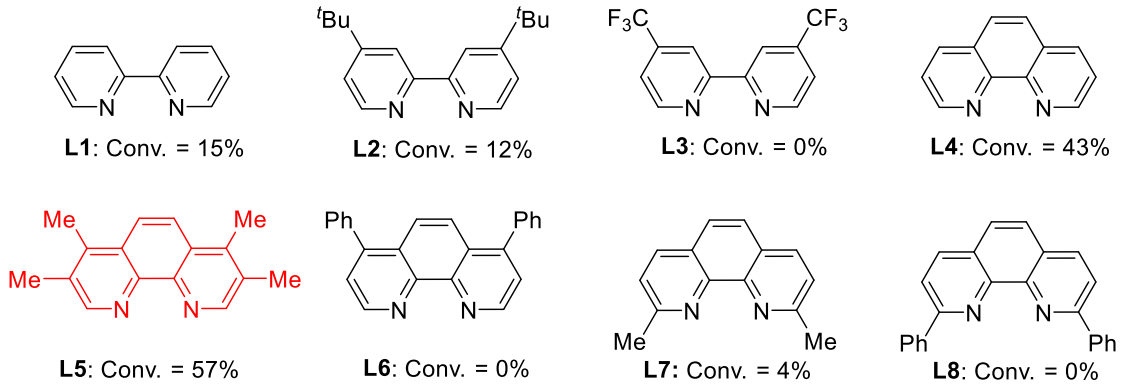
Very recently in 2021, our group reported a *meta*-carbon-hydrogen borylation of sterically influenced and neutral substrates directed by an electrostatic interaction.[14] Here, SO_2CF_3, SO_2CH_3, $COCF_3$, $COCH_3$ protected aniline substrates gave high meta selectivity with bench stable 1,10-phenanthroline ligand. A variety of challenging and bulky 4-substituted substrates gave selective meta isomer. An electrostatic interaction between partial positive and partial negative charge of ligand and substrate plays an important role for selective meta borylation **(Scheme 4.2 A)**. With the encouraging results of aniline *meta*-borylation, we were curious to examine the C(sp^3)-H borylation chemistry. For that, we investigated various alkyl amine substrates. The working hypothesis for the C(sp^3)-H borylation is based on the proposed electrostatic model, depicted in **Scheme 4.2 B,** where the partial negative charge of *N*-protected amine interacts with partial positive ligand. Utilizing this concept, we designed different *N*-protected alkyl amines and explored the C(sp^3)-H borylation.

4.2 Results and Discussion

We started our investigations with hexyl amine substrate (**1a**) having a methyl protected *N*-Tf group [(Me)N-SO_2CF_3] with the readily available ligands (**Table 1**). Utilizing the concept of *meta* borylation, at first, we performed borylation reaction using bipyridine (**L1**) and B_2pin_2 (1.0 equiv.) at 80 °C, the resulted the borylated product **2a** with 15% GC/MS conversion. Instead of simple bipyridine core, when we used electron donating (**L2**) and electron deficient ligand (**L3**), the reaction resulted in 12% and 0% product conversion respectively. As reported earlier, phenanthroline framework show high reactivity towards aliphatic C-H bonds, so we next switched the ligand from bipyridine core to different phenanthroline frameworks. When the reaction was run with the simple 1,10-phenanthroline ligand (**L4**), it gave 43% borylated product (**2a**). Next, borylation reaction was performed with more electron rich Me_4Phen ligand (**L5**) and resulted in increase of the product conversion up to 57%. Although, the other phenanthroline ligand like (**L6** and **L8**) gave no borylated product.

Table 1: Ligand Optimization[a]

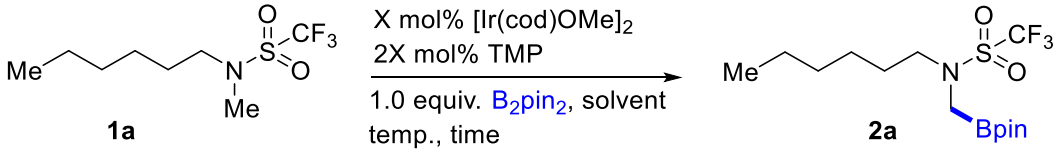




[a]All reactions were performed with 0.1 mmol scale. GC/MS conversions are reported.

Ligand 2,9-dimethyl phenanthroline (L7) gave only 4% borylated product. With these results, we concluded that the tetramethyl phenanthroline (**L5**) showed high reactivity towards triflate protected alkylamine.

Table 2: Reaction Optimization[a]

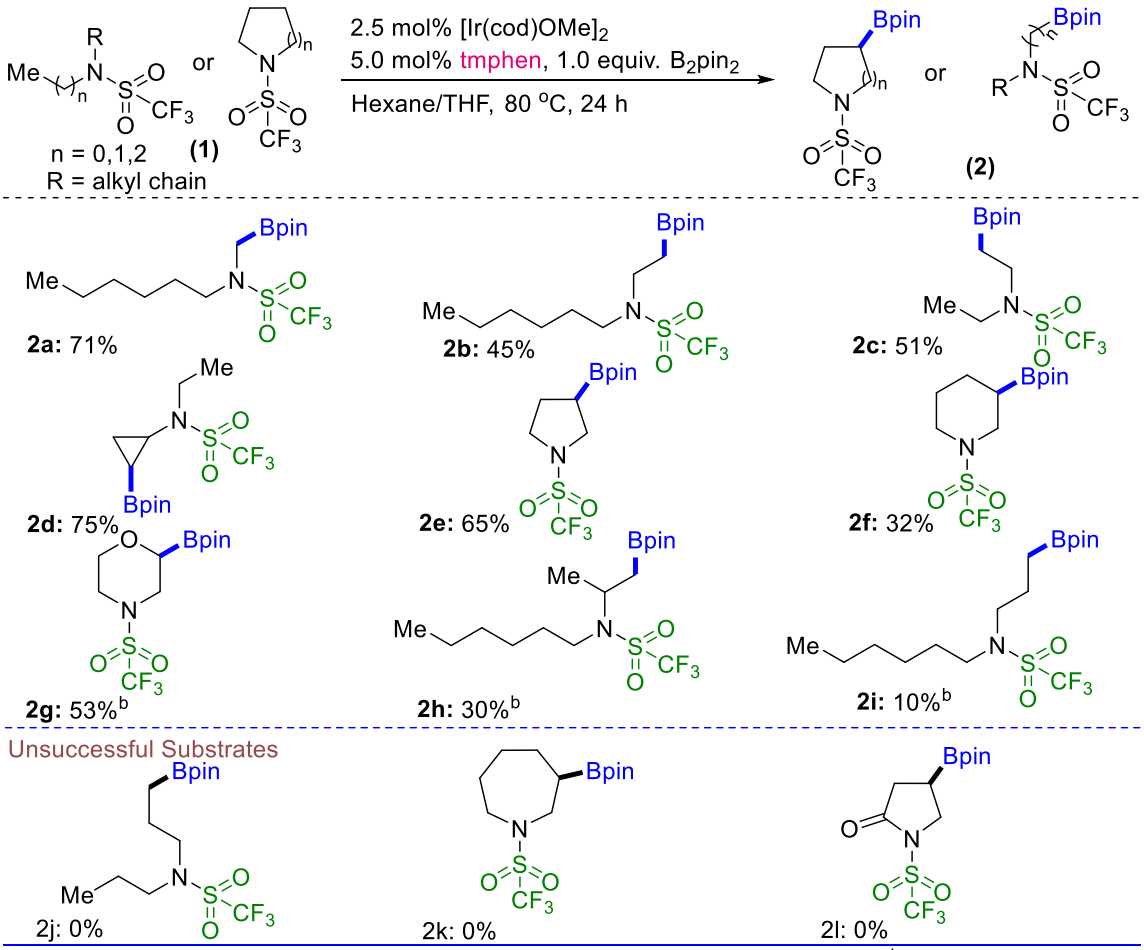


S.No.	Catalyst (mol%)	B_2pin_2 (equiv.)	Solvent	Temp.	Time (h)	Conv.
1.	1.5 mol%	1.0 equiv.	THF	80 °C	24	40%
2.	2.5 mol%	1.0 equiv.	THF	80 °C	24	57%
3.	2.5 mol%	1.0 equiv.	MTBE	80 °C	24	20%
4.	2.5 mol%	1.0 equiv.	CPME	80 °C	24	11%
5.	2.5 mol%	1.0 equiv.	Dioxane	80 °C	24	10%
6.	2.5 mol%	1.0 equiv.	CyH	80 °C	24	42%
7.	2.5 mol%	1.0 equiv.	Cyclooctane	80 °C	24	62%
8.	**2.5 mol%**	**1.0 equiv.**	**Hexane**	**80 °C**	**24**	**78 (71%)**
9.	2.5 mol%	1.0 equiv.	neat	80 °C	24	75%
10.	2.5 mol%	1.0 equiv.	Hexane	100 °C	24	78%

[a]All reactions were performed with 0.1 mmol scale. Conversions were reported by GC/MS. In parenthesis, isolated yield is reported.

We further elaborated our reaction conditions with different parameters. At first, borylation reaction was performed with Me4phen ligand and $[Ir(cod)OMe]_2$ catalyst, that resulted in decrease the production conversion (**Table 2; entry 1**). On the other hand, the borylation was performed with MTBE in place of THF, it gave only 20% borylated product **(Table 2; entry 3)**. Moreover, we found that CPME and dioxane solvent did not prefer the C(sp^3)-H borylation reaction, gave only 11% and 10% borylated product respectively **(Table 2; entry 4 & 5)**. However, when the borylation reaction performed with non-polar solvents like cyclohexane, cyclooctane and hexane, the conversion of borylated product increase respectively **(entry 6, 7 & 8)**. It is interesting to see the outcome of borylation reaction in neat condition, that resulted in good product conversion **(entry 9)**. While increasing the temperature from 80 °C to 100 °C, no change was observed in reaction outcome **(entry 10)**.

Table 3: Substrate Scope[a]



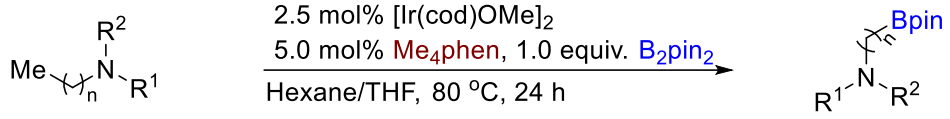
[a]All reactions were performed with 0.25 mmol scale. Isolated yields are reported. [b]Conversions were reported by crude NMR analysis.

Next, we designed and explored various alkyl amines for the C(sp^3)-H borylation with $[Ir(cod)OMe]_2$ (2.5 mol%) and Me4phen ligand (5.0 mol%) in hexane/THF solvent at 80

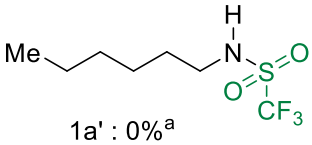
°C for 24 h **(Table 3)**. Substrate **1a** showed high reactivity in non-polar solvent. However, when the borylation reaction was performed with other than **1a** substrate in non-polar solvent, the outcome of borylation reaction was not good, which is due to solubility issue of substrates. Notably, most of the substrates worked well in THF solvent.

Next, we increased the chain length of the substrate and when methyl group is replaced by the ethyl group (**1b),** it resulted in borylation at the terminal position (**2b**). The substrates **(1h)** bearing an isopropyl group showed low product conversion due to the steric crowding of the CH_3 unit. The isopropyl group is replaced by *n*-propyl group, which resulted in only 10% product conversion analyzed by GC/MS **(2i)**. Next, we selected triflate protected *N,N*-diethyl substrate **(1c)** and performed the borylation reaction. The resulted borylated product showed more product conversion with respect to (**2b)**, while the substrate **(2j)** did not give any borylated product. We assumed that long chain on *N*-atom does not prefer the suitable transition state for borylation reaction. Substrate **(1d)** preferred borylation at the cyclopropyl ring rather than the ethyl group due to high reactivity of this ring. Along with alkylamines, some cyclic amines also afforded borylated products under the developed conditions. A triflate protected pyrrolidine **(1e)** and piperidine **(1f)** substrate showed borylation at the β position to *N*-atom with 65% and 32% isolated yield respectively. However, Tf-protected cyclic azepine (**1k**) and 2-pyrrolidone (**1l**) did not show any reactivity towards the borylation reaction even at high temperature. The *N*-protected piperidine (**1f**) substrate showed good reactivity towards the borylation. After that, we tested *N*- protected morpholine substrate **(1g)** and it afforded corresponding C(sp^3)-H borylated product **(2g).**

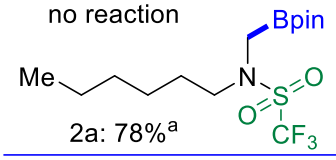
4.3 Control Experiment

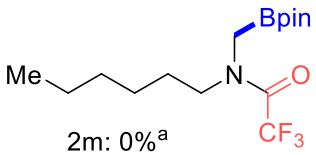


n = 0,1, 2
R^1 = alkyl chain
R^2 = H, SO_2CF_3, $COCF_3$, SO_2CH_3

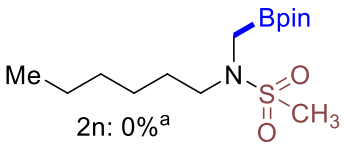


In case 1a' (free NH)
no reaction





When N-atom is protected with $COCF_3$(2m) : No borylation



When N-atom is protected with SO_2CH_3(2n) : No borylation

Reaction scale 0.1 mmol. [a]Conversion is based on GC/MS analysis

Triflate protected alkylamines showed high reactivity towards the C(sp^3)-H borylation at moderate reaction temperature. When the trifluoromethane sulfonyl group is replaced by the $COCF_3$ group and SO_2CH_3 group (substrate **1m** & **1n**), it resulted in no borylation reaction even at high temperature. This result showed the importance of the SO_2CF_3 group for the aliphatic C-H borylation of alkyl amine substrate.

4.4 Conclusion

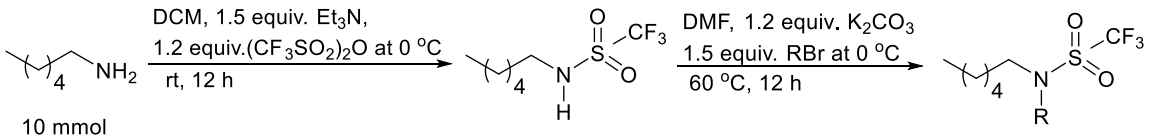
We have developed an aliphatic C-H borylation strategy of the *N*-protected alkylamines. In general, borylation of C(sp^3)-H bond required high temperature (100 °C- 130 °C) or special type of ligand system. In this context, we reported a C(sp^3)-H borylation with a bench stable 3,4,7,8-tetramethylphenanthroline ligand at moderate reaction temperature. We believe that this C(sp^3)-H borylation strategy will useful for the synthesis of various alkylboron reagents and would be widely used in pharmaceutical industries, natural product synthesis and drug discovery.

4.5 Experimental Section

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBpin) and bis(pinacolato)diboron (B_2pin_2) were procured from Sigma-Aldrich. Bis(1,5-cyclooctadiene)di-μ-methoxy-diiridium(I) $[Ir(cod)OMe]_2$ was procured from Sigma-Aldrich. Tetrahydrofuran (THF), 1,4-dioxane, cyclohexane, hexane and MTBE were refluxed over sodium/benzophenone ketyl, distilled and degassed twice before reaction. Dichloromethane (DCM), acetonitrile (MeCN) and dimethylformamide (DMF) were distilled over CaH_2. Column chromatography was performed on flash silica gel (ACME). Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm). ^1H, ^{13}C and ^{11}B NMR spectra were recorded on Bruker 400 MHz NMR spectrometer.

The boron bearing carbon atom was not observed in ^{13}C-NMR spectra due to the quadrupolar relaxation. Due to low solubility and relaxation problem of some borylated compounds, few carbon peaks are missing and the peak corresponding to the Bpin group has appeaed with low intensity. All coupling constants (J) are apparent, J values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet, ddd = doublet of doublets of doublets). High-resolution mass spectra (HRMS) were obtained at the Centre of Biomedical Research Mass Spectrometry Service Center using a Waters GCT Premier instrument run on electron ionization (EI) direct probe or a Waters QTOF Ultima instrument run on electrospray ionization (ESI). GC/MS (Agilent Technology) was obtained from Centre of Biomedical Research Institute and for the analysis RAM temperature was used 50 °C for each sample.

4.5.1 *General procedure for the synthesis of 1, 1,1,1-trifluoro-N-hexyl-N-alkylmethanesulfonamide:*



Step-I: In a 100 mL round-bottom flask, hexyl amine (1.01g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting

reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (5 % ethyl acetate in hexane as eluent) gave 2.03 g (87%) of 1,1,1-trifluoro-*N*-hexylmethanesulfonamideas colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 1H), 3.31-3.28 (m, 2H), 1.64-1.56 (m, 2H), 1.37-1.24 (m, 6H), 0.91-0.88 (m, 3H).

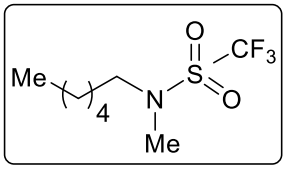
^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.7 (q, *J* = 319.2 Hz), 44.5, 31.1, 30.1, 25.9, 22.4, 13.9.

HRMS (ESI) *m/z* calcd $C_7H_{14}F_3NO_2S$ $[M+Na]^+$ 256.0595, found 256.0603.

Step-II: In a 50 mL round-bottom flask, 1,1,1-trifluoro-*N*-hexylmethanesulfonamideas (1.17 g, 5.0 mmol**)** was dissolved in dry DMF (10.0 mL) and K_2CO_3 (829.2 mg, 1.2 equiv.) added. The reaction mixture was cooled to 0 ^{o}C and stir for 5 minutes. Then, alkyl bromide or iodide (1.5 equiv.) was added dropwise at 0 ^{o}C and then reaction mixture was warmed to room temperature and reflux it at 60 ^{o}C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (ethyl acetate in hexane as eluent) gave corresponding 1,1,1-trifluoro-*N*-hexyl-*N*-alkylmethanesulfonamideas as a colorless liquid.

Synthesis of 1,1,1-trifluoro-N-hexyl-N-methylmethanesulfonamide:

1,1,1-trifluoro-*N*-hexyl-*N*-methylmethanesulfonamide was prepared using general procedure **4.5.1** Here, we used methyl iodide as an alkylating reagent.



Reaction time: 24 h; 83% isolated yield, (eluent: 3% ethyl acetate in hexane)

Properties: Colorless Liquid

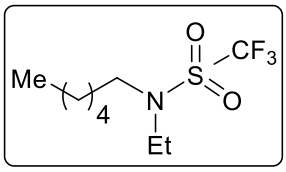
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (m, 2H), 3.01 (m, 3H), 1.64-1.57 (m, 2H), 1,31 (m, 6H), 0.91-0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 120.3 (q, *J* = 322.0 Hz), 50.9, 34.9, 31.2, 27.6, 25.8, 22.5, 13.9.

HRMS (ESI) *m/z* calcd for $C_8H_{17}F_3NO_2S$ $(M+H)^+$ 247.0854 found 247.0859.

Synthesis of 1,1,1-trifluoro-N-hexyl-N-ethylmethanesulfonamide:

1,1,1-trifluoro-*N*-hexyl-*N*-ethylmethanesulfonamide was prepared using general procedure **4.5.1** Here, we used ethyl bromide as an alkylating reagent.



Reaction time: 24 h; 80% isolated yield, (eluent: 1% ethyl acetate in hexane)

Properties: Colorless Liquid

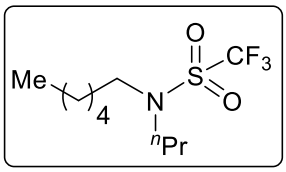
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47-3.42 (m, 2H), 3.34 (m, 2H), 1.64-1.60 (m, 2H), 1.32-1.30 (m, 6H), 1.26-1.23 (m, 3H), 0.91-0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 120.1 (q, *J* = 321.6 Hz), 47.8, 43.1, 31.3, 28.3, 26.0, 22.5, 13.9

HRMS (ESI) *m/z* calcd for $C_9H_{19}F_3NO_2S$ $(M+H)^+$ 261.1010 found 261.1016.

Synthesis of 1,1,1-trifluoro-N-hexyl-N-propylmethanesulfonamide:

1,1,1-trifluoro-*N*-hexyl-*N*-ethylmethanesulfonamide was prepared using general procedure **4.5.1** Here, we used 1-bromopropane as an alkylating reagent.



Reaction time: 24 h; 86% isolated yield, (eluent: 1% ethyl acetate in hexane)

Properties: Colorless Liquid

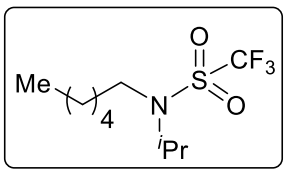
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (m, 4H), 1.68-1.60 (m, 4H), 1.29-1.25 (m, 6H), 0.94-0.87 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 120.1 (q, *J* = 321.7 Hz), 49.9, 48.4, 31.3, 28.3, 26.1, 22.5, 22.6, 13.8, 10.8.

HRMS (ESI) *m/z* calcd for $C_{10}H_{21}F_3NO_2S$ $(M+H)^+$ 275.1167 found 275.1172.

Synthesis of 1,1,1-trifluoro-N-hexyl-N-isopropylmethanesulfonamide:

1,1,1-trifluoro-*N*-hexyl-*N*-isopropylmethanesulfonamide was prepared using general procedure **4.5.1** Here, we used 2-bromopropane as an alkylating reagent.



Reaction time: 24 h; 78% isolated yield, (eluent: 2% ethyl acetate in hexane)

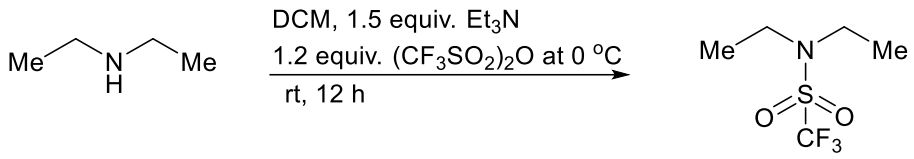
Properties: Colorless Liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19-4.12 (m, 1H), 3.26-3.22 (m, 2H), 1.67-1.66 (m, 2H), 1.29-1.27 (m, 12H), 0.90-0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 120.1 (q, *J* = 321.6 Hz), 52.0, 44.5, 31.5, 26.5, 22.5, 13.9.

HRMS (ESI) *m/z* calcd for $C_{10}H_{21}F_3NO_2S$ $(M+Na)^+$ 298.1065 found 298.1072

Synthesis of N,N-diethyl-1,1,1-trifluoromethanesulfonamide:



10 mmol 87%

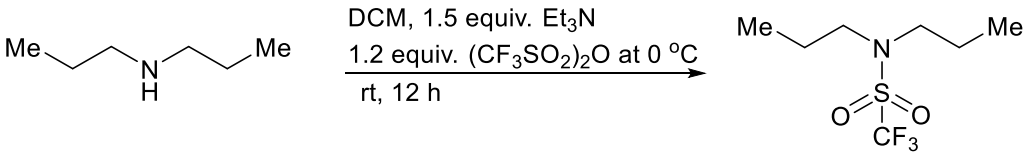
In a 100 mL round-bottom flask, *N*,*N*-diethylamine (731.4 mg,10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as eluent) gave 1.79 g (87%) of *N*,*N*-diethyl-1,1,1-trifluoromethanesulfonamide colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.46-3.44 (m, 4H), 1.27-1.24 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.0 (q, *J* = 321.3 Hz), 42.7, 13.9.

HRMS (ESI) *m/z* calcd $C_5H_{10}F_3NO_2S$ $[M+H]^+$ 206.0463, found 206.0469.

Synthesis of 1,1,1-trifluoro-N,N-dipropylmethanesulfonamide:



10 mmol 83%

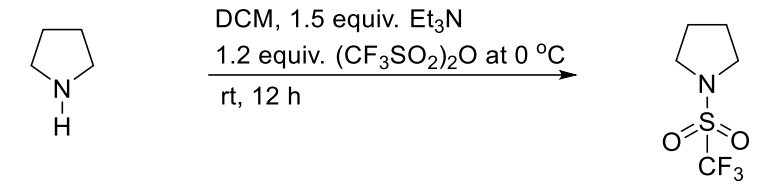
In a 100 mL round-bottom flask, *N*,*N*-dipropylamine (1.02 g, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 1.94 g (83%) of 1,1,1-trifluoro-*N*,*N*-dipropylmethanesulfonamide as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.30 (m, 4H), 1.70-1.61 (m, 4H), 0.95-0.91 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.1 (q, *J* = 321.6 Hz), 50.0, 21.6, 10.8.

HRMS (ESI) *m/z* calcd $C_7H_{14}F_3NO_2S$ $[M+Na]^+$ 256.0595, found 256.0599.

Synthesis of 1-((trifluoromethyl)sulfonyl)pyrrolidine:



10 mmol

82%

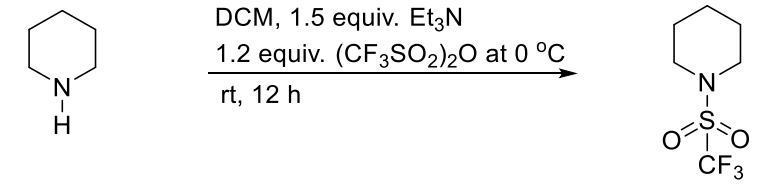
In a 100 mL round-bottom flask, pyrrolidine (711.2 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 1.67 g (82%) of 1-((trifluoromethyl)sulfonyl)pyrrolidine as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.84 (m, 4H), 2.34-2.30 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.4 (q, J = 322.1 Hz), 48.8, 25.8.

HRMS (ESI) *m/z* calcd $C_5H_8F_3NO_2S$ $[M+H]^+$ 204.0306, found 204.0311.

Synthesis of 1-((trifluoromethyl)sulfonyl)piperidine:



10 mmol

89%

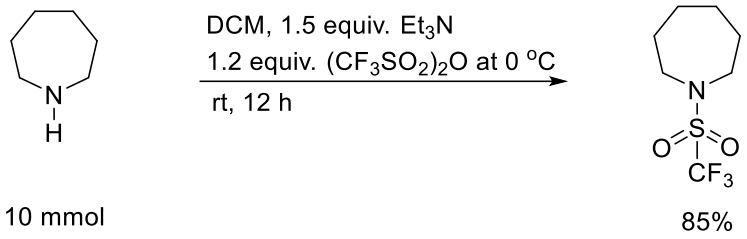
In a 100 mL round-bottom flask, piperidine (851.5 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 1.93 g (89%) of 1-((trifluoromethyl)sulfonyl)piperidine as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.44 (m, 4H), 1.65 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.1 (q, J = 321.5 Hz), 47.5, 25.5, 23.2.

HRMS (ESI) *m/z* calcd $C_6H_{10}F_3NO_2S$ $[M+H]^+$ 218.0463, found 218.0471.

Synthesis of 1-((trifluoromethyl)sulfonyl)azepane:



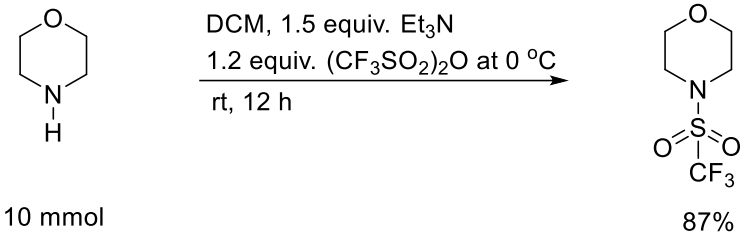
In a 100 mL round-bottom flask, azepane (991.8 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (2% ethyl acetate in hexane as eluent) gave 1.97 g (85%) of 1-((trifluoromethyl)sulfonyl)azepane as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.49-3.45 (m, 4H), 1.78 (m, 4H), 1.65 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.2 (q, J = 322.1 Hz), 49.5, 29.2, 26.5.

HRMS (ESI) *m/z* calcd $C_7H_{12}F_3NO_2S$ $[M+H]^+$ 232.0619, found 232.0626.

Synthesis of 4-((trifluoromethyl)sulfonyl)morpholine:



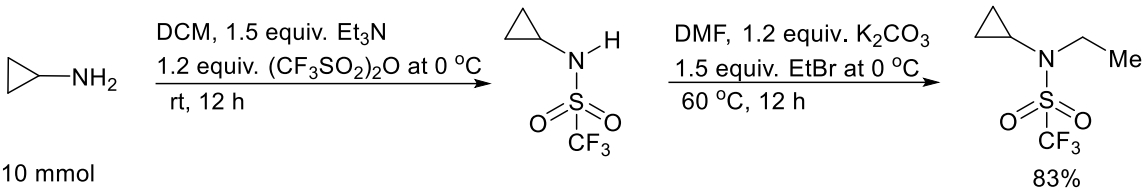
In a 100 mL round-bottom flask, morpholine (871.2 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 ^oC and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and chromatographic separation with silica gel (10% ethyl acetate in hexane as eluent) gave 1.91 g (87%) of 4-((trifluoromethyl)sulfonyl)morpholine as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.37 (m, 4H), 3.48 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.0 (q, *J* = 321.4 Hz), 66.4, 46.4.

HRMS (ESI) *m/z* calcd $C_5H_8F_3NO_3S$ $[M+H]^+$ 220.0255, found 220.0262.

Synthesis of N-cyclopropyl-N-ethyl-1,1,1-trifluoromethanesulfonamide:



10 mmol

83%

Step-I: In a 100 mL round-bottom flask, cyclopropanamine (571.0 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minutes. Then, $(CF_3SO_2)_2O$ (2.0 mL, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated under reduced pressure and crude product used in next step without further purification.

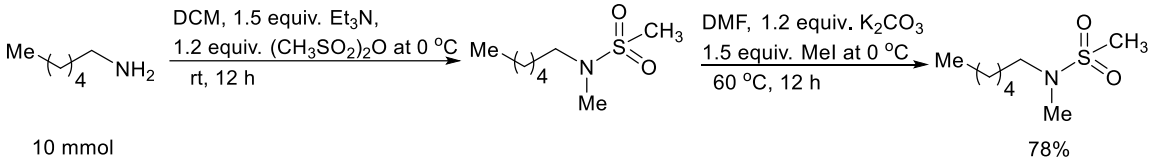
Step-II: In a 50 mL round-bottom flask crude *N*-cyclopropyl-1,1,1-trifluoromethanesulfonamide (10.0 mmol**)** was dissolved in dry DMF (10.0 mL) and K_2CO_3 (1.65 gm, 1.2 equiv.) added. The reaction mixture was cooled to 0 °C and stir for 5 minutes. Then, ethyl bromide (1.1 mL, 1.5 equiv.) was added dropwise at 0 °C and then reaction mixture was warmed to room temperature and reflux it at 60 °C temperature for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as eluent) gave 1.80 g (83%) of *N*-cyclopropyl-*N*-ethyl-1,1,1-trifluoromethanesulfonamide as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.48-3.42 (m, 2H), 2.68 (m,1H), 1.32-1.22 (m, 3H), 0.92-0.84 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.8 (q, *J* = 322.3 Hz), 46.1, 29.5, 13.8, 7.8.

HRMS (ESI) *m/z* calcd $C_6H_{10}F_3NO_2S$ $[M+H]^+$ 218.0463, found 218.0469.

Synthesis of N-hexyl-N-methylmethanesulfonamide:



Step-I: In a 100 mL round-bottom flask, hexylamine (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 15 minutes. Then, $(CH_3SO_2)_2O$ (2.10 gm, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding *N*-SO_2CH_3 protected hexylamine quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 5 minutes. Then, MeI (934.2 µL, 1.5 equiv.) was added at 0 ^oC and reaction mixture was warmed to room temperature and heated it at 60 ^oC for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The

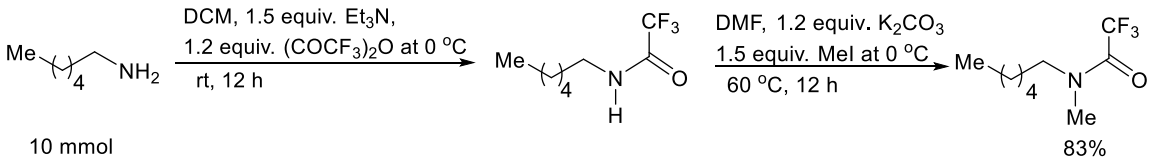
combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and chromatographic separation with silica gel (5% ethyl acetate in hexane as eluent) gave 1.51 g (78%) of *N*-hexyl-*N*-methylmethanesulfonamide as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.08-3.03 (m,2H), 2.78-2.71 (m, 6H), 1.53-1.51 (m, 2H), 1.25-1.21 (m, 5H), 0.84-0.82 (m, 3H), 0.02-0.01 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 49.8, 35.1, 34.3, 31.2, 27.6, 26.0, 22.4, 13.8.

HRMS (ESI) *m/z* calcd for $C_8H_{19}NO_2S$ $[M+H]^+$ 194.1215, found 194.1221.

Synthesis of 2,2,2-trifluoro-N-hexyl-N-methylacetamide:



Step-I: In a 100 mL round-bottom flask, hexylamine (930 mg, 10 mmol), 20 mL dry DCM and dry Et_3N (2.10 mL, 1.5 equiv.) was added. The reaction mixture was cooled to 0 ^oC

and stirred for 15 minutes. Then, $(COCF_3)_2O$ (1.67 mL, 1.2 equiv.) was added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 30 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford corresponding *N*-$COCF_3$ protected hexylamine quantitatively which was used directly without further purification for the next step.

Step-II: In a 50 mL round-bottom flask, crude material was dissolved in dry DMF (15.0 mL) and K_2CO_3 (1.66 g, 1.2 equiv.) was added. The reaction mixture was cooled to 0 ^oC and stirred for 5 minutes. Then, MeI (934.2 µL, 1.5 equiv.) was added at 0 ^oC and reaction mixture was warmed to room temperature and heated it at 60 ^oC for 12 h. Upon completion (checked by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL x 3), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and chromatographic separation with silica gel (8% ethyl acetate in hexane as eluent) gave 1.75 g (83%) of 2,2,2-trifluoro-*N*-hexyl-*N*-methylacetamide as colorless liquid.

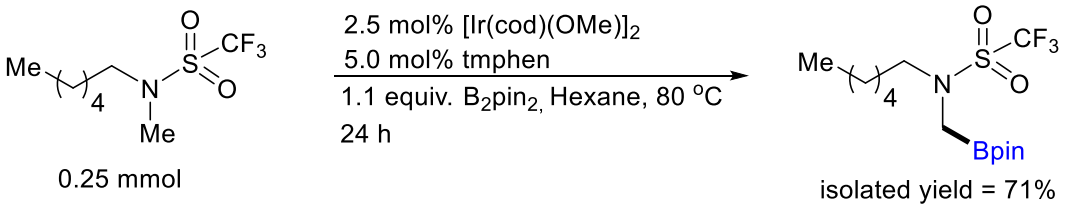
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.34-3.35 (m, 2H), 3.10-3.01 (m, 3H), 1.64-1.56 (m, 2H), 1.29-1.25 (m, 6H), 0.89-0.87 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 49.6, 34.5, 31.4, 28.2, 26.2, 22.5, 13.9.

HRMS (ESI) *m/z* calcd for $C_9H_{16}F_3NO$ $[M+H]^+$ 212.1262, found 212.1269.

4.5.2 *Borylation of alkylamines:*

Borylation of 1,1,1-trifluoro-N-hexyl-N-methylmethanesulfonamide:



In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^oC. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), CyH

was removed under reduced pressure and chromatographic separation with silica gel gave 66.2 mg (71%) of corresponding borylated product.

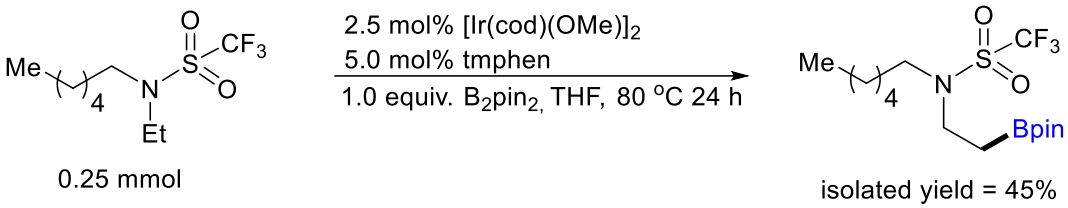
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.46-3.35 (m, 2H), 3.12-3.03 (m, 2H), 1.60-1.57 (m, 3H), 1.26 (s, 12 H), 0.89-0.83 (m, 8H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.2 (q, *J* = 322.3), 84.5, 50.3, 31.3, 29.7, 26.0, 24. 7, 14.0.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 32.0.

HRMS (ESI) *m/z* calcd for $C_{14}H_{30}BNO_4S$ $[M+Na]^+$ 396.1604, found 396.1614.

Borylation of 1,1,1-trifluoro-N-hexyl-N-ethylmethanesulfonamide:



0.25 mmol

isolated yield = 45%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as an elutant) gave 43.6 mg (45%) corresponding borylated product.

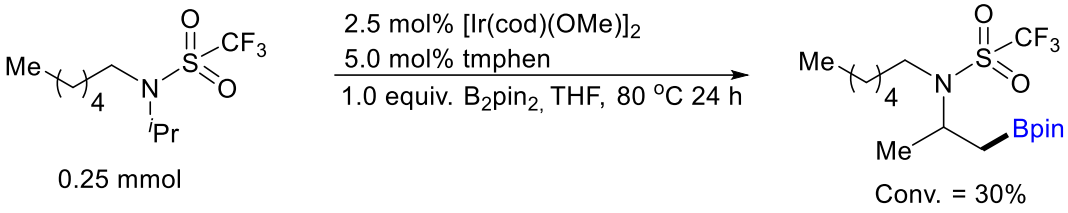
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.52-3.48 (m, 2H), 3.33 (m, 2H), 1.59 (m, 2H), 1.29 (m, 6H), 1.24 (s, 12H), 0.90-0.84 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.0 (q, *J* = 321.8 Hz), 82.6, 46.7, 43.5, 30.3, 27.3, 25.1, 23.8, 21.5, 12.9.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 32.9.

HRMS (ESI) *m/z* calcd for $C_{15}H_{32}BNO_4S$ $[M+Na]^+$ 410.1760, found 410.1787.

Borylation of 1,1,1-trifluoro-N-hexyl-N-isopropylmethanesulfonamide:

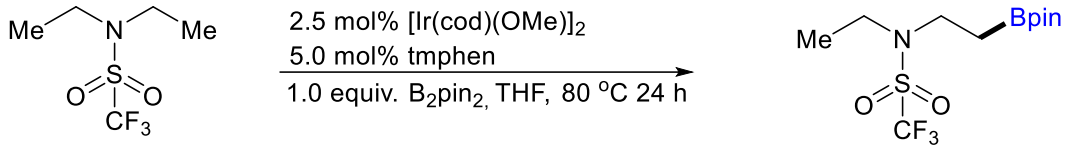


0.25 mmol

Conv. = 30%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^{o}C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and conversion was based on crude NMR analysis.

Borylation of N,N-diethyl-1,1,1-trifluoromethanesulfonamide:



0.25 mmol

isolated yield = 51%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected aniline (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^{o}C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as an elutant) gave 42.2 mg (51%) of corresponding borylated product.

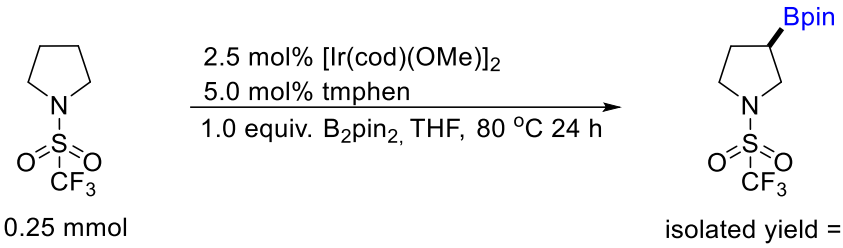
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.51-3.43 (m, 4H), 1.25 (s, 12H), 1.21-1.18 (m, 2H), 0.91-0.83 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.0 (q, J = 312.2 Hz), 83.6, 44.0, 42.5, 13.9.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 32.1.

HRMS (ESI) *m/z* calcd for $C_{11}H_{24}BNO_4S$ $[M+Na]^+$ 354.1134, found 354.1147.

Borylation of 1-((trifluoromethyl)sulfonyl)pyrrolidine:



0.25 mmol

isolated yield = 65%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^{o}C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as an elutant) gave 53.5 mg (65%) corresponding borylated product.

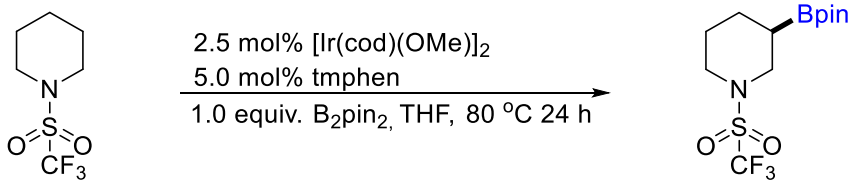
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.74-3.60 (m, 2H), 3.48-3.40 (m, 2H), 2.18-2.11 (m, 1H), 1.98-1.88 (m, 1H), 1.77-1.68 (m, 1H), 1.24 (s, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.4 (q, *J* = 322.2 Hz), 84.0, 51.1, 50.0, 28.4, 24.0.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 33.1.

HRMS (ESI) *m/z* calcd for $C_{11}H_{22}BNO_4S$ $[M+Na]^+$ 352.0978, found 352.0995.

Borylation of 1-((trifluoromethyl)sulfonyl)piperidine:



0.25 mmol

isolated yield = 32%

In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 ^{o}C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and chromatographic separation with silica gel (3% ethyl acetate in hexane as an elutant) gave 27.5 mg (32%) corresponding borylated product.

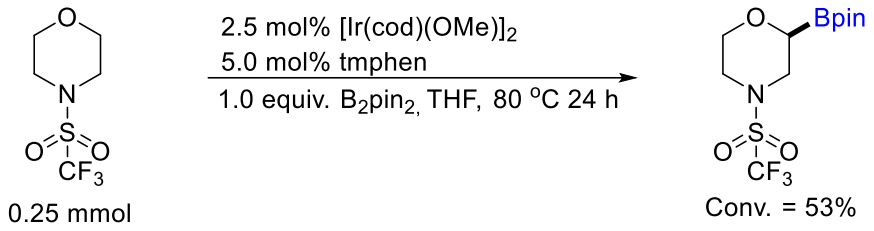
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.89-3.79 (m, 2H), 3.11-3.06 (m, 2H), 1.92-1.89 (m, 1H), 1.79-1.74 (m, 1H), 1.64-1.54 (m, 1H), 1.23 (s, 12H), 0.89-0.82 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.9 (q, J = 315.3 Hz), 83.6, 48.7, 47.4, 29.7, 24.9, 24.7.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 31.8.

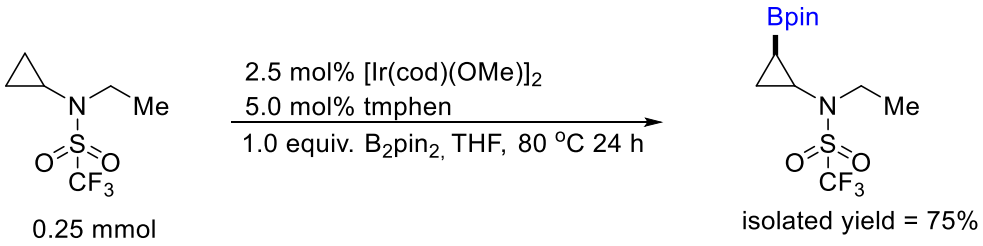
HRMS (ESI) *m/z* calcd for $C_{12}H_{24}BNO_4S$ $[M+Na]^+$ 366.1236, found 366.1128.

Borylation of 4-((trifluoromethyl)sulfonyl)morpholine:



In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected aniline (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and conversion is based on crude NMR analysis.

Borylation of N-cyclopropyl-N-ethyl-1,1,1-trifluoromethanesulfonamide:



In an argon filled glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (4.14 mg, 2.5 mol%), tmphen (2.95 mg, 5.0 mol%), B_2pin_2 (63.50 mg, 1.0 equiv.) and dry hexane (1.0 mL). The reaction mixture was stirred for 2 minutes at room temperature. To this mixture, *N*-protected amine (0.25 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into pre-heated aluminium block at 80 °C. The reaction mixture was stirred for 24 h. After completion (judged by GC/MS), THF was removed under reduced pressure and chromatographic separation with silica gel (3%

ethyl acetate in hexane as an elutant) gave 64.34 mg (75%) corresponding borylated product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.51-3.35 (m, 2H), 2.82-2.78 (m, 1H), 1.30-1.26 (m, 4H), 1.21 (s, 12H), 1.06-1.00 (m, 1H), 0.42-0.37 (m, 1H).

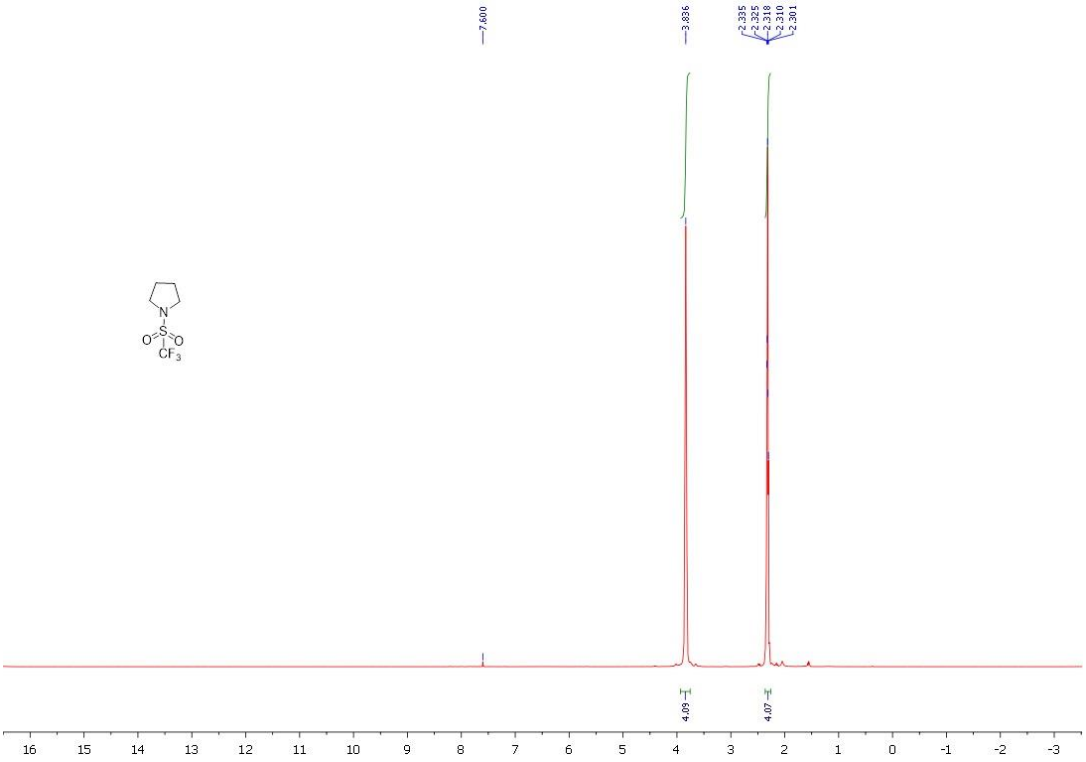
^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.8 (q, J = 322.2 Hz), 83.7, 46.2, 34.5, 24.6, 13.8, 13.3.

^{11}B-NMR (128 MHz, $CDCl_3$): δ 32.0.

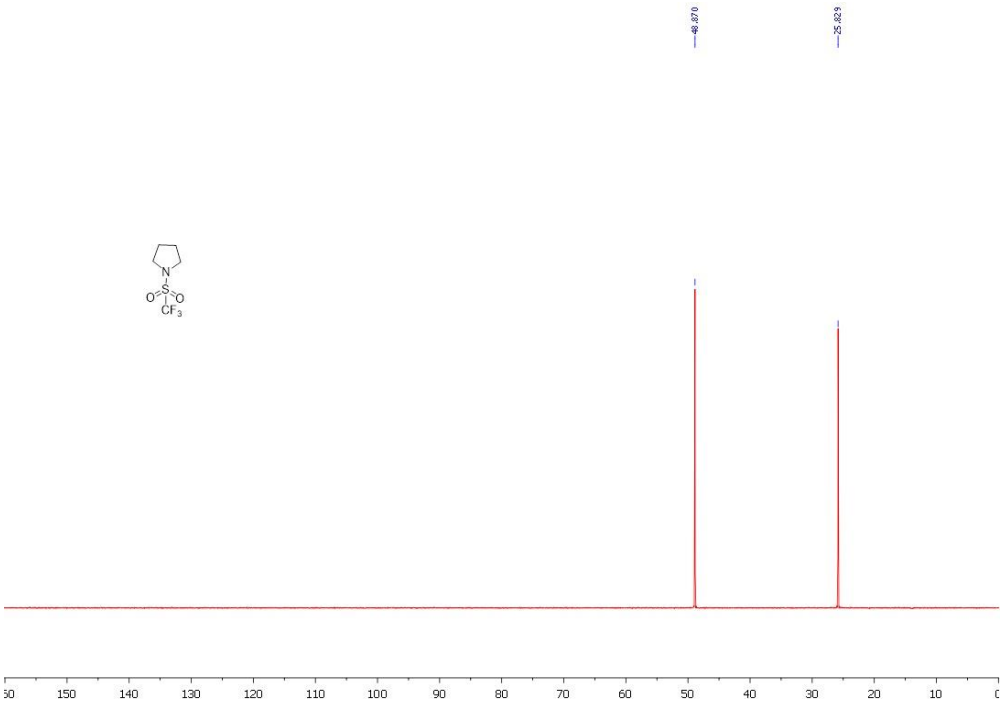
HRMS (ESI) *m/z* calcd for $C_{12}H_{21}BF_3NO_4S$ $[M+Na]^+$ 366.1134, found 366.1152.

4.5.3 Spectral Copies

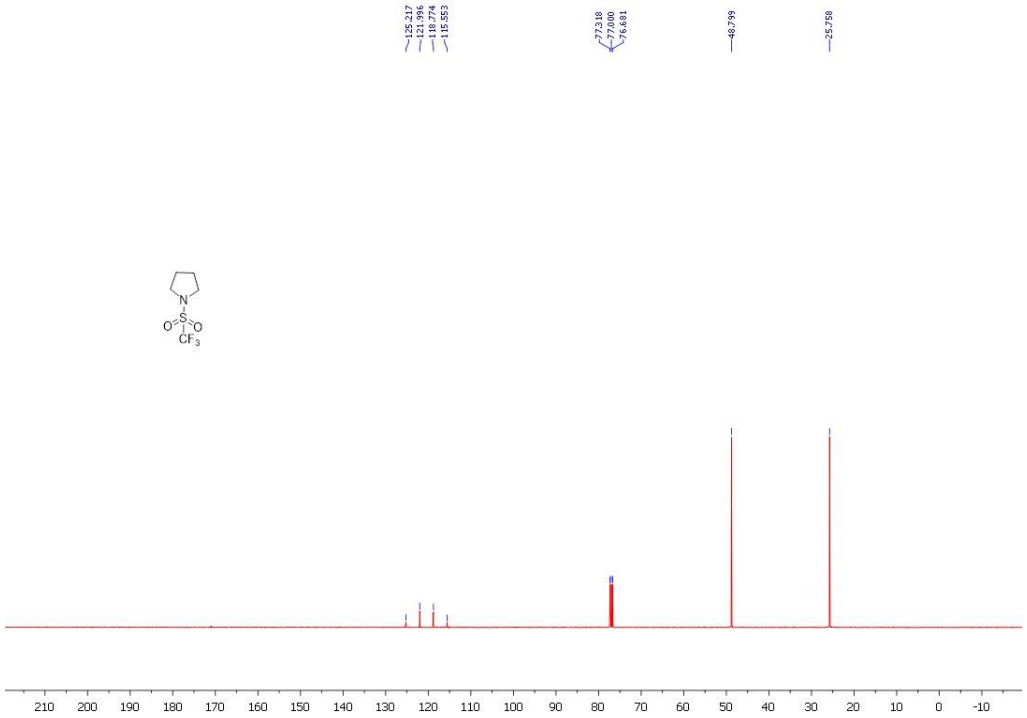
^{1}H ,^{13}C & ^{13}C-DEPT NMR of 1-((trifluoromethyl)sulfonyl)pyrrolidine **(1e):**



^{1}H NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

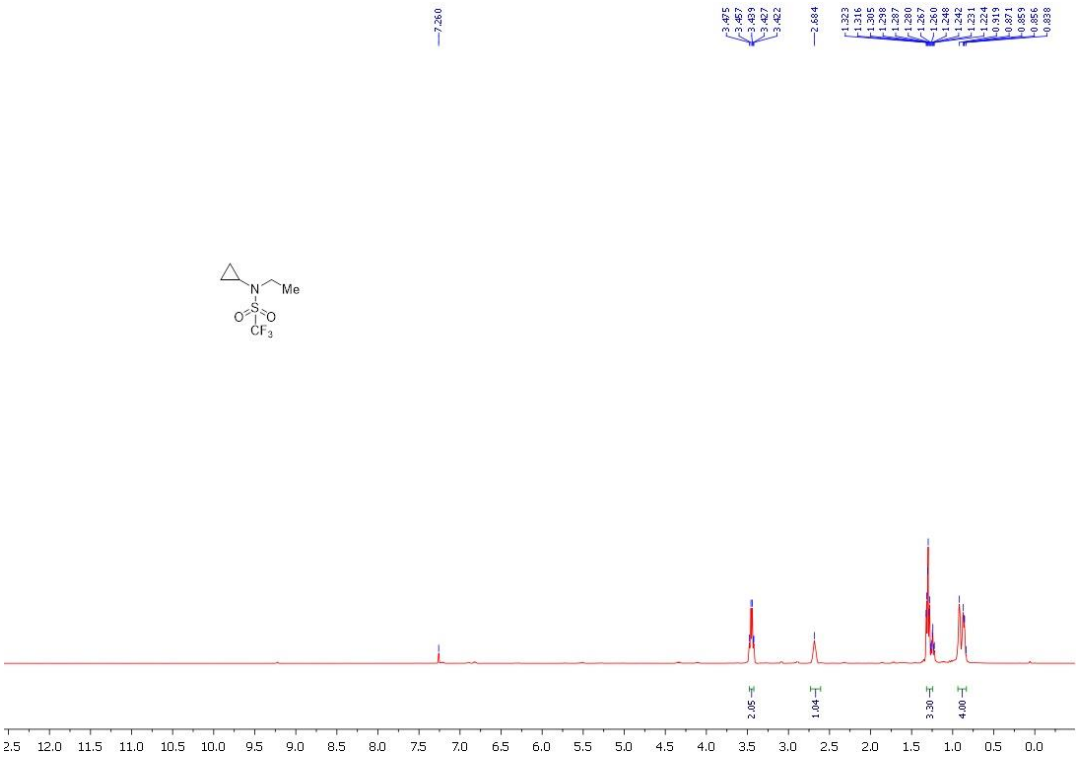


^{13}C DEPT-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

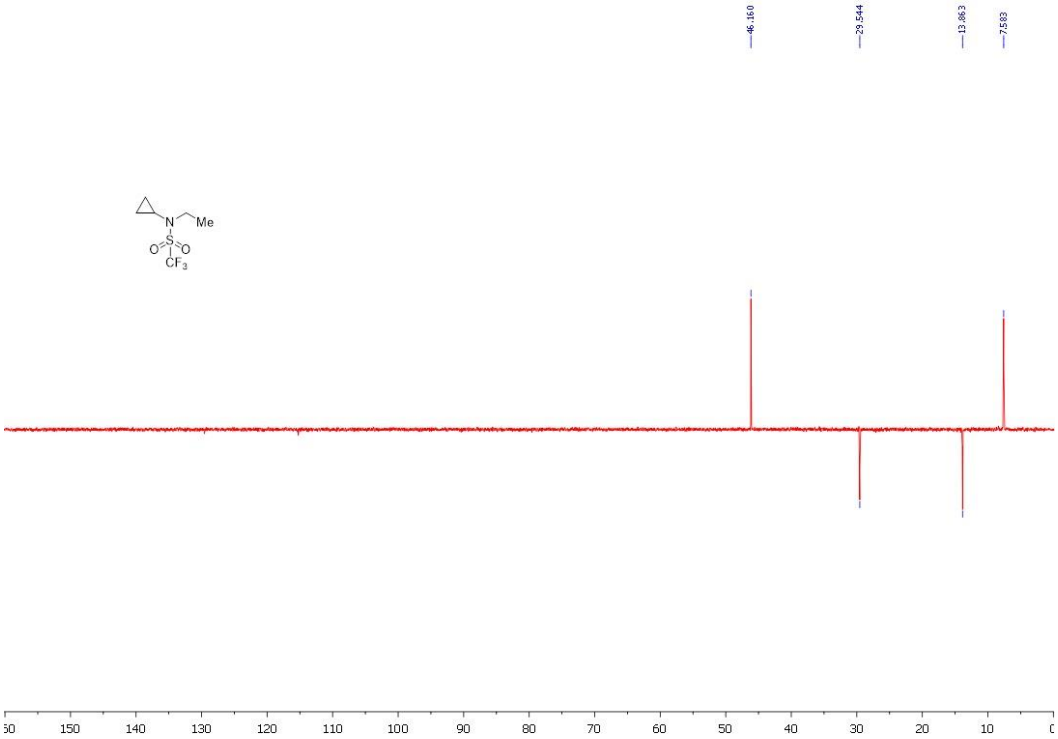


^{13}C NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

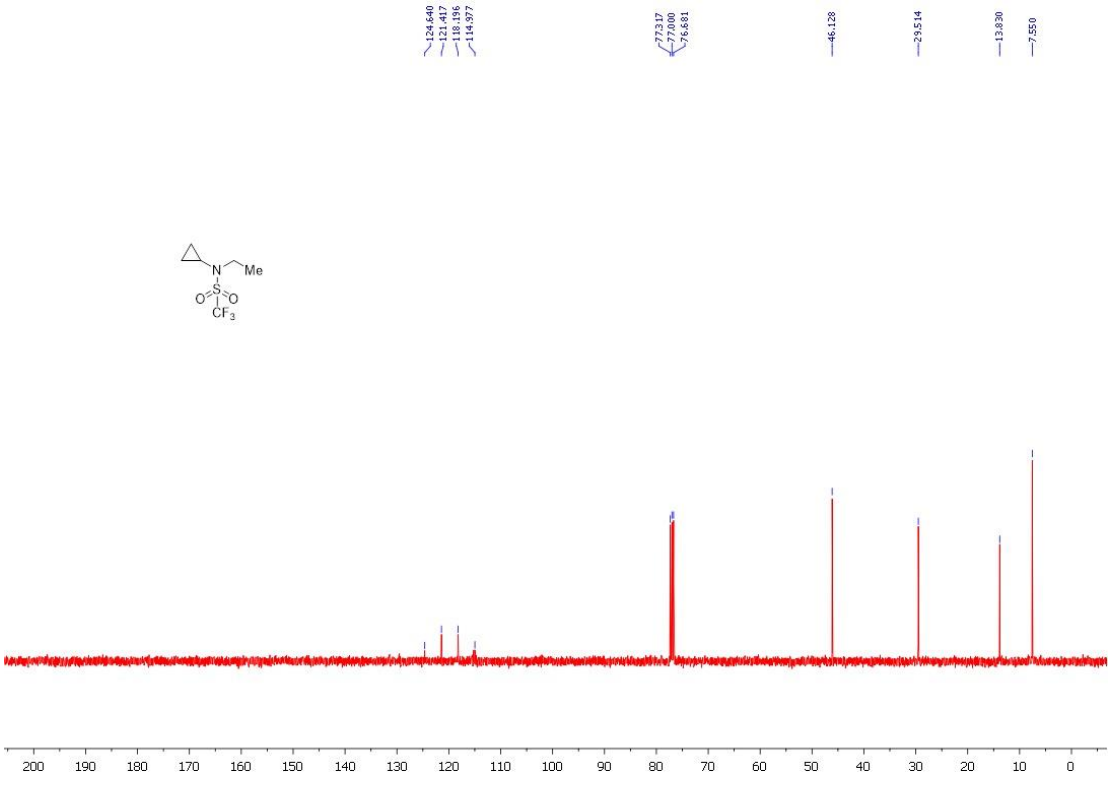
^{1}H,^{13}C & ^{13}C-DEPT-NMR of *N*-cyclopropyl-*N*-ethyl-1,1,1-trifluoromethanesulfonamide (1d):



^{1}H NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

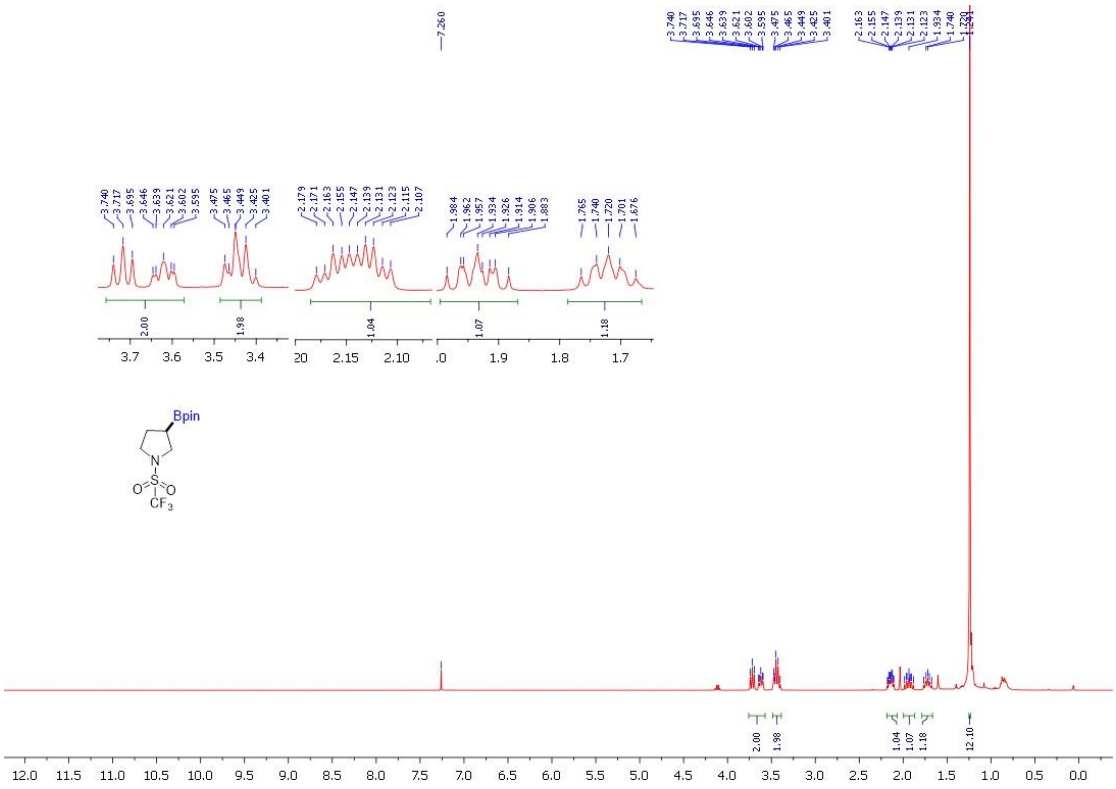


^{13}C DEPT-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

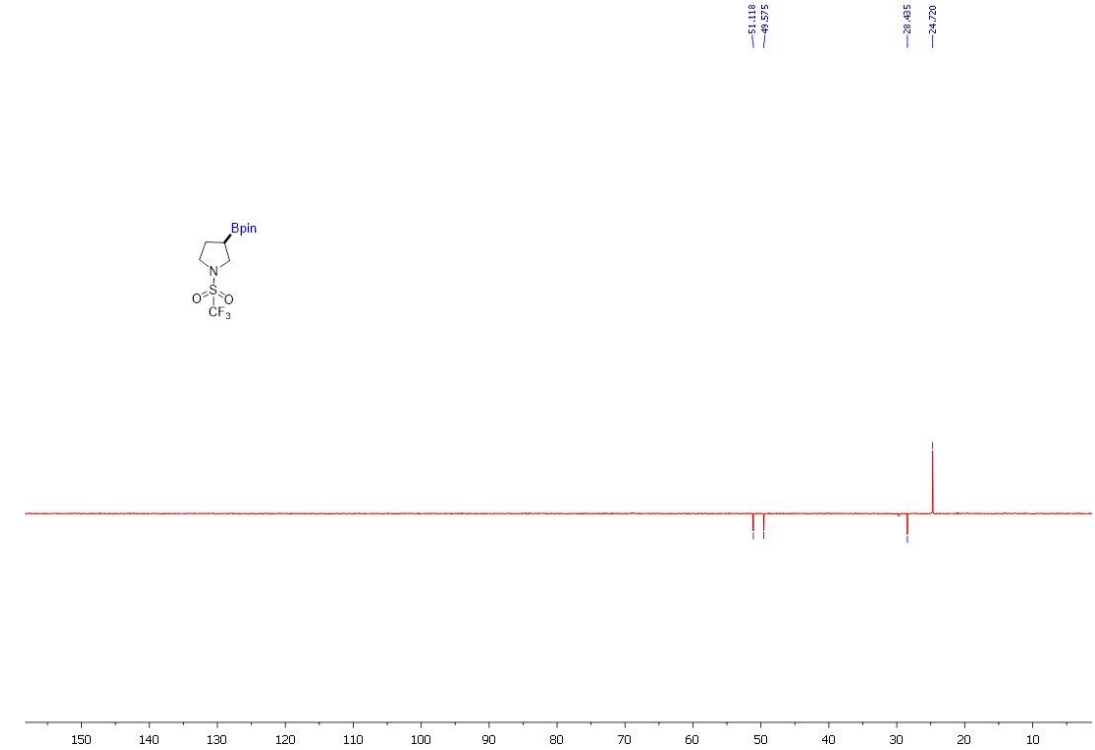


^{13}C NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

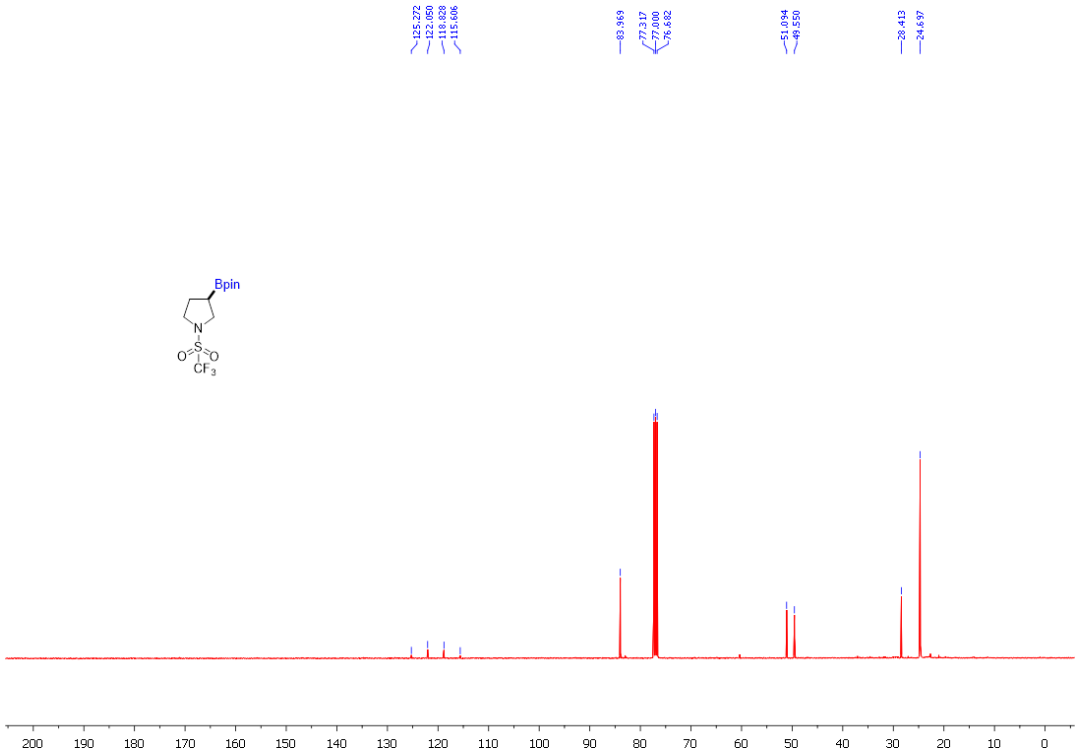
^{1}H,^{13}C & ^{13}C-DEPT-NMR of borylated compound **(2e):**



^{1}H NMR (25 ^{o}C, 400 MHz, $CDCl_3$)

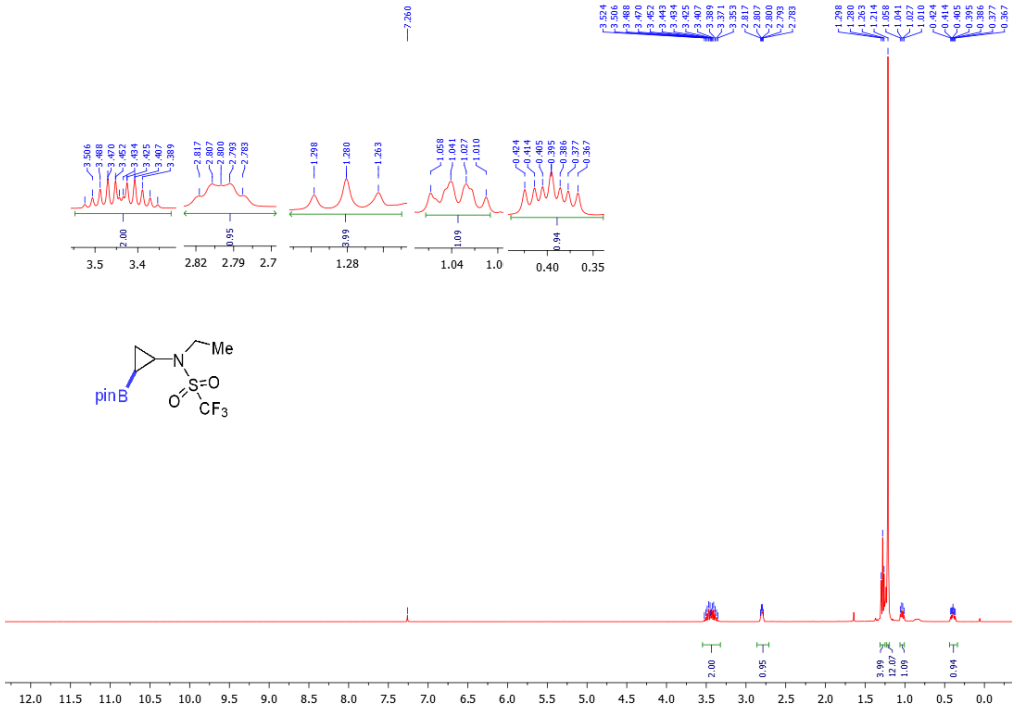


^{13}C DEPT-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

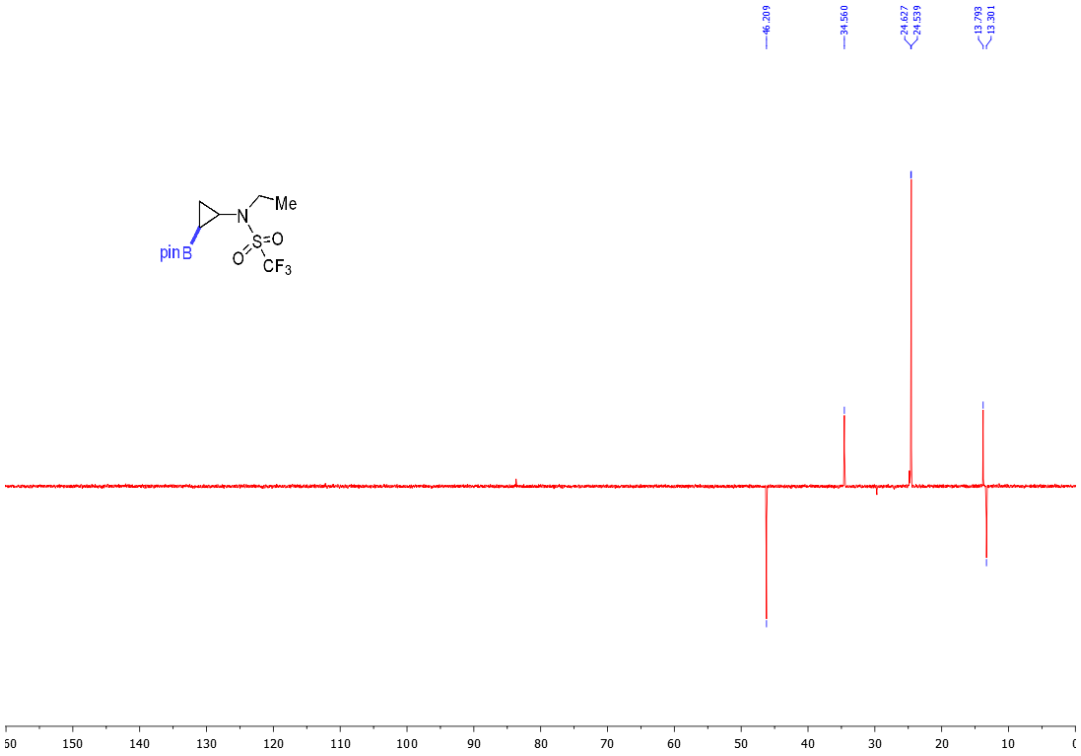


^{13}C NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

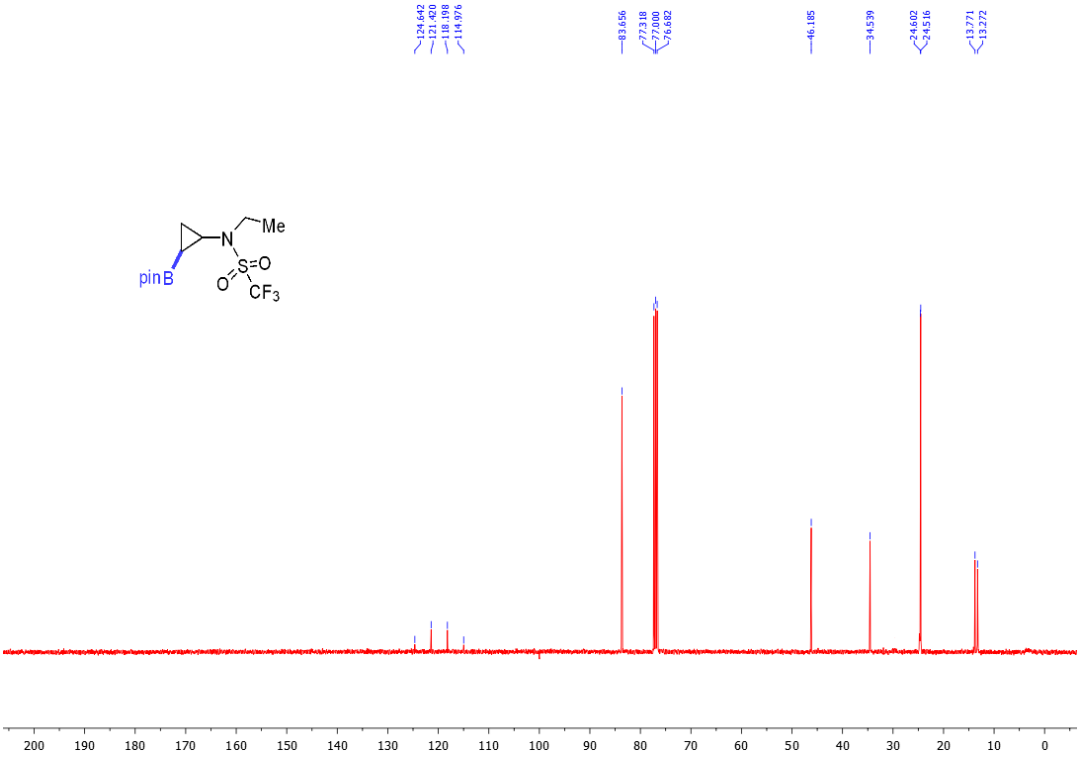
^{1}H,^{13}C & ^{13}C-DEPT-NMR of borylated compound (2d):



^{1}H NMR (25 ^{o}C, 400 MHz, $CDCl_3$)



^{13}C DEPT-NMR (25 ^{o}C, 100 MHz, $CDCl_3$)



^{13}C NMR (25 ^{o}C, 100 MHz, $CDCl_3$)

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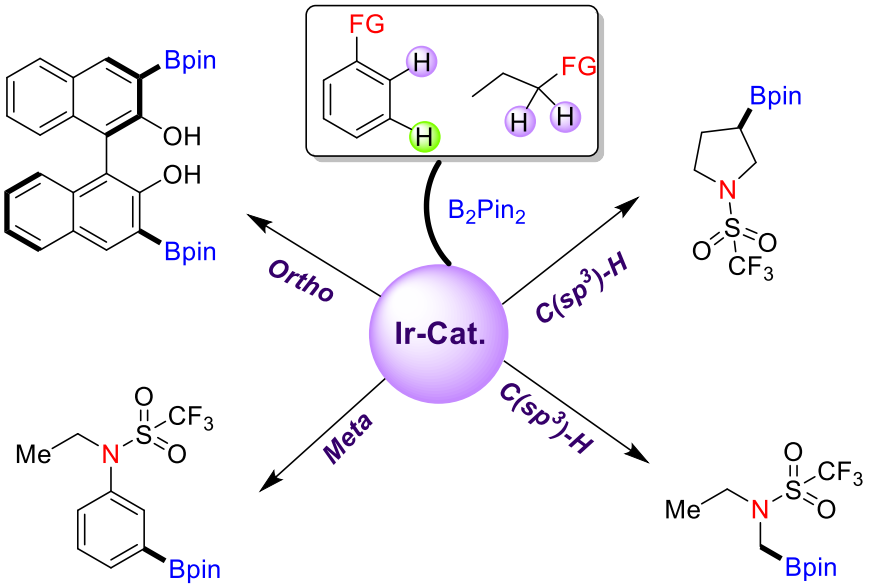
CHAPTER 5

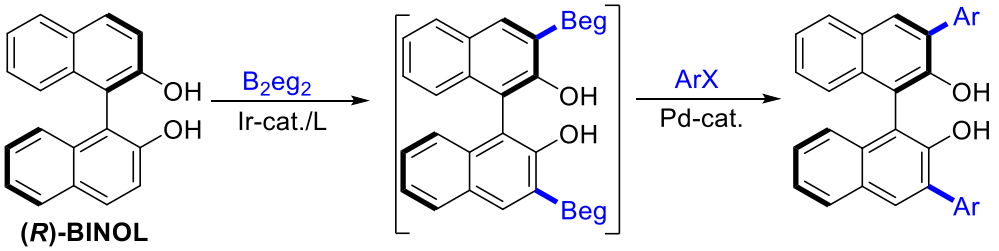
Summary of Research Work



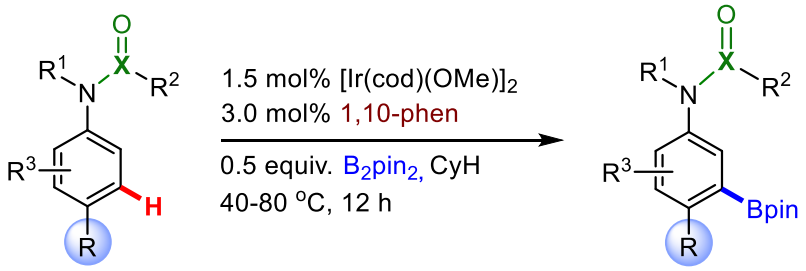
Research Summary

Recently, carbon hydrogen bond activation and subsequent borylation have laid the cornerstone in the area of organic synthesis. Since the discovery, borylation reaction using transition metal-catalyst emerged as a straightforward and step-economy strategies to get access of high-valued boronate esters. Due to the widespread application of organoborane compounds in the area of natural product synthesis, pharmaceuticals, fine chemicals and so forth, borylation strategy is extremely effective and advances many advantages over existing methods. Apart from steric effect to govern the site selectivity of borylation reaction, noncovalent interaction, traceless directing group, designing of substrates have also gained much interest and have studied steadily to regulate the regioselectivity. The work described in this thesis summarizes the growth of arene C-H borylation reaction along with inert C(sp^3)-H bond borylation reaction.

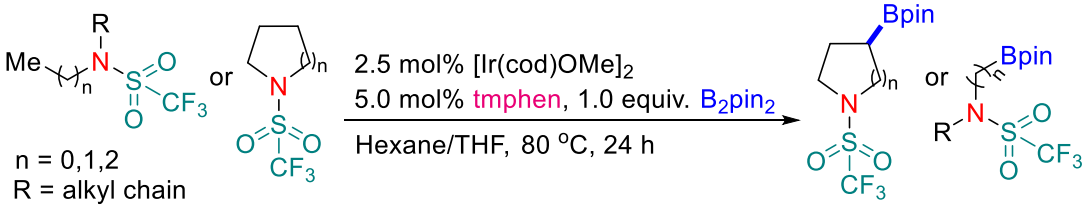
- **Chapter 1** describes many elegant directed and non-directed metal-catalyzed arene and aliphatic borylation reaction along with several seminal works. This chapter also highlights the synthetic efficacy of borylation reaction in medicinal chemistry and drug discovery also.
- **Chapter 2** demonstrates a double fold *ortho*, *ortho'*-diborylation/arylation strategy of BINOLs. It has been mentioned that an electrostatic interaction determines the regioselectivity (*ortho* selectivity). A one pot strategy i.e., borylation followed by Suzuki coupling has been established. Applying the developed one pot method, a number of 3,3'-diaryl BINOLs could be synthesized with good yield and enantioselectivity. It should be mentioned that highly important chiral 3,3′-biaryl BINOL compound could be synthesized in gram scale from commercially obtainable inexpensive (*R*)-BINOL.



- **Chapter 3** represents a novel concept of *meta* borylation of *N*-protected aniline and other arene systems. The *meta* selectivity is governed by an electrostatic interaction between the *N*-protected arenes and 1,10-phenanthroline ligand. The developed catalytic system can borylate a number of 2-substituted, 3-substituted, disubstituted arenes with good selectivity and yield. Interestingly, a variety of *para*-substituted arenes could be borylated with a good *meta* selectivity, which remains a significant challenge. It is worth mentioning that developed *meta* borylation method requires only 0.5 equiv. of B_2pin_2.The synthetic usefulness of this Ir-based catalytic system is illustrated by transforming the borylated product into many new functionalities.



- **Chapter 4** displays a Ir-based C(sp^3)-H borylation of alkyl and cyclic triflate protected amine systems. The developed catalytic system is capable of borylating various alkyl chain along with cyclic amines with good selectivity. This borylation method does not need high temperature and extra amount of substrate or neat conditions.



List of Publications

1. Double-Fold Ortho and Remote C-H Bond Activation/Borylation of BINOL: A Unified Strategy for Arylation of BINOL. Bisht, R.; **Chaturvedi, J**.; Pandey, G.; Chattopadhyay, B. *Org. Lett.* **2019**, *21*, 6476-6480.
2. Meta Selective C-H Borylation of Sterically Biased and Unbiased Substrates Directed by Electrostatic Interaction. **Chaturvedi, J**.; Haldar, C.; Bisht, R.; Pandey, G.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2021**, *143*, 7604-7611.
3. Iridium-catalyzed para-selective C-H borylation reactions. **Chaturvedi, J**.; Hassan, M. M. M.; Haldar, C.; Chattopadhyay, B. *Handbook of C-H bond Functionalizations*. **2021** in press (Wiley).
4. Ir-catalyzed proximal and distal C–H borylation of arenes. Haldar, C.; Hoque, E. M.; **Chaturvedi, J**.; Hassan, M. M. M.; Chattopadhyay, B. *Chem. Commun.* **2021**, *57*, 13059-13074.
5. Iridium-catalyzed C(sp^3)-H activation and borylation of *N*-protected alkylamines. **Chaturvedi, J**.; Guria, S.; Chattopadhyay, B. (Unpublished results)
6. Ir-Catalyzed Ligand Free Directed C-H Borylation of Arenes and Pharmaceuticals: Detailed Mechanistic Understanding. Hassan, M. M. M.; Mondal, B.; Singh, S.; Haldar, C.; **Chaturvedi, J**.; Bisht, R.; Sunoj, R. B.; Chattopadhyay. B. (Manuscript submitted).
7. Ligand Controlled Para C-H Borylation at Room Temperature. Haldar, C.; Bisht, R.; **Chaturvedi, J.**; Guria, S.; Ram, B.; Chattopadhyay, B. (Manuscript in preparation).
8. Electrostatically Directed Meta Selective Borylation of Arenes. **Chaturvedi, J**.; Haldar, C.; Chattopadhyay, B. (Manuscript in preparation).
9. C-H Borylation–A Mainstream Reaction: Recent Developments. Bisht, R.; Haldar, C.; Hassan, M. M. M.; Hoque, E. M.; **Chaturvedi, J**.; Chattopadhyay, B. (Review article submitted).

Seminars Attended

1. Double-Fold Ortho and Remote C–H Bond Activation/Borylation of BINOL: A Unified Strategy for Arylation of BINOL. JNOST-XIV, CSIR-Indian Institute of Chemical Technology, Hyderabad. (Poster Presentation)
2. Method of meta-selective C-H borylation of aromatic molecules via electrostatic interaction. JNOST-XVI, Indian Institute of Science, Bangalore, India. (Oral Presentation)

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Double-Fold Ortho and Remote C−H Bond Activation/Borylation of BINOL: A Unified Strategy for Arylation of BINOL

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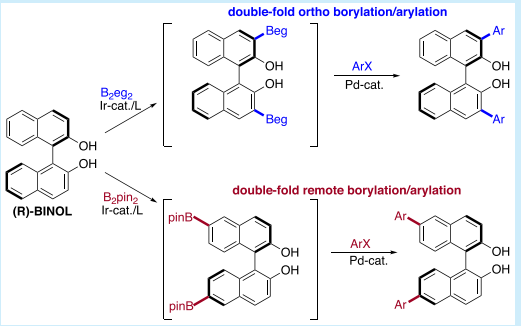
Supporting Information

ABSTRACT: A double-fold ortho and remote C−H borylation of BINOL is described. The proposed mechanisms involved electrostatically and sterically directed ortho and remote C−H activation processes, respectively. While B_2eg_2 (eg = ethylene glycolate) directs the C−H activation at ortho positions, a combination of HBpin and B_2pin_2 activates remote C−H bonds. The strategy was combined with Suzuki arylation as a one-pot protocol for the rapid synthesis of BINOL derivatives with retention of chirality.



While numerous C−H bond functionalizations[1] are now available, C−H bond borylation has potential because of the versatile synthetic transformations[2] of B−C bonds. Usually, a major challenge in C−H bond borylation of arenes is the site selectivity.[3] For the selective ortho-borylation of arenes, the common strategies are the directed metalation[4] and functional group[5] directed borylation. However, these are highly dependent on what kind of functional groups are present on the substrates. On the other hand, remote C−H borylations are still difficult to realize but nevertheless practically beneficial.[6] Recently, few strategies have been developed for the remote C−H borylation using various noncovalent interactions.[7] However, there is no general method available to achieve the remote borylations, and every method has its own restriction. Moreover, examples for the selective ortho and remote C−H activation/borylation from the same substrate are almost rare,[7a] although extremely desirable.

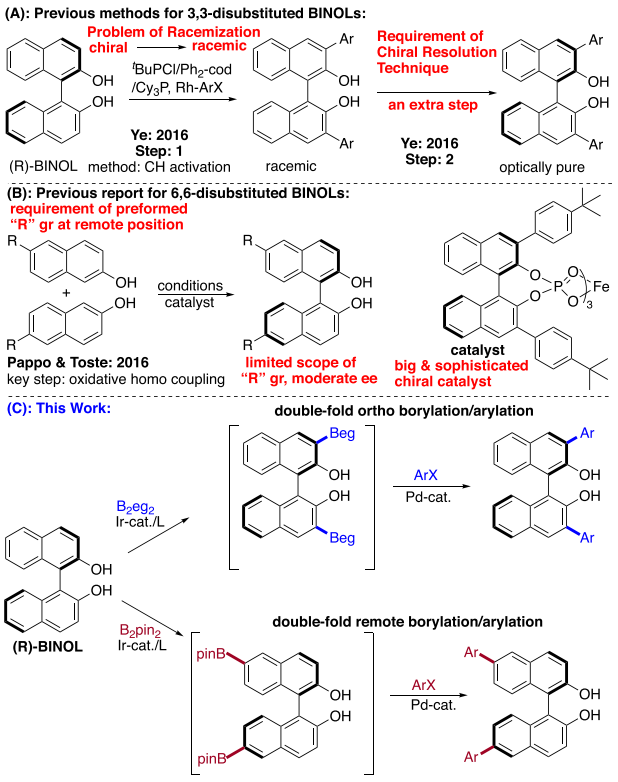


Figure 1. Previous works and new challenge.

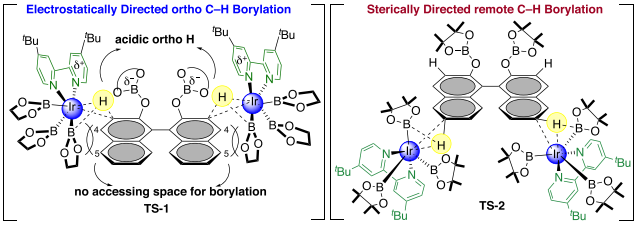


Figure 2. Proposed working model for ortho and remote borylation.

On the other hand, 3,3′-biaryl and 6,6′-biaryl BINOLs have been recognized as the ideal backbones for chiral ligands that are being tremendously utilized in asymmetric catalysis.[8−10] There

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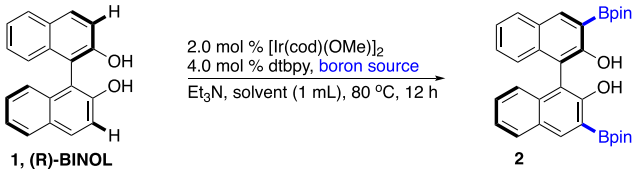
Table 1. Optimization of the Double-Fold Ortho Borylation[a]



entry	boron source (equiv)	base (equiv)	solvent	yield (%) (**2**)
1	B_2eg_2 (2.5)	Et_3N (2.5)	PhMe	solvent borylation
2	B_2eg_2 (2.5)	Et_3N (2.5)	CyH	complex mixture
3	B_2eg_2 (2.5)	Et_3N (2.5)	*p*-xylene	solvent borylation
4	B_2eg_2 (2.5)	Et_3N (2.5)	THF	53[b]
5	**B_2eg_2(4.0)**	**Et_3N (4.0)**	**THF**	**79**[b]
6	HBpin (4.0)	Et_3N (4.0)	THF	complex mixture
7	B_2pin_2 (4.0)	Et_3N (4.0)	THF	complex mixture

[a]Scale of reaction 0.1 mmol. [b]Isolated yields after transesterification with pinacol.

are four different methods to prepare 3,3′-biaryl BINOLs, such as (i) Snieckus's five-step protocol,[11] (ii) Jorgensen's six-step protocol,[12] (iii) Fu's three-step method,[13] and (iv) Clark's three-step method.[14] Importantly, the use of large amounts of air-sensitive alkyl lithium salts, multistep reactions, and long reaction time significantly limit the synthetic utility of the Snieckus and Jorgensen methods. Likewise, employment of the directing groups in C−H activation methods require extra steps and generation of the stoichiometric waste from the attaching and detaching that limits the wide applicability of Fu's and Clark's method. More recently, Ye and co-workers reported an efficient one step route to access varieties of 3,3′-biaryl BINOLs (Figure 1A).[15]

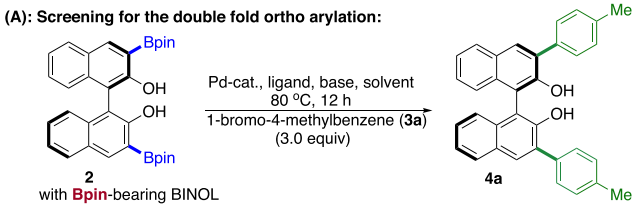
However, the major problem of this method is the racemization of the chiral BINOLs and the corresponding arylated products under the employed reaction conditions. To obtain the optically pure isomer it needs a chiral resolution technique, which adds an extra step. Thus, these findings are indicative of a lack of efficient methods for the preparation of chiral 3,3′-biaryl BINOLs. Moreover, direct preparation of chiral 6,6′-biaryl BINOLs remains an unmet challenge due to the difficulty of the remote C−H bond functionalization. There are only a few reports for the preparation of chiral 6,6′-biaryl BINOLs via electrophilic bromination and Fe-based catalyst by Pappo and Toste (Figure 1B).[16] Herein, we report the discovery of double fold ortho and remote C−H arylation of chiral BINOL using a C−H activation/borylation strategy directed by an electrostatic interaction and a steric control (Figure 1C).

Recently, it has been demonstrated[17] that ortho C−H borylation of phenol is possible via an electrostatic interaction between a partial negatively charged in situ generated OBpin/OBeg group and a partial positively charged ligand of the Ir catalyst. Thus, we hypothesized that there is a fair possibility for the electrostatic interaction[9] between the positively charged ligand and the negatively charged OBeg intermediate, which might selectively increase the acidity of both the ortho C−H bonds of BINOL (Figure 2, **TS-1**), although BINOL has many similar types of C−H bonds relative to the small phenol substrate.

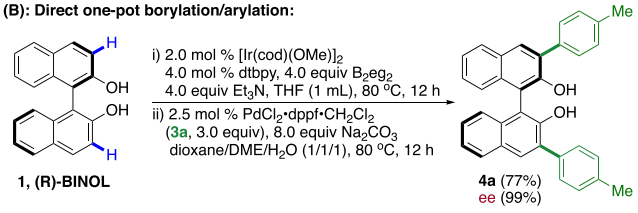
Moreover, we anticipated that by altering the boron functionality from small Beg to the larger Bpin, the ortho C−H bonds of BINOL would be inaccessible (for steric reason), enforcing the remote borylation (Figure 2, **TS-2**). Notably, other remote C−H bonds might be competitive (C5 or C7), but due to the combined steric and electronic factors of the relatively larger OBpin groups they might facilitate the remote 6,6′-borylation.[16a,b,18]

First, we focused on the double-fold ortho C−H borylation with the (*R*)-BINOL. We studied the borylation of (*R*)-BINOL using recently reported phenol's ortho borylation conditions.[17] Thus, (*R*)-BINOL, 2.5 equiv of B_2eg_2, and 2.5 equiv of Et_3N were heated in PhMe (Table 1, entry 1) and it was found that phenol's borylation conditions is unsuccessful, which afforded only solvent borylation. To avoid the solvent borylation, we

Table 2. Optimization of Double-Fold Ortho Arylation[a]



entry	catalyst (mol %)	ligand (mol %)	base (equiv)	solvent	conv[b] (%)
1	$Pd(PPh_3)_4$ (5)		K_2CO_3 (2)	PhMe/H_2O (6/1)	nr
2	$Pd(PPh_3)_4$ (5)		K_2CO_3 (2)	DME/H_2O (1/1)	nr
3	$Pd(PPh_3)_4$ (5)		CsF (3)	THF/H_2O (10/1)	nr
4	Pd_2dba_3·$CHCl_3$ (2)	P(*o*-tolyl)$_3$ (4)	K_2CO_3 (8)	THF/H_2O (10/1)	85
5	**$PdCl_2$·dppf·CH_2Cl_2(2.5)**		**Na_2CO_3(8)**	**dioxane/DME/H_2O(1/1/1)**	**90 (79)**[c]



[a]Scale of reaction: 0.1 mmol. [b]NMR conversion. [c]In parentheses, isolated yields.

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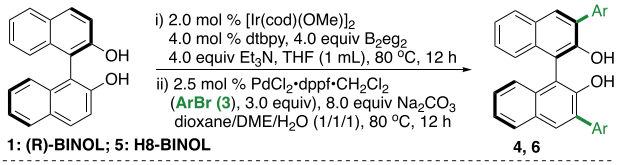
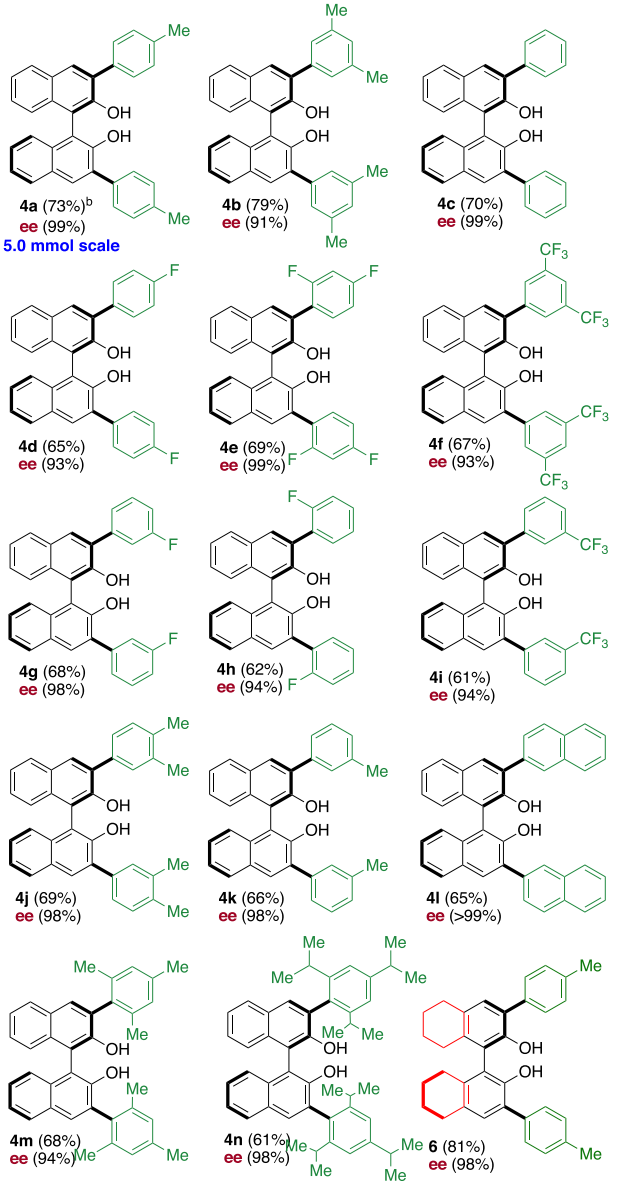
Scheme 1. Scope of Double-Fold Ortho Borylation/Arylation[a]

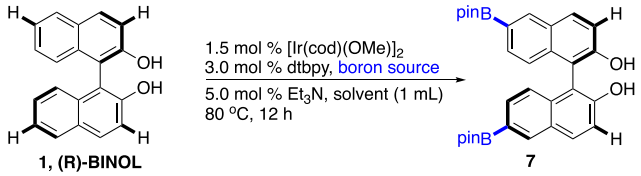




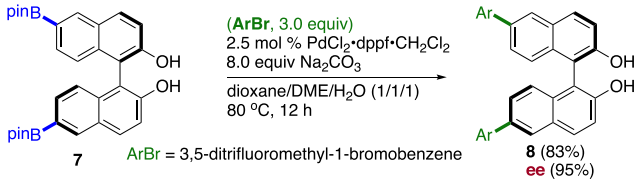
[a]Scale of reaction 0.1 mmol; isolated yields. [b]Reaction scale 5.0 mmol. [c]Undetermined.

attempted the borylation in cyclohexane (CyH) or *p*-xylene; however, in both cases, we did not observe our desired product (entries 2 and 3). When the borylation was performed in THF, no solvent borylation was detected and an appreciable amount of the desired product was found by crude NMR analysis. Notably, attempted isolation of the Beg-borylated product was not successful due to the rapid proto-deborylation process. Thus, when the borylation was completed, the eg (ethylene glycolate) group was transesterified by treating the crude reaction mixture with 2.5 equiv of pinacol in dry $CHCl_3$, and the

Table 3. Remote Double-Fold Borylation/Arylation[a]



entry	HBpin (equiv)	B_2pin_2 (equiv)	solvent	conv (%) (7)
1	4.0		THF	complex mixture
2		2.0	THF	complex mixture
3[b]	2.5	2.0	PhMe	solvent borylation
4[b]	2.5	2.0	CyH	multiple borylation
5[b]	2.5	2.0	THF	44
6[b]	**3.0**	**2.5**	**THF**	**95 (87)**[c]



[a]Scale of reaction 0.1 mmol scale; NMR conversion. [b]In this case, sequence of addition is important. For details, see the SI. [c]Isolated yields after 16 h are shown in parentheses.

relatively more stable Bpin product was isolated in 53% yield (entry 4).

Remarkably, by repeating the same reaction using 4.0 equiv of B_2eg_2 and 4.0 equiv of Et_3N, we isolated the double-fold relatively stable Bpin product in 79% after transesterification (entry 5) along with some amount of the monoborylated product. It should be mentioned that due to the rapid protodeborylation, we were unable to measure the ratio of the mono-/bis-borylated products. As expected, by performing the borylations using either HBpin or B_2pin_2 we found that the borylations were nonselective (entries 6 and 7).

Next, we examined the arylation of *o*,*o*-diborylated BINOL (**2**) with 1-bromo-4-methylbenzene (**3a**) employing 5 mol % of $Pd(PPh_3)_4$ catalyst and K_2CO_3 in PhMe/H_2O at 80 °C (Table 2A, entry 1). However, no desired arylated product was observed. Use of other bases and solvents were ineffective (entries 2 and 3). Pleasingly, employment of Pd_2dba_3·$CHCl_3$ and *o*-tolylphosphine gave 85% conversion of the product (entry 4). Performing the reaction in the presence of $PdCl_2$·dppf·CH_2Cl_2 and Na_2CO_3 in dioxane/DME afforded the product in 90% conversion (entry 5). Subsequently, we successfully combined this two-step method in a one-pot method, which afforded the desired product in 77% isolated yield with 99% ee (Table 2B).

To show the synthetic usefulness of the protocol, a large-scale (5 mmol) double-fold ortho C−H borylation/arylation of (*R*)-BINOL was performed, which afforded the target 3,3′-biaryl BINOL (**4a**) in 73% yield with 99% ee (Scheme 1, entry 1). Notably, this one-pot preparation of highly important chiral 3,3′-biaryl BINOL (average cost ∼$1000/gram) using less expensive (*R*)-BINOL ($1.0−4/gram) demonstrates that the developed method would be a useful synthetic tool for chiral 3,3′-biaryl BINOL.

Next, we explored the scope of the reaction (Scheme 1). For example, use of electron-rich aryl bromide (**3b**) and electronically neutral bromobenzene (**3c**) afforded 79% (91% ee) and 70% (99% ee) yields, respectively. Electron-deficient aryl

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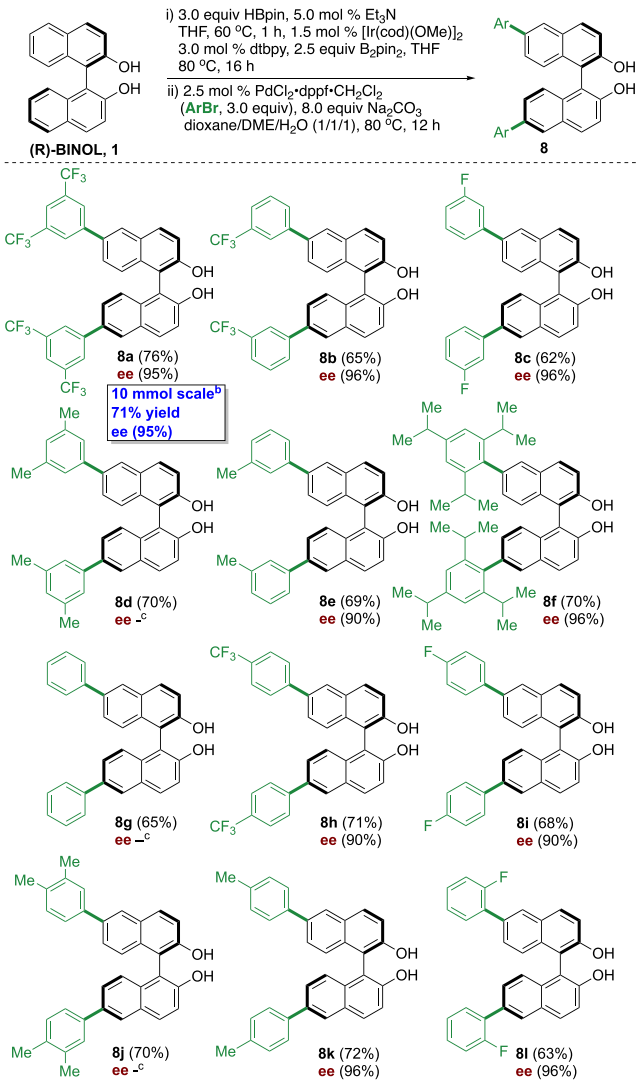
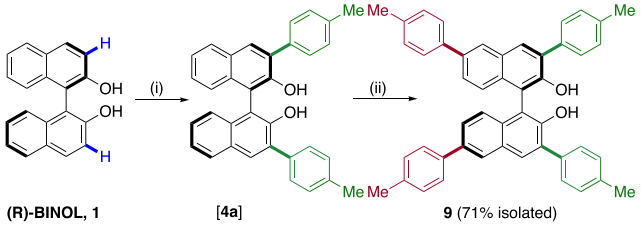
Scheme 2. Scope of Double-Fold Remote Borylation/Arylation[a]



[a]Scale of reaction 0.1 mmol; isolated yields. [b]10 mmol scale. [c]Undetermined.

Scheme 3. Sequential Double-Fold Ortho and Remote Borylation and Arylation[a]



[a]Conditions: (i) 2.0 mol % of Ir, 4.0 mol % of dtbpy, 4.0 equiv of B_2eg_2, 4.0 equiv of Et_3N, THF, 80 °C, 12 h; then 2.5 mol % of $PdCl_2$·dppf·CH_2Cl_2, 3.0 equiv of **3a**, 8.0 equiv of Na_2CO_3, dioxane/DME/H_2O (1/1/1), 80 °C, 12 h; then short column filtration and dried; (ii) 3.0 equiv of HBpin, 5.0 mol % of Et_3N, THF, 60 °C for 1 h, then 1.5 mol % of Ir, 3.0 mol % of dtbpy, 2.5 equiv of B_2pin_2, THF, 80 °C, 16 h; then 2.5 mol % of $PdCl_2$·dppf·CH_2Cl_2, 3.0 equiv of **3a**, 8.0 equiv of Na_2CO_3, dioxane/DME/H_2O (1/1/1), 80 °C, 12 h.

bromides such as **3d**–**3i** were also appeared to be compatible under the developed conditions affording good isolated yields and ee (**4d**–**4i**). Moreover, the method successfully underwent double-fold borylation/arylation with a number of electron-rich and sterically demanding coupling partners with good yields and ee (**4j**–**4n**). Notably, while preparation of chiral 3,3′-H8–BINOLs[19] is not straightforward and requires multiple synthetic steps,[20] we have demonstrated that our developed method could be applied to achieve the synthesis of such compound with high isolated yield (81%) and ee (98%, entry **6**).

Next, we focused on the remote 6,6′-double-fold C–H activation and borylation of (*R*)-BINOL. Thus, a THF solution of (*R*)-BINOL was treated with 4.0 equiv of HBpin, 5.0 mol % of triethylamine, 1.5 mol % of Ir, and 3.0 mol % of dtbpy ligand (Table 3, entry 1). Surprisingly, the outcome was a complex mixture. When the boron source was changed from HBpin to B_2pin_2 no improvement occurred. Next, we conducted the borylation in two different solvents (PhMe and CyH). However, what we observed is the solvent borylation for PhMe as the solvent and multiple borylations for CyH as the solvent (entries 3 and 4). Interestingly, when the same reaction was performed in THF solvent, we found 44% remote 6,6′-double-fold borylation of the BINOL (entry 5) and some amount of monoborylated product. Gratifyingly, by repeating the same reaction with an increased amount of HBpin and B_2pin_2 for longer reaction time (16 h), we found almost quantitative conversion into the desired double-fold remote borylation product (along with trace amount of other isomers), which was isolated in 87% pure product (entry 6). After the double-fold remote 6,6′-diborylation of chiral BINOL was applied, we applied our developed arylation conditions (Table 2, entry 5), which afforded the desired remote 6,6′-bis-arylated BINOL with high yield (Table 3, bottom). In this context, it deserves mentioning that HPLC experiment showed that during either double-fold C–H activation/borylation or double-fold arylation, no racemization occurred, which afforded excellent enantioselectivity (95%).

After establishing the double-fold remote borylation and arylation, we subsequently became interested to develop this two-step process in one-pot way without isolating the remote bis-borylated intermediate (**7**). Pleasingly, this two-step protocol was successfully accomplished in a one-pot method, giving the desired product (**8a**) in 76% isolated yield with high ee (95%) (Scheme 2, entry **8a**). Moreover, to check the synthetic utility of the method, a large-scale (10 mmol) double-fold remote C–H borylation/arylation reaction of simple (*R*)-BINOL was performed under the optimal conditions, which gave the target 6,6′-biaryl BINOL (**8a**) in 71% yield without compromising the enantioselectivity. Next, we investigated the scope of the other coupling partners. All the reactions were performed in a single flask without isolating the bis-borylated product. We observed that the reactions are very general affording good amount of the isolated yields and good to excellent enantioselectivity with various coupling partners. For example, electron-deficient, electron-rich, and electronically neutral aryl bromides are highly suitable for the arylations. Moreover, sterically demanding aryl bromides (**8d**, **8f**, and **8j**) are also compatible, giving good yields. Importantly, all of the compounds (**8**) are new except **8a**, which was reported by Pappo and co-workers with high yield with moderate ee. Notably, due to difficulty in the chiral separation of products **8d**, **8g**, and **8j**, the ee was not determined.

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Finally, further application of this method for 4-fold C−H activation/borylation followed by arylation was tested sequentially with (*R*)-BINOL. Thus, (*R*)-BINOL was subjected under two different sets of conditions (for example, ortho and remote), which afforded the complex tetra-arylated BINOL[21] in good yield (Scheme 3). This example showcases the efficiency of this method for the development of new ligand and catalyst design in organocatalysis for asymmetric synthesis.

In conclusion, a double-fold ortho and remote C−H bond activation and borylation of BINOL has been developed. While ortho borylation is solely controlled by an electrostatically directed mechanism, remote borylation is controlled by a steric effect. The developed strategy was successfully combined with cross-coupling as one-pot way for the rapid synthesis of a variety of useful chiral 3,3′-disubstituted and 6,6′-disubstituted BINOL derivatives, which overcomes the previous shortcomings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02347.

Experimental details, spectral data, copies of ^{1}H and ^{13}CNMR spectra, and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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Communication

Meta Selective C−H Borylation of Sterically Biased and Unbiased Substrates Directed by Electrostatic Interaction

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ABSTRACT: An electrostatically directed meta borylation of sterically biased and unbiased substrates is described. The borylation follows an electrostatic interaction between the partially positive and negative charges between the ligand and substrate. With this strategy, it has been demonstrated that a wide number of challenging substrates, especially 4-substituted substrates, can selectively be borylated at the meta position. Moreover, unsubstituted substrates also displayed excellent meta selectivity. The reaction employs a bench-stable ligand and proceeds at a milder temperature, precluding the need to synthesize a bulky and sophisticated ligand/template.

Over time, transition-metal-catalyzed C−H bond functionalization[1−5] has been recognized as one of the most important methods to construct carbon−carbon and carbon−heteroatom bonds for the synthesis of a complex molecular architecture. But, the key challenge lies in a site-selective[6−10] functionalization owing to the presence of multiple C−H bonds in organic molecules. In this context, while the last few decades have seen numerous developments in ortho selective functionalization,[11−14] the developments of meta and para functionalization[15,16] are much less compared to the ortho functionalization. Achieving the remote meta and para selectivity in an arene C−H functionalization by overcoming the steric demands is a major challenge. Consequently, the functionalization of a remote C−H bond often necessitates the attachment and detachment of a bulky directing template, which limits the practicability of this method.

In this context, among various C−H bond functionalizations, an iridium-catalyzed borylation[17−20] has been demonstrated as one of the most important synthetic tools due to the versatility of the C−B bonds.[21−24] While there are many useful methods that are now available for the ortho selective C−H borylation including the directed ortho metalations (DoM),[25,26] meta and para selective C−H borylations are still difficult to realize. Earlier only one type of meta borylation was possible via iridium catalysis from 1,3-disubstituted arenes—a seminal contribution by Smith, Maleczka, and Hartwig.[27−30] Apart from other directed meta borylations,[31,32] recently, one new paradigm of meta selective borylation has been developed by means of various noncovalent interactions[33−39] (Chart 1A). Moreover, the use of a noncovalent interaction and Lewis acid−base interaction has also been seen for para C−H borylations.[40−43]

However, despite the ingenuity of the noncovalent interaction in C−H borylation, several aspects limit its wide application. First, because of the weak nature of this interaction, a big competition is encountered for those substrates having a substituent next to the C−H borylation site. For example, the meta C−H borylation is still not possible for 4-substituted substrates. The reason behind this is solely the steric effects that hamper the noncovalent interaction next to the borylation site. Second, the requirement of customized ligands or catalysts bestows a barrier to those looking to use "standard reagents" for a practical application.[28] Herein we report a concept based on the electrostatic interaction for the meta borylation of arenes bearing $-SO_2CF_3$, $-SO_2CH_3$, $-COCF_3$, $-COCH_3$, and $-CO^tBu$ at mild reaction conditions. Moreover, we demonstrate that, with the developed concept, meta borylation can be possible with those arenes featuring a substitution at the para position with a high meta selectivity. The inspiration of this meta borylation concept is based on the recently developed electrostatically directed ortho borylation of phenols developed by Smith, Maleczka, and Singleton (Chart 1B, **TS-1**).[44] Thus, with this inspiring concept, we questioned if this strategy could be further extended toward the meta borylation of arenes.

The working hypothesis of this present work is based on the following key considerations: (i) generation of the tris(boryl)(Ir) complex from Ir-precatalyst and diborane reagent, (ii) examination of commercially available bidentate nitrogen ligands instead of the customized ligands for the in situ formation of the pentacoordinated Ir complex that would likely be the partially positive charge in nature, (iii) use of such type of functionalities attached with arenes, which by virtue of resonance could develop a partial negative charge at any given heteroatom, and (iv) an appropriate electrostatic interaction between the ligand and substrate (Chart 1B, **TS-2**).

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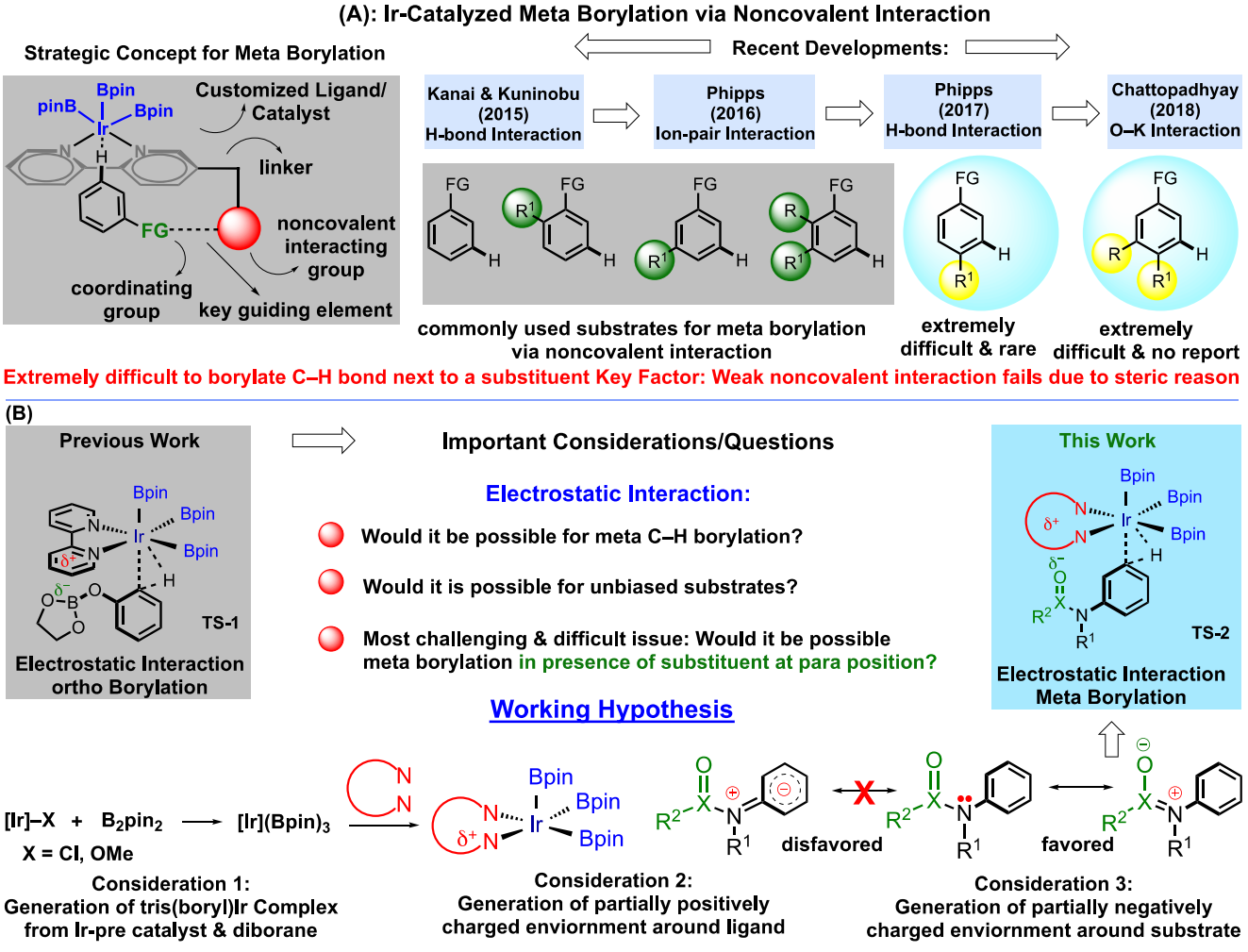
Chart 1. Noncovalent Catalysis for Meta Borylation: Previous and Present Work



We began our studies using arene (**1a**) bearing an (Et)N–SO_2CF_3 group with the commercially available ligands (Chart 2). As per our hypothesis for an electrostatic interaction, the borylation was performed in cyclohexane using bipyridine (**L1**) at 40 °C with 1.0 equiv of bis(pinacolato)diboron (B_2pin_2) (entry 1). We observed that, while the borylation gave promising meta selectivity, it also produced significant diborylated products. Thus, to minimize the diborylation, subsequent optimizations were conducted with 0.5 equiv of the boron source (i.e., B_2pin_2). The selectivity is based on a gas chromatography/mass spectrometry (GC/MS) analysis of the reaction.

Accordingly, when the borylations were performed with bipyridine ligands (**L1**, **L2**, & **L3**) with the reduced amount of B_2pin_2 a clear trend in the enhancement of the meta selectivity was observed as the bipyridine ligands were made electron-deficient. For example, whereas bipyridine ligand (**L1**) and electron-rich bipyridine ligand (**L2**) resulted in 5.6/01 (entry 2) and 4.8/01 (entry 3) meta-to-para selectivities, respectively, an electron-deficient bipyridine ligand (**L3**) produced a much higher proportion of meta selectively (10.1/01), although with poor conversion (entry 4). From this selectivity pattern with electronically different bipyridine ligands, it may be stated that the electron-withdrawing bis-CF_3 groups attached with the bipyridine ligand (**L3**) pull the electron from the ligand system, making it more electro-positive after coordination with the iridium that interacts well with the partial negatively charged oxygen atom of the functional group of the arene via an electrostatic interaction. Next, we considered electronically different 1,10-phenanthroline ligands that are not much explored in C–H borylations.[45,46] The 1,10-phenanthroline is a rigid, planar, electron-poor heteroaromatic chelating ligand. Moreover, the two N-donor atoms point inward and are juxtaposed to each other in contrast to the bipyridine ligand. The inward inclination of N donor atoms can be disrupted by a free rotation along the single bond. Another distinctive property of the phenanthroline ligand is its π-electron deficiency, which makes it a suitable π-acceptor.[47] Thus, considering these important special properties of the phenanthroline framework, we conducted a reaction using ligand (**L4**) (entry 5). To our delight, a high meta selectivity was achieved (meta/para = 32/01) with 91% isolated borylated product (**2a**). Modification of the 1,10-phenanthroline ligand by introducing an electron-withdrawing group (**L5**) also appeared to be comparable (entry 6), although the conversion was sacrificed largely. Notably, the use of an electron-donating 3,4,7,8-tetramethylphenanthroline ligand (**L8**) and 5-amino phenanthroline ligand (**L7**) exhibited poor meta selectivity (entries 9 and 8). Moreover, we found that, while the ligand (**L6**) showed moderate meta selectivity (entry 7), the ligand (**L9**) failed completely for the borylation

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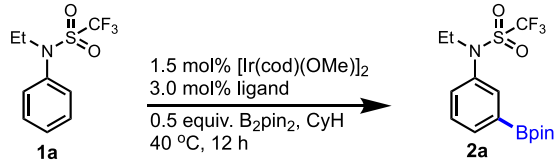
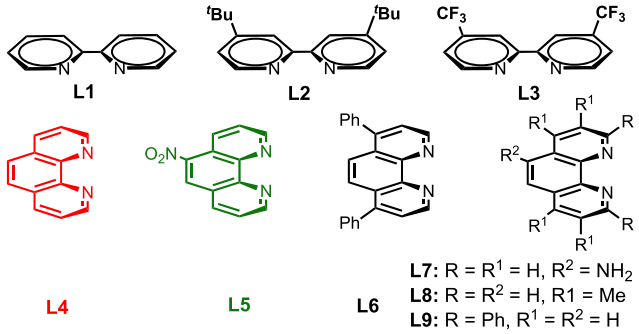
Chart 2. Reaction Optimization

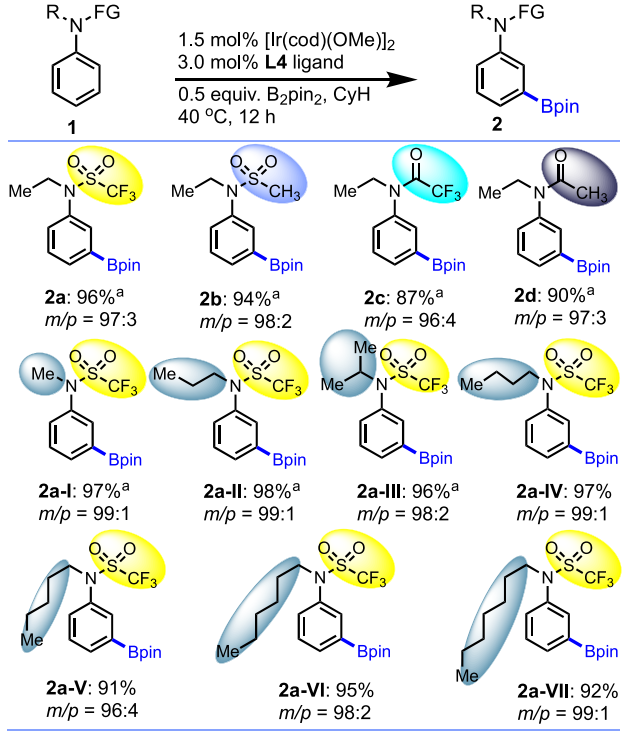


#	ligand	B_2pin_2	*meta/para*	Conv. (%)
1	L1	1.0 (equiv.)	5/1[a]	99
2	L1	0.5 (equiv.)	5.6/1	83
3	L2	0.5 (equiv.)	4.8/1	92
4	L3	0.5 (equiv.)	10.1/1	45
5	L4	0.5 (equiv.)	32/1	96 (91)
6	L5	0.5 (equiv.)	33/1	10
7	L6	0.5 (equiv.)	4/1	61
8	L7	0.5 (equiv.)	3.5/1	25
9	L8	0.5 (equiv.)	3.3/1	99
10	L9	0.5 (equiv.)	-	NR



Reactions were performed with 0.2 mmol scale. In parenthesis, Isolated yield is reported. Selectivity is based on GC/MS analysis of the reaction. [a]In addition to this meta/para isomer, significant diborylation occurred.

Chart 3. Meta Borylation of Monosubstituted Arenes



Reactions performed with 0.5 mmol scale. Isolated yields are given. [a]In these cases, very minor amount of *m,m*-diborylation occurred. But, due to the stability issue, we were unable to isolate.

(entry 10). For this failure, we reasoned that the bulky phenyl substitution at the C6 position of the ligand (**L9**) creates steric crowding that inhibited the borylation.

With these promising results, we then intended to test if the electrostatic interaction will be validated for other functionalities, such as Et(N)−SO_2CF_3, Et(N)−SO_2CH_3, Et(N)−$COCF_3$, and Et(N)−$COCH_3$. We found that all these functionalities exhibited a high meta selectivity (Chart 3, **2a**−**2d**). Thus, borylations were conducted with several alkyl groups containing substrates,[48] for example, methyl (**1a-I**), propyl (**1a-II**), isopropyl (**1a-III**), butyl (**1a-IV**), pentyl (**1a-V**), hexyl (**1a-VI**), heptyl (**1a-VII**), and found that an increase in chain length does not hamper the meta selectivity.

Next, we examined the scope of the meta borylation of those substrates featuring a substituent at the para position (Chart 4). To our delight, testing numerous 4-substituted substrates with five different functional groups, we found that almost all the substrates produced meta borylation products exclusively. For example, the functional groups like R(N)−SO_2CF_3, R(N)−SO_2Me, R(N)−$COCF_3$, R(N)−COMe, and R(N)−CO^{t}Bu with electronically and sterically different substituents smoothly underwent meta borylations. The bulky *tert*-butyl group at the 4-position also afforded the meta borylation (meta/para = 90/10) (entry **4c-IV**), but it was isolated via cross-coupling due to a stability issue of the borylated product. The substrate (**3c-V**) bearing a benzyl group instead of an alkyl group also selectively underwent meta borylation without disturbing the C−H bonds of the benzyl group. Importantly, conducting the borylation under the same conditions with the (**3aa**) and (**3bb**) that do not have any noncovalent interacting sites failed to undergo borylations, which demonstrates the necessity of the above-mentioned functional groups for the successful electrostatically directed meta borylation.

At this point, we were curious whether benzylamines (**3cc**−**3ff**) would be suitable substrates or not considering the greater distance compared to the anilines. Accordingly, borylation was performed with these substrates, and we found that, while unsubstituted substrate (**3cc**) and 4-fluoro substrate (**3ee**) gave good meta selectivity, 2-chloro (**3dd**) and 4-methoxy (**3ff**) provided moderate meta selectivity. This indicates that the electrostatic interaction is not strong enough for benzylamine substrates to give a high meta selectivity especially for those benzylamines bearing a substituent at the ortho or para position. For further elaboration, we attempted meta borylations with arenes bearing other functionalities. We observed that, while an arene with sulfonamide (**3gg**) exhibited good meta selectivity (m/p = 72/28), benzamide (**3hh**) and phosphonate ester (**3ii**) failed to undergo borylation—indicating the lack of an appropriate electrostatic interaction. To see the effect of other ligands (**L1** and **L2**) borylation was performed with a 4-substituted arene (**3a-II**) using (**L1** & **L2**). We found that, while (**L4**) gave a quantitative conversion, ligands (**L1**) and (**L2**) also afforded meta borylation, although with a poor conversion (49% and 53%, respectively), which suggests a significant substrate effect with the ligand (**L4**) affording

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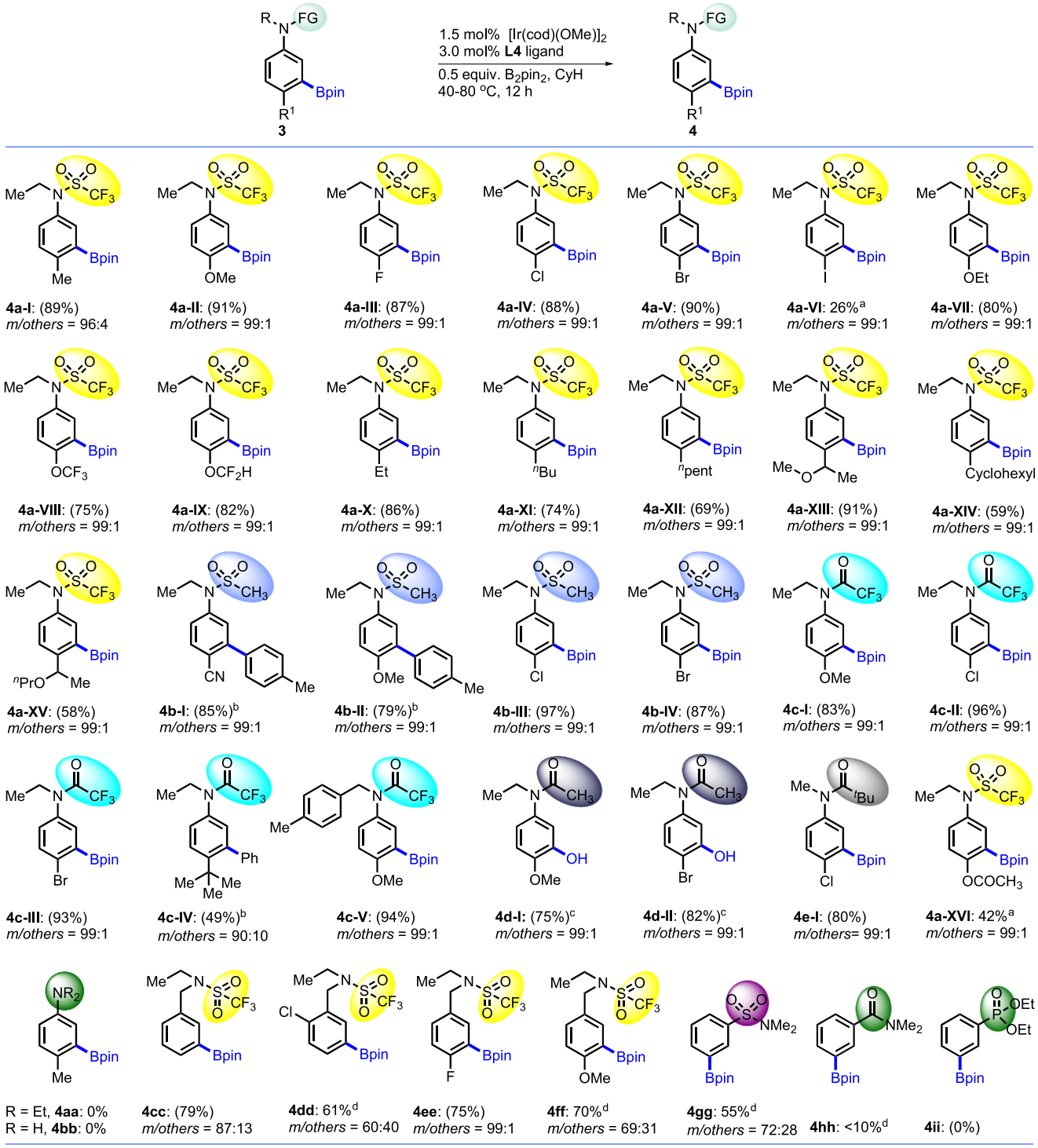
Chart 4. Substrate Scope for 4-Substituted Arenes



All reactions were performed with 0.5 mmol scale. Isolated yields are reported. Selectivity is based on the GC/MS analysis of the reaction. For details see, SI. [a]Crude NMR conversion is given. [b]Products were isolated after cross coupling (SI for details). [c]Products were isolated after oxidation. [d]GC/MS conversions are reported. Borylation of (**3a-II**) using **L1** and **L2** ligand afforded 49% and 53% conv. respectively.

higher efficiency. This may be attributed to the unique properties[47] of the phenanthroline ligand (**L4**).

The scope of the developed method was then evaluated for the substrates bearing substitution at the different positions of the arene (Chart 5). In all cases, a high meta selectivity was obtained with high isolated yields of the borylated products (entries **6a-I** to **6a-VIII**) including the 2,5-difluoro substrate (**6a-VI**). Notably, while the 4-F and 4-CN substrates (Chart 4) afforded a complete meta borylation (which usually gives borylation next to the F and CN group), 3-F and 3-CN substrates (Chart 5) did not give borylation completely next to these groups but, instead, resulted in a meta borylated product as the major product. This result is a further indication of an electrostatic interaction as per the proposed

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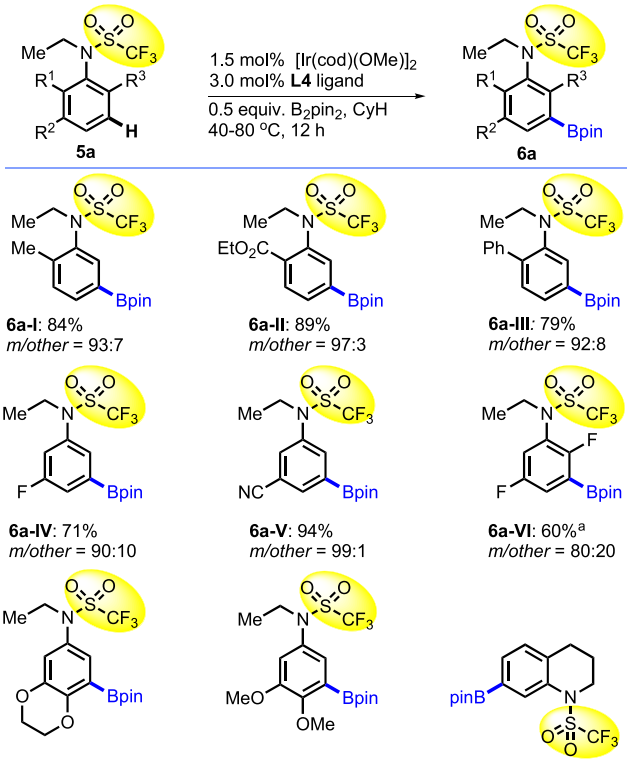
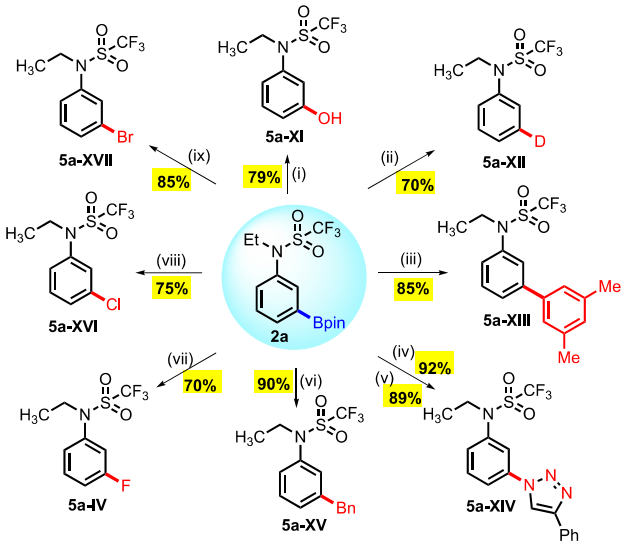
Chart 5. Substrate Scope for Substituted Arenes



Reactions were performed with 0.5 mmol scale. Isolated yields are reported. For details see: SI. [a]GC/MS conversion is reported.

Chart 6. Synthetic Transformations[a]



[a]**Conditions:** (i) 1.2 equiv of oxone, (3/1) acetone/water, 0 °C to rt, 2 h. (ii) 1.0 mol % [Ir(cyclooctadiene)OMe]$_2$, (4/1) (tetrahydrofuran/D_2O), 80 °C, 12 h. (iii) 2.5 mol % $Pd(PPh_3)_4$. 2.0 equiv of K_2CO_3, 1.1 equiv of 5-bromo-*m*-xylene, (1/1) dimethoxyethane/H_2O, 100 °C, 12 h. (iv) 10 mol % $Cu(OAc)_2$, 1.5 equiv of NaN_3, MeOH, 55 °C, under air, 24 h. (v) 1.2 equiv of phenylacetylene, 3.0 mol % sodium ascorbate, H_2O, MeOH, rt, 24 h. (vi) 1.0 mol % Pd_2(dibenzylideneacetone)$_3$.$CHCl_3$, 4.0 mol % PPh_3, 4.0 equiv of K_2CO_3, 1.2 equiv of BnBr, (10/1) tetrahydrofuran/H_2O, 100 °C, 24 h. (vii) 4.0 equiv of TFA, 2.0 equiv of $Cu(OTf)_2$, CH_3CN, 60 °C, 20 h. (viii) 3.0 equiv of $CuCl_2$, (1/1) MeOH/H_2O, 80 °C, 12 h. (ix) 3.0 equiv of $CuBr_2$, (1/1) MeOH/H_2O, 80 °C, 12 h.

hypothesis. Interestingly, we also found that the heterocyclic substrate (**5a-IX**) proceeded with the C−H borylation affording a high meta borylation.

To demonstrate the synthetic utility, we showed that the borylated compound (**2a**) can be transformed to many useful synthons employing known transformations, such as hydroxylation,[17] fluorination,[49] chlorination,[50] bromination,[50] deuteration,[51] arylation,[21] benzylation,[52] and azidation followed by cycloaddition[53] (Chart 6).

The standard reaction mechanism of the C−H borylation of arene was reported[54] earlier, and the present meta borylation possibly follows the same mechanism. But, to get an understanding of the proposed electrostatic model (Chart 7A, **TS-2**), we first analyzed the electronic effects of ligands. Earlier it has been demonstrated that, for electrostatically directed ortho borylation (**TS-1**),[44] an electronic alteration of the ligand framework affects the ortho selectivity.

Analyzing the electronic effects of the various 1,10-phenanthroline ligands,[47] we observed that the meta borylation follows the same trend (Chart 7B) that is consistent with the previous electrostatic model. For a further understanding, several control experiments were performed. As per our hypothesis, the lone-pair electrons of the nitrogen atom will be delocalized through the trifluoromethanesulfonyl group rather than the arene ring (Chart 7A) due to its strong electron-withdrawing nature, and thus the substrate (**1**) will develop a partial negative charge at the oxygen atom (**1A**) instead of the arene ring (**1B**), which would interact with the partial positive charge of the ligand. We envision that, if this hypothesis is correct, then a functional group alteration of the nitrogen atom should affect the meta selectivity. Following this hypothesis, we performed a borylation with substrates bearing several functional groups (Chart 7C) and found that substrates without suitable functional groups (**9**, **10**, & **11**) resulted in either no reaction or a nonselective borylation. Next, borylation was performed with the substrates (**12a**, R = triflate (Tf)) having a free NH unit, and it was found that the conversion was poor indicating that protection is necessary to augment the electron delocalization into the $-SO_2CF_3$ group by restricting the chelation with the catalyst. Moreover, when the R group is altered from Tf to either acetyl (Ac) (**12b**) or trifluoroacetic acid (TFA) (**12c**), almost the same trend is observed. Moreover, protection of both the H atoms of aniline (**13**) with the $-SO_2CF_3$ group afforded a regioisomeric mixture of the meta and para borylation products in statistical ratios with a moderate conversion. Thus, this finding indicates the necessity of an alkyl group as the lone pairs of N atom are delocalized over two $-SO_2CF_3$ groups and diminish the negative charge density on the carbonyl O atom. Collectively, all these control experiments are suggestive of an electrostatic model for the meta borylation.[55]

In conclusion, we have developed a method for the meta borylation of arenes via an electrostatic model. The method shows a broad substrate scope, especially for those substrates bearing a substituent adjacent to the borylation site, which was an utmost challenge. While the most iridium-catalyzed remote C−H borylations require minimum 1.0 equiv of diborane (B_2pin_2), our method requires only half of the B_2pin_2 (0.5 equiv), demonstrating the practicality of the

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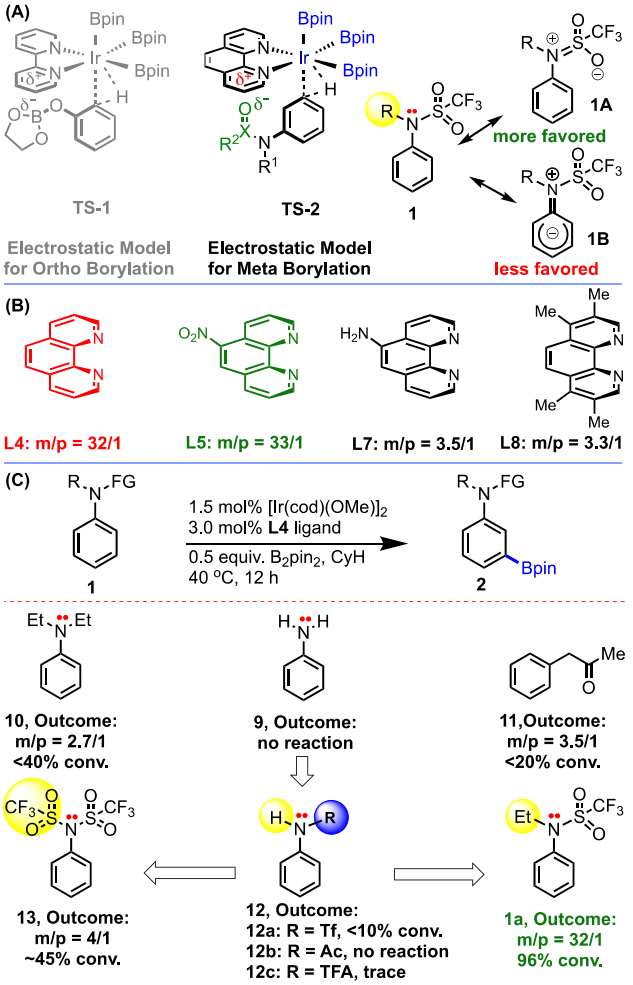
Chart 7. Validation of Proposed Electrostatic Model



All the reactions were conducted with 0.2 mmol scale. GC/MS ratios are given. GC/MS conversions are reported of the crude reaction.

developed method.[56] We anticipate that the method should find wide application in the context of boron-bearing small molecules for the drug discovery, natural product synthesis, and pharmaceutical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01770.

Full characterization, copies of all spectral data, experimental procedures (PDF)

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Notes

The authors declare the following competing financial interest(s): We have filed a patent based on this work.

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