IRIDIUM-CATALYZED ORTHO-AND META-SELECTIVE C-H BOND BORYLATION AND SILYLATION OF AROMATIC MOLECULES

THESIS
SUBMITTED TO
BABASAHEB BHIMRAO AMBEDKAR UNIVERSITY
(A CENTRAL UNIVERSITY)
LUCKNOW

BABASAHEB
BHIMRAO
AMBEDKAR
UNIVERSITY
LUCKNOW
प्रज्ञा शील करुणा
ESTABLISHED 1996

FOR THE DEGREE OF
Doctor of Philosophy
IN
APPLIED CHEMISTRY

Submitted by
Ranjana Bisht
ENROLMENT NUMBER. 100/15

Co-Supervisor
Dr. Buddhadeb Chattopadhyay
Assistant Professor
Centre of Biomedical Research (CBMR)
SGPGIMS Campus, Raebareli Road
Lucknow 226014, Uttar Pradesh, India

Supervisor
Dr. Gajanan Pandey
Professor
Department of Applied Chemistry
School for Physical Sciences
Babasaheb Bhimrao Ambedkar University
LUCKNOW-226 025

2019

Dedicated to
My Mother

CERTIFICATE

This is to certify that the thesis titled "**IRIDIUM-CATALYZED ORTHO-AND META-SELECTIVE C-H BOND BORYLATION AND SILYLATION OF AROMATIC MOLECULES**" submitted by Ms./Mr.**Ranjana Bisht** 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.

Co-Supervisor

Supervisor

Head of department

31·01·2019

DECLARATION

I, Ranjana Bisht declare that the thesis entitled **"IRIDIUM-CATALYZED ORTHO- AND META-SELECTIVE C-H BOND BORYLATION AND SILYLATION OF AROMATIC MOLECULES"** submitted by me for the degree of Doctor of Philosophy in the record of work carried out by me under the supervision of **Prof. Gajanan Pandey** at Department of Applied Chemistry, School for Physical Science, Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow and co-supervision of **Dr. Buddhadeb Chattopadhyay** Asst. Prof. at CBMR, SGPGIMS, Lucknow has not formed the basis for the award of any degree, diploma, associate ship, fellowship, titles 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 acknowledged in the thesis.

Ranjana Bisht

Date: 31.1.19

Place: Lucknow

Ranjana Bisht
Department of Applied Chemistry
Babasaheb Bhimrao Ambedkar University
Lucknow-226025
India

Acknowledgement

In the pursuit of completion of foundation step towards my careers ultimate goal I express my foremost and sincere gratitude to my supervisors Dr. Gajanan Pandey (Professor, Dept. of Applied Chemistry) and Dr. Buddhadeb Chattopadhyay (Assistant Professor, CBMR, Lucknow). Without their guidance this would not have been possible.

I would like to pay my sincere thanks to Professor Kaman Singh (Dean-School for Physical Sciences) and Professor Ganesh Pandey (Director CBMR, Lucknow) for motivating and providing research infrastructural facilities.

I want to express my gratitude to the faculty of Dept. of Applied Chemistry for their valuable suggestions during our progress report presentations.

I deeply appreciate cooperative behaviour of all the office staff of BBAU, Mr. Sarvesh, Mr. Pankaj, Mr. Anuj and Mr. Om.

I would like to sincerely thank the NMR and HRMS volunteer of CBMR who have taught me the basics of instrument in my initial years. Sincere thanks to the office staff of CBMR.

Special thanks to my labmates Satyajit, Chabush, Emdadul, Sandip, Jagriti, Hillol, Mirza, Abhishek, Dr. Biplab for all wonderful memories that I will cherish my whole life. You all are inspirational in different ways. Thanks to Dr. Biplab, Chabush, Satyajit, for helping me with problems while I was compiling this work. Thanks to Jagriti for always being a listening ear to all my stuff.

Above all Iam thankful to my family, my mother, my elder brother Madhukar and my younger sister Ritu for their unconditional love and support throughout these years. Without their emotional support this would not have been possible.

I am grateful to Ramanujan Grant and CSIR-New Delhi for providing SRF fellowship.

Also, I would like to thank the authors of various research articles and books whose work has been consulted, utilized and cited in my thesis.

I sincerely express my gratitude to my guide Dr. Buddhadeb Chattopadhyay for believing in me and not giving up on me. His contagious enthusiasm for research motivates every lab member. He has always encouraged us by saying that "Nothing is impossible".

I would like to dedicate my thesis to my mother Mrs. Radhika Bisht, words are powerless in front of her sacrifices she made for us. Her indomitable spirit and never to give up attitude under any circumstances is the backbone of my personality.

Ranjana Bisht

Ranjana Bisht

(Research Scholar)

Abstract

Iridium-catalyzed C-H activation/borylation has augmented appositeness and sophistication of transition metal-catalyzed direct C-H functionalization which was being availed for molecule synthesis over the past century. Unarguably, the advent of C-H borylation has tackled various unresolved problems prevalent in organic synthesis such as synthesis of 3,5-bromochlorophenol, which was multistep and laborious task. In contrast, Ir-catalyzed C-H borylation enabled its synthesis in just two steps. But the main governing factor for determination of product regioselectivity was sterics. With constant development in this protocol such as employment of directing groups strategy realizes the *ortho* C-H activation/borylation to proceed in a placid fashion, then further advancement occurred as the concept of traceless directing group was introduced. The flaws of early concepts paved the way for the influx of novel approach of amalgamation of transition metal catalysis with noncovalent interaction to achieve the goal of proximal and distal C-H activation/borylation.

The prominent features of this approach are mildness, versatility of C-B bonds, atom as well as step economic and environmentally benign which makes it more popular than the protocols which were practised for C-H functionalization before its inception.

The work compiled in this thesis, is divided into five chapters. First chapter summarizes the seminal events in Iridium-catalyzed *ortho* and *meta* C-H borylation and C-H silylation method. The two methodologies hold considerable promise in activating the inert C-H bonds of arenes, heteroarenes and aliphatic systems. The significant role played by organosilicon and organoboron compounds in a broad array of fields such as organic synthesis, pharmaceutics, polymer and ceramic industry amplifies the efficacy of these protocols.

Second chapter explains the decisive role of nature of ligand in determining the product regioselectivity. Usage of traceless directing group and hemilabile ligand leads to *ortho* functionalization, while employing electronically rich 3,4,7,8 tetramethylphenanthroline ligand facilitated noncovalent interaction (electrostatic and B-N interaction) to accomplish remote '*meta*' functionalization of same benzaldehyde substrate.

The third chapter presents how by prudent designing of ligand on the catalyst (modification of Bpin by Beg) and employment of traceless directing group led to exquisite *ortho*-selectivity of aniline, its derivatives and heteroaromatics, releasing it from the shackles of all previous shortcomings.

The fourth chapter describes achievement of previously unmet challenge of accessing and activating 6,6’-position of Binol by maneuvering the sterics of catalyst-ligand assembly. In situ protection with HBpin followed by borylation with B_2pin_2 afforded regioselectively remote (6,6') diborylation. Corresponding diarylated products are formed through subsequent Suzuki cross-coupling.

Fifth chapter discusses the development of an efficient methodology for *ortho* C-H activation/silylation of aromatic, heteroaromatic benzaldehydes and phenylpyridines, in addition to this it elucidates the role played by silylating reagent in devising a distinct catalytic manifold from existing catalytic systems for *ortho* C-H silylation.

In the last, sixth chapter summary of all the work has been discussed.

Table of Contents

Chapter 1.	Introduction of C-H borylation and C-H silylation	**1-52**
Chapter 2.	Formal Ir-catalyzed ligand-enabled *ortho*- and *meta*-borylation of aromatic aldehydes via in situ generated imines	**53-107**
Chapter 3.	Achieving high *ortho* selectivity in aniline C–H borylations by modifying boron substituents	**108-119**
Chapter 4.	Double-fold remote C-H Bond activation/borylation of BINOL: A unified strategy for direct arylation of BINOL	**120-140**
Chapter 5.	*Ortho*-selective C(sp^2)–H silylation of arenes and heteroarenes: Detailed mechanistic investigation of various Ir(I)-Ir(III) and Ir(III)-Ir(V) catalytic cycle	**141-166**
Chapter 6.	Summary of research work	**167-169**
List of Publications and Seminars attended		**170**

List of Abbreviations

Ar	Aryl
aq.	Aqueous
$AsPh_3$	Triphenylarsine
8-AQ	8-Aminoquinoline
B	Boron
-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	Bispinacolatodiborane
$B_2(OH)_4$	Tetrahydoxydiboron
Bn	Benzyl
bpy	Bipyridine
BQ	1,4-Benzoquinone
Br	Bromine
Bu	Butyl
B-N	Boron-Nitrogen Bond
Boc	*tert*-butyloxycarbonyl
Beg	Ethyleneglycolatoboron
BINOL	Binaphthol
$^tBuF_2Si_2$	1,2-di-*tert*-butyl-1,1,2,2-tetrafluorodisilane
$^sBuF_2Si_2$	1,2-di-sec-butyl1,1,2,2-tetrafluorodisilane
^tBu	Tertiary Butyl, also called *tert*-Butyl
°C	Degree Celsius
Cp	Cyclopentadiene or Cyclopentadienyl
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
CMD	Concerted Metallation Deprotonation
C-Si	Carbon-Silicon Single Bond
C-O	Carbon-Oxygen Single Bond
C-TM	Carbon bonded to transition metal
C-X	Carbon Singly Bonded to any Halogen
Si-H	Silicon-Hydrogen Single Bond
$CDCl_3$	Deuterated Chloroform, NMR solvent
CyH	Cyclohexane
cod	1,5-Cyclooctadiene
coe	Cyclooctene
Cl	Chlorine
CHO	Aldehyde Functional Group
CF_3	Trifluoromethyl Group
D	Deuterium
δ	delta, NMR Chemical shift
d	doublet, double peak in NMR spectrum
dd	doublet of doublets
dba	Dibenzylideneacetone
DCM	Dichloromethane
4-DMAP	4-Dimethylaminopyridine
dtbpy	4,4’-Di-*tert*-butyl-2,2’- bipyridine
dmpe	Dimethylphosphinoethane
DMG	Directed Metalation Group
DME	1,2 Dimethoxyethane
DoM	Directed *ortho* Metalation
EAS	Electrophilic Aromatic Substitution
EDG	Electron Donating Group
EI	Electron Impact
ESI	Electron Spray Ionization
Et_3N	Triethylamine

EtOAc	Ethylacetate
EWG	Electron Withdrawing Group
equiv.	Equivalent
F	Fluorine
FG	Functional Group
GC	Gas Chromatograph
GC-FID	Gas Chromatograph with Flame Ionizing Detector
GC-MS	Gas Chromatograph with Mass Spectrometer
H	Hydrogen atom
h	Hour
Hz	Hertz (cycles per second)
HRMS	High Resolution Mass Spectroscopy
$HSiEt_3$	Triethylsilane
$HSiPh_3$	Triphenylsilane
Ir	Iridium
-I	Inductive Effect
$[Ir(cod)(OMe)]_2$	Bis(η^4-1,5-cyclooctadiene)-di-μ-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
J	NMR Coupling Constant
KIE	Kinetic Isotope Effect
KOAc	Potassium Acetate
KOH	Potassium Hydroxide
K_2CO_3	Potassium Carbonate
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	Millilitre
MHz	Megahertz
MOF’s	Metal Organic Framework
NMP	N-Methyl pyrrolidone
NMR	Nuclear Magnetic Resonance
NHC	N-Heterocyclic Carbene
NCI	Noncovalent Interaction
NMe_2	*N*,*N*-Dimethylamine
Nu:	Nucleophile
o	*ortho*-Substituted or directing to ortho position
o/p	Directing to the ortho or para positions
P	Phosphorous atom
PCy_3	Tricyclohexyl Phosphine
Pd	Palladium
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium (0)
$Pd_2(dba)_3.CHCl_3$	Tris(dibenzylideneacetone)dipalladium (0) chloroform adduct
$PdCl_2dppf$	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
Ph_2SiH_2	Diphenylsilane
$PhMeSiH_2$	Diphenylmethylsilane
p-xylene	Paraxylene
^{i}Pr	Isopropyl
Pt	Platinum
rt	Room Temperature
Ru	Ruthenium
Rh	Rhodium

Re	Rhenium
s	singlet peak in NMR spectrum
SMAP	**S**ilica-constrained **M**onodentate tri**a**lkyl **P**hosphine
s	second
Si	Silicon
S	Sulphur
S_EAr	Elecrophilic Aromatic Substitution
THF	Tetrahydrofuran
TMP	3,4,7,8-tetramethyl-1,10-phenanthroline
TNT	2,4,6-Trinitrotoluene
TM	Transition Metal
TS	Transition State
TON	Turnover Number
tol	Toluene
W	Tungsten
Xylyl	Xylene

List of Figures

Figure No.		Page No.
1.1.	Silica supported phosphine ligand- Ir system	18
1.2	Preferred conformers of *ortho*-borylated aryl pyridine and aromatic *N*,*N*-dimethylhydrazones	21
1.3.	Si tethered N donor ligand	23
1.4.	Proposed transition state for regioselective *ortho*-borylation	25
1.5.	Proposed transition state for regioselective *ortho*-borylation	26
1.6.	Proposed transition state for regioselective *ortho*-borylation	27
1.7.	Proposed transition state for regioselective *ortho*-borylation	28
1.8.	Proposed transition state for regioslective *ortho*-borylation	30
1.9.	Proposed transition state for regioselective *meta*-borylation	32
1.10.	Possible transition states	34
1.11.	Proposed transition state for regioselective *meta*-borylation	35
1.12.	Proposed transition state for regioselective *meta*-borylation	36
1.13.	Proposed transition state for regioselective *meta*-borylation	38
2.1.	NMR spectra representing crude reaction mixture of imine-borylated material	56
2.2.	Hypothesis for the origin of *meta*-selectivity	60
3.1.	Proposed transition states for *ortho*-borylations of anilines and phenols	110
4.1.	Probable transition state for remote diborylation	120
5.1.	Plausible Mechanism for Ir(I)–Ir(III) Cycle	146
5.2.	Plausible Mechanism for Ir(III)–Ir(V) Cycle	147
5.3	Proposed mechanism with triphenylsilane	148
5.4	Studies of KIE with the *d*-labeling substrates	149
6.1	Transition states for *ortho*-borylation and *meta*-borylation of benzaldehydes	167
6.2	Transition state for H-bond directed *ortho*-borylation of anilines and heteroaromatics	168
6.3	Transition state for sterically controlled remote diborylation of BINOL	168
6.4	Transition state for *ortho*-silylation by hemilabile ligand	169

List of Tables

Table No.		Page No.
2.1.	Evaluation and optimization of reaction conditions	55
2.2.	*Ortho*-borylation of substituted benzaldehydes	58
2.3.	Ligand screening for *meta*-borylation	59
2.4.	Effect of imine substituent: Proof of hypothesis for *meta*-borylation	61
2.5	*Meta*-borylation of substituted benzaldehydes	62
3.1	Evaluation for the *ortho* C–H borylation conditions	111
4.1.	Evaluation for the remote C–H borylation conditions: General Procedure	122
4.2.	Optimization for the Suzuki cross coupling reaction: General procedure	123
4.3.	Substrate scope of remote C-H borylation/Suzuki reaction	124
5.1.	Evaluation of reaction conditions	143
5.2.	Scope of o*rtho*-silylation for benzaldehydes	144

List of Schemes

Scheme No.		Page No.
1.1.	Early example of transition metal-catalyzed C-H bond cleavage	1
1.2.	First example of transition metal-catalyzed functionalization of arene	1
1.3	Ruthenium-catalyzed C-H bond functionalization of aromatic ketones	2
1.4.	Mechanisms of C-H activation/ functionalization	3
1.5	Synthetic transformation of Bpin group	4
1.6.	Traditional synthesis of arylboron compounds	5
1.7.	Approaches for C-Si bond formation	6
1.8.	Synthetic transformation of Silyl group	6
1.9.	Thermodynamics of methane borylation	7
1.10.	Stoichiometric borylation catalyzed by Iron-boryl complex	8
1.11.	First report of thermal catalytic aromatic borylation	8
1.12.	Borylation of arenes catalyzed by the combination of (Ind)Ir(cod) and phosphine ligands	9
1.13.	Borylation of arenes catalyzed by the combination of $[Ir(cod)Cl]_2$ and 2,2'-bipyridine	10
1.14.	Synthesis of Iridium-trisboryl complex	10
1.15.	Mechanism for the Iridium-catalyzed borylation of arenes	11
1.16.	Synthesis of Rhazinicine	12
1.17.	Synthesis of SM-130686	13
1.18.	Synthesis of 3-choro-5-bromophenol	13
1.19.	Total synthesis of Verruculogen and Fumitremorgin A	14
1.20.	Silyl directed *ortho*-borylation of alkylarenes	15
1.21.	Silyl directed *ortho*-borylation of phenol and arylamines	15
1.22.	Mechanism of relay directed borylation	16
1.23.	*Ortho* C-H borylation of aromatic esters	16
1.24.	*Ortho* C-H borylation of aryl ketones and benzoates	17

1.25. *Ortho*-borylation of arenes by the Silica-SMAP-Ir System 18
1.26. Proposed mechanism with *N,N* hemilabile Ligand 19
1.27. *N,N* ligands with hemilabile character 20
1.28. Directed borylation of aryl pyridines/isoquinolines and Aromatic dimethylhydrazones 20
1.29. Synthetic utility of developed directed borylation 20
1.30. Directed *o,o*'-diborylation of hydrazones and sequential functionalization 21
1.31. Substrate directed C-H borylation of benzylic amines 22
1.32. *Ortho*-borylation of alkylbenzoates with bidentate Si, P Ligand 23
1.33. *Ortho*-borylation of benzaldehydes via in situ generated imines 24
1.34. *Ortho*-borylation of N-Boc anilines 26
1.35. *Ortho*-borylation of anilines and aminopyridines by traceless Bpin group 27
1.36. Traceless Beg directed borylation of anilines and heterocycles 28
1.37. *Ortho*-borylation of aryl sulphides 29
1.38. *Ortho*- borylation of phenol and aniline 29
1.39. Traceless Bpin-directed borylation of phenols 30
1.40. Traceless Beg directed borylation of phenols 31
1.41. H-bond controlled *meta*-borylation 33
1.42 Electrostatic and B-N bond directed *meta*-borylation of aromatic aldehydes 34
1.43 Ion-pair directed *meta*-borylation of aromatic quarternary ammonium salts 35
1.44. *Meta*-selective C-H borylation of benzylamine- phenethylamine-, and phenylpropylamine-derived amides 37
1.45. *Meta*-selective borylation of quaternized phenethylamines and phenylpropylamines 38
1.46. Synthesis of Aryl Halosilanes by $({}^{t}\mathrm{BuF_2Si})_2$ 39
1.47 Aromatic C-H silylation of arenes with $({}^{s}\mathrm{BuF_2Si})_2$ 40
1.48. Aromatic C–H silylation of arenes with 1-hydrosilatrane 40
1.49 (Hydrido)silyl-directed *ortho*-borylation of arenes 41
1.50. Secondary amine directed silylation of aromatic and benzylic C- 42

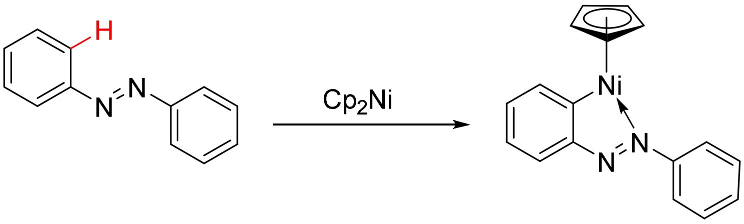
H bonds
1.51. Hydrosilylation and dehydrocyclization reaction for synthesis of dihydrobenzosiloles from styrenes 42
1.52. Pyridyl and Iminyl directed dehydrogenative *ortho*-C-H silylation of arenes 43
1.53. Silylation of aryl and heteroaryl C-H bonds 44
1.54. *Ortho*-silylation of benzylicsilyl ethers catalyzed by bipy-UiO-Ir 44
1.55. Dehydrogenative silylation of polycyclic aromatic hydrocarbons 45
1.56. Dehydrogenative silylation of azulene 46
1.57. Dehydrogenative silylation of azulene with different silanes 46
1.58. *Ortho*-selective C-H silylation of arenes through Lewis acid-base Interaction 47
1.59. Intramolecular C-H silylation with arylsilanols 48
1.60. Intramolecular C-H silylation with benzylsilanols 48
1.61. Intramolecular C-H silylation with phenoxysilanols 49
3.1. Comparison of Kanai-Kuninobu C-H borylation of N-Acylated Anilines to Our work 110
3.2. Analogy of C-H borylation of aniline with B_2eg_2 and B_2pin_2 112
3.3. *Ortho*- borylation of substituted anilines with B_2eg_2 113
3.4. Comparison of regioselective outcome of C-H borylation of aniline with Bpin and Beg reagents 113
4.1. Enantioselective oxidative coupling of 2- naphthols by iron phosphate complex [Fe] 121
4.2. Sequential double-fold *ortho* and remote borylation and arylation of BINOL 125

Chapter 1

General introduction of C-H activation, borylation and silylation

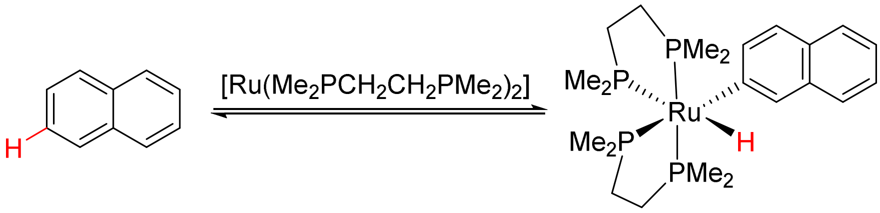
Introduction:

The functionalization of ubiquitous alkyl and aryl C-H bond is a long standing challenge in synthetic chemistry. Transition metal-catalyzed C-H bond functionalization has made an impressive progress in this perspective realizing the selective transformation of aryl C-H bonds to C-C, C-O, C-N and C-X bonds[1,2] and alkyl C-H bonds to C-C, C=C, C-O bonds.[3,4] In 1963, Klieman and Dubeck[5] showed the activation of *ortho* C-H bond of azobenzene on addition of stoichiometric amount of dicyclopentadienyl nickel as shown in **Scheme 1.1** through formation of 5-membered nickelacycle.



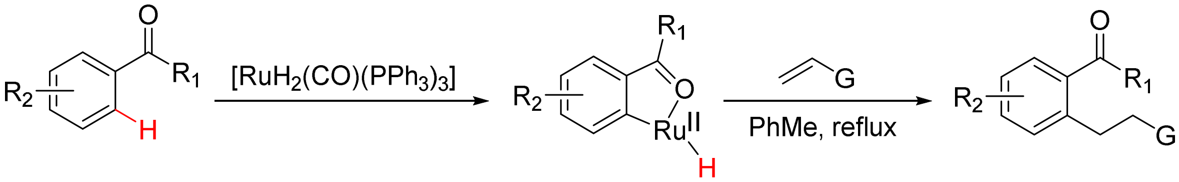
Scheme 1.1. Early example of transition metal-catalyzed C-H bond cleavage

In 1965 Chatt and Davidson demonstrated the pioneering example of transition metal-mediated C-H bond activation of arenes. Zero-valent[6] Ru species on treatment with naphthalene yielded the C-H activated Ru-complex depicted in **Scheme 1.2**.



Scheme 1.2. First example of transition metal-catalyzed functionalization of arene

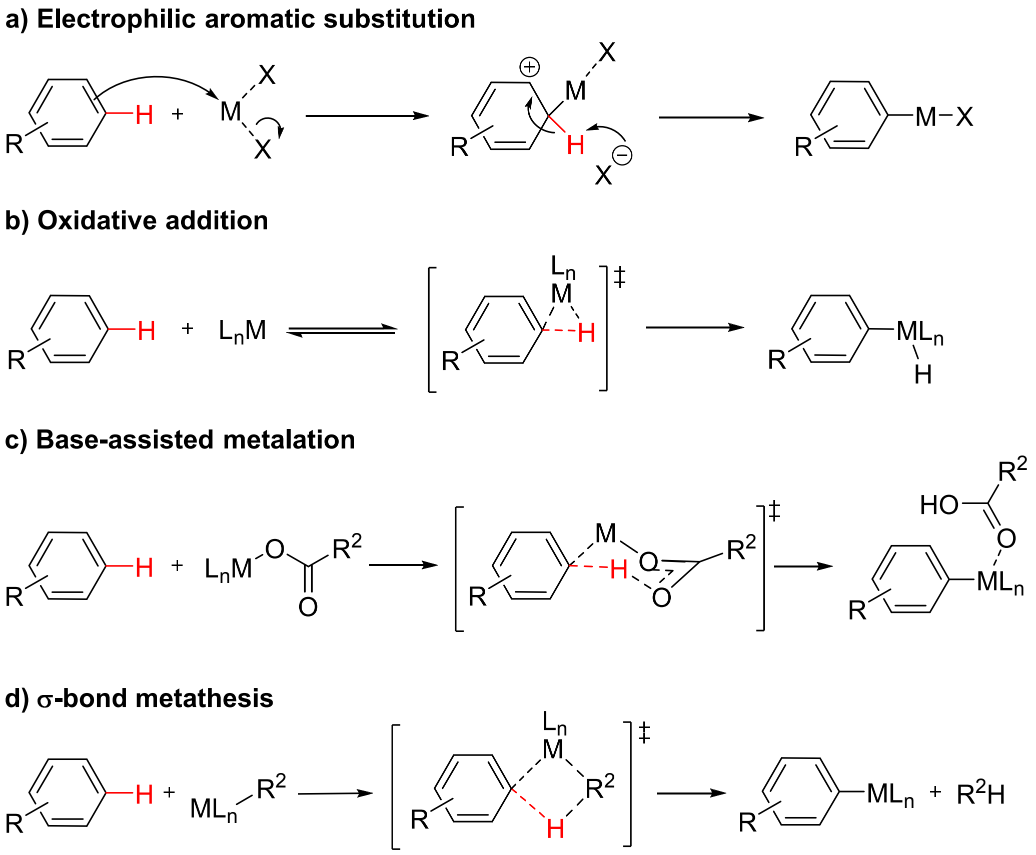
Development of catalytic metal mediated C-H bond cleavage took a long time, until in 1993 Murai reported an exceptional discovery of Ru-catalyzed selective *ortho* C-H functionalization of aromatic ketones with olefins (**Scheme 1.3**).[7]



Scheme 1.3. Ruthenium-catalyzed C-H bond functionalization of aromatic ketones

C-H activation *v/s* functionalization:

The transformation of a C-H bond by a different functional group termed as "C-H functionalization". This may proceed via different pathways in which C-TM intermediates (TM = transition metal) are formed and subsequently converted to products. The conversion of a C-H bond to a C-TM bond may occur via inherent reactivity of substrate (e.g., S_EAr for the case of an electron rich aromatic substrate and an electrophilic metal center), or via a pathway due to the specific properties of the metal species or ligands. The C-H to C-TM bond conversion depending on the properties of the TM complex is termed C-H activation. Four of the most common mechanisms[8] are shown in **Scheme 1.4**. Generally, an electrophilic activation occurs with electrophilic late transition metal species, whereas oxidative addition pathways are seen more commonly with electron-rich transition metal centers. Base-assisted C-H activation can be seen in the reactions based on assistance by a carboxylate or carbonate base via a six-membered transition state. This is sometimes termed "concerted metalation deprotonation", or CMD.[9] The final example, σ-bond metathesis, it is known to occur for metals with a d^0 electronic configuration. S_EAr is considered not to be an activation, because the C-H bond is broken after the Wheland intermediate forms, in contrast, only a specific transition metal species can carry out an oxidative addition into a C-H bond (i.e the C-H bond is activated by the metal).



a) Electrophilic aromatic substitution

b) Oxidative addition

c) Base-assisted metalation

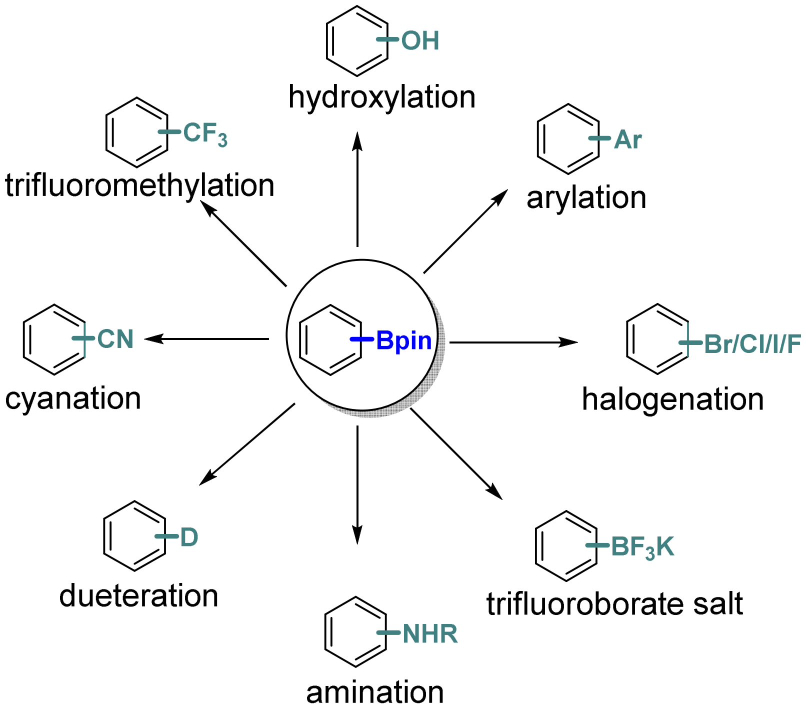
d) σ-bond metathesis

Scheme 1.4. Mechanisms of C-H activation/functionalization

Conventionally, derivatization of organic molecules was achieved by electrophilic aromatic substitution developed by Friedel and Craft where the electronics of directing group yields the predictable outcome. For example, while electron donating groups directs the incoming electrophile to *ortho* or *para* position, electron withdrawing group directs to *meta* position. But the poor regioselectivity as well as failure in achieving transformations that does not follow these basic rules limits its scope.

Another traditional method is the directed *ortho* metalation (*DoM*) developed independently by Gilman[10] and Wittig.[11] Since then several research groups[12] have expanded the scope of directed metallation groups which speeded up the pace of application of this methodology. Despite immense utility, usage of stoichiometric amount of strong base and employment of harsh cryogenic conditions enforces the development of alternative and competent strategy that surpasses these limitations.

The direct borylation of hydrocarbons deserves mentioning in this perspective attributing to the broad utility and versatility conferred to the C-B bonds. Numerous significant transformations[13] summarized in **Scheme 1.5** such as halogenation, oxidation, cross coupling, amination, cyanation, dueteration[14], azidation[15] and trifluoromethylation[16] can be done to derivatize the installed boron functionality.



Scheme 1.5. Synthetic transformation of Bpin group

Traditionally organoboron compounds are prepared first, by conversion of an aryl halide to a Grignard or lithium reagent,[17] subsequently reaction of this organometallic reagent with trialkylborate. Addition of either diol or acid converts organoboron compound to arylboronate ester and arylboronic acid respectively. Second method involves palladium catalyzed Miyaura borylation[18] of aryl halides as illustrated in **Scheme 1.6**. Recent development includes transition metal free borylation of aryl halides.[19]

Scheme 1.6. Traditional synthesis of arylboron compounds

Thus the direct C-H borylation of arenes is a highly desirable synthetic transformation which precludes relying on availability of aryl halides but also gives access to arylboronate esters which are difficult to prepare otherwise. In this introduction part early stoichiometric reaction for aromatic C-H borylation, development of catalyst with high turnover number, detailed mechanistic insight of the C-H borylation and applicabilty as well as synthetic utility will be discussed.

Iridium-catalyzed C-H bond silylation:

Owing to the efficacy of organosilicon compounds in the field of organic synthesis, materials science and pharmaceuticals, the protocols leading to the synthesis of arylsilicon compounds substantially needed more to be explored.

Conventional approach for the preparation of organosilicon compound includes reaction of chlorosilanes[20,21] by employment of either Grignard or organolithium reagents but functional group incompatibility of these organometallic reagents and production of large amount of metal salts byproducts limits its utility (**Scheme 1.7a**).

Other approach is transition metal-catalyzed cross coupling of arylhalides with hydrosilanes[22,23] and disilanes[24,25] as shown in **Scheme 1.7b**. Although, this method overcomes the shortcomings associated with above approaches but prior functionalization before reaction makes it also undesirable. Thus, direct C-H functionalization via silylation appears to be an appealing alternative that transcends the drawbacks of traditional methods for the installation of silyl moeity.

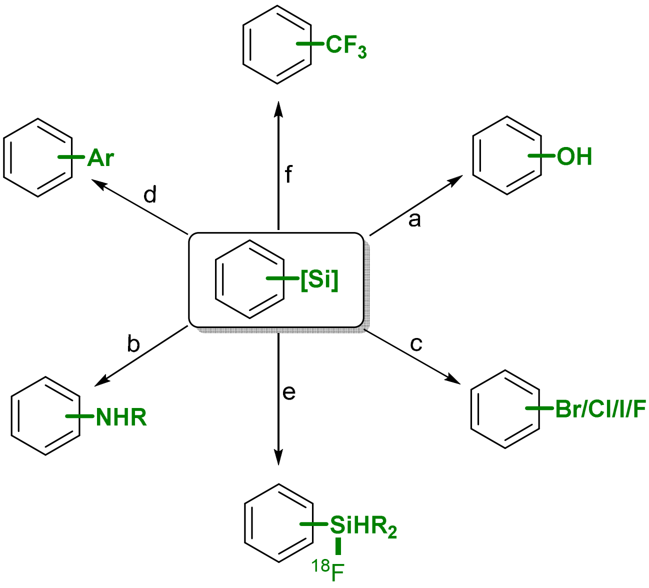
$$\text{C-M} \quad + \quad \text{X-Si} \xrightarrow[\text{M = Li, MgX}]{} \text{C-Si} \quad + \quad \text{M-X} \qquad \text{(a)}$$

$$\text{C-X} \quad + \quad \text{Y-Si} \xrightarrow[\text{Y= SiR'}_3\text{, H}]{\text{cat. metal}} \text{C-Si} \quad + \quad \text{H-X} \qquad \text{(b)}$$

$$\text{C-H} \quad + \quad \text{H-Si} \xrightarrow[\text{H}_2\text{ acceptor}]{\text{cat. metal}} \text{C-Si} \quad + \quad \text{H-H} \qquad \text{(c)}$$

Scheme 1.7. Approaches for C-Si bond formation

Transition metal catalyzed C-H silylation like C-H borylation is a straightforward, atom and step economical process as it doesnot requires prefunctionalization of arene as well as delivers organosilicon products with orthogonal regioselectivity from that observed in traditional methods.



a- Oxidation; b- amination; c- halogenation; d- arylation e- radiochemistry f- trifluoromethylation.

Scheme 1.8. Synthetic transformation of Silyl group

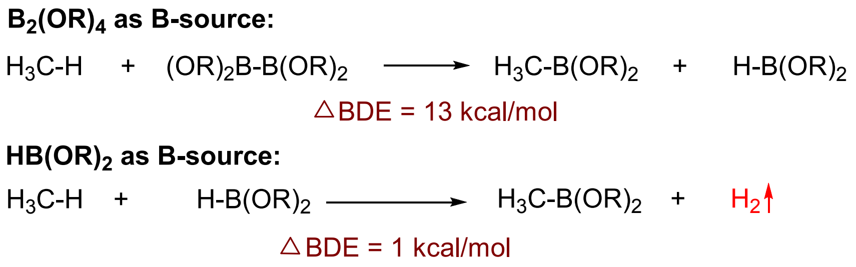
As a consequence of the diagonal relationship of B and Si, both organoboron and organosilicon compounds possess few similarities as both serves as transient intermediates for further significant transformations such as arylation,[26] amination[27] and oxidation[28] summarized in **Scheme 1.8** for Si, both show semiconductor behaviour but in contrast natural abundance of silicon is 4 times in magnitude to boron[29] in earths crust and silanes are more stable than boranes in terms of handling and storage.

Despite the versatility possessed by C-Si bonds, the C-H silylation is less developed than the complementary protocol C-H borylation. The limitations which restricts the practicality of catalytic C-H silylation reaction are requirement of harsh reaction conditions like high temperature (>100 ^{o}C) and unrealizable ratio of arene to silane. Although recent developments have overcome these above mentioned shortcomings but still many challenges are to be surmounted to harness the inherent usefulness of C-H silylation process.

Literature review:

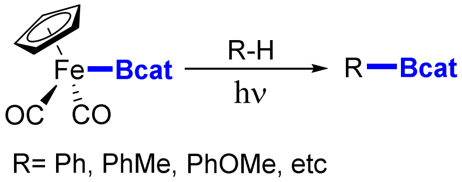
C-H Borylation

Formation of B-C bonds from C-H bonds is thermodynamically and kinetically feasible[30,31] reaction (**Scheme 1.9**) on the basis of calculated bond energies. Strong σ-donor properties of boryl group and presence of lowest unoccupied molecular orbital due to empty p_z orbital of boryl group stabilizes C-H bond cleavage transition state. Suitable electronic property of boryl group and hydrocarbyl ligand allows the smooth B-C bond formation.



Scheme 1.9. Thermodynamics of methane borylation

In 1993, in the supporting information of a paper published by Marder et al[32] regarding synthesis of first trisboryl iridium complex, a GC-MS data of two regioisomers resulting from the borylation of toluene solvent was mentioned. In 1995, Hartwig et al,[33] performed photochemical reaction of arenes and alkenes with metal-boryl complexes. $CpFe(CO)_2(Bcat)$ on irradiation in benzene that afforded PhBcat product in 87% yield as shown in **Scheme 1.10**. Since then other metals like Rh, Re, W, Pd were employed to make this reaction more synthetically useful.



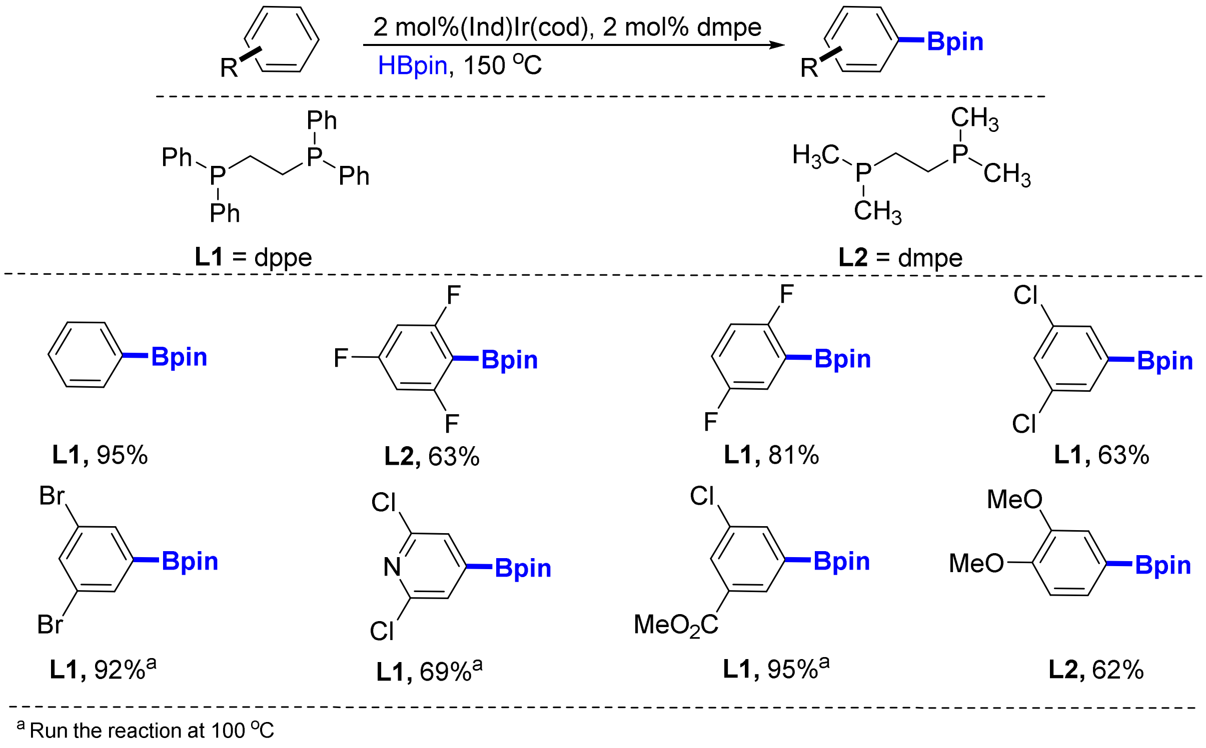
Scheme 1.10. Stoichiometric borylation catalyzed by Iron-boryl complex

A catalytic version of this reaction was demonstrated in 1999 by Smith and coworker[34] represented in **Scheme 1.11** where $Cp^*Ir(PMe_3)(H)(Bpin)$ catalyzes borylation of C_6H_6 using HBpin, the reaction was sluggish with (TON-3) at 150 °C with 53% yield.

$$\text{HBpin} + \text{PhH} \xrightarrow[150\ ^{o}\text{C, 120 h}]{17\ \text{mol\% Cp*Ir(PMe}_3\text{)(H)(Bpin)}} \text{Ph—Bpin} + \text{H}_2\uparrow$$

Scheme 1.11. First report of thermal catalytic aromatic borylation

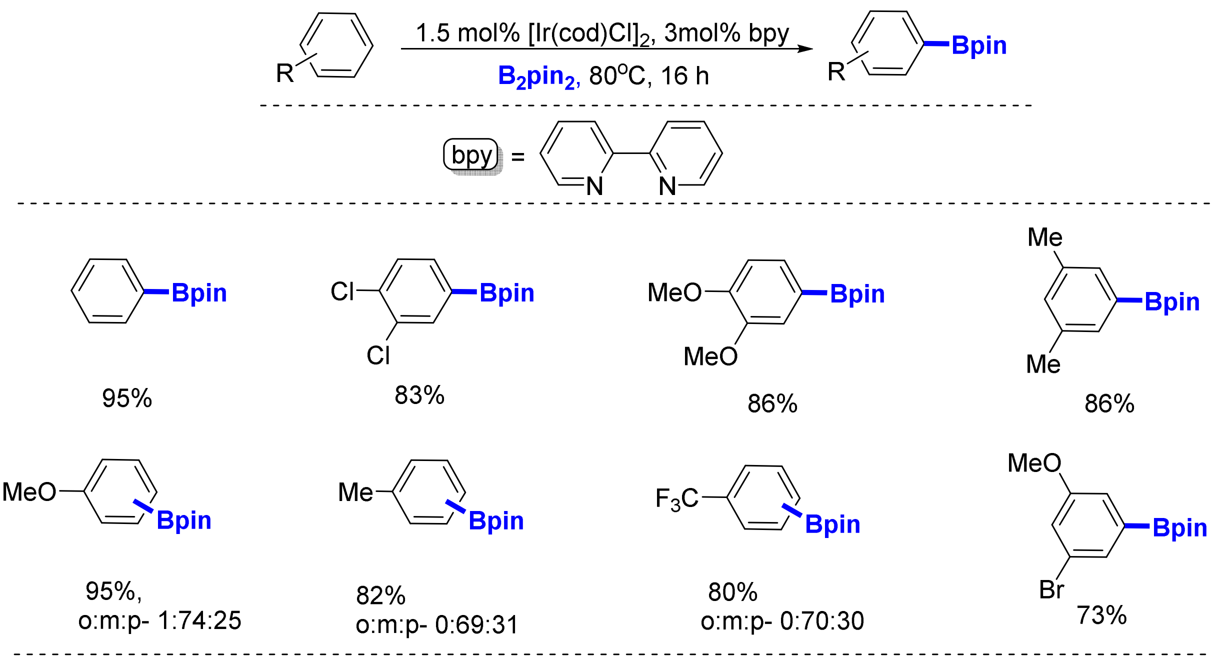
To develop more efficient catalytic system, the same group[35] employed combinations of (Ind)Ir(cod) to be used as a catalyst and various phosphine ligands such as PMe_3, 1,2-bis(diphenylphosphino)ethane (dppe), 1,2-bis(dimethylphosphino)ethane (dmpe) and HBpin as borylating agent (**Scheme 1.12**). Consequently, the modified method catalyzes C-H borylation at higher rates with broad functional group tolerance. Steric effect predominantly governs the outcome of borylation, where 1,3 disubstituted arene selectively reacted at 5 position providing complementary route to synthesize 1,3,5 trisubstituted arene analogous to electrophilic aromatic substitution.



Scheme 1.12. Borylation of arenes catalyzed by the combination of (Ind)Ir (cod) and phosphine ligands

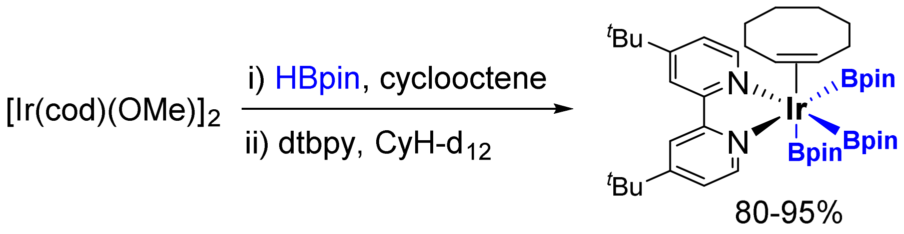
In 2002, Ishiyama, Miyaura, Hartwig and their coworkers[36] described borylation of arenes catalyzed by iridium complexes of bipyridine and 4,4 ' di*tert*-butylbipyridine and concluded that iridium containing bipyridine derivatives is more reactive catalytic system than phosphine ligated iridium.

Steric effects governs regioselectivity and results are summarized in **Scheme 1.13**, 1,3-disubstituted arenes yielded 3,5-disubstituted arylboronate exclusively and the reaction of monosubstituted arenes such as anisole, toluene and trifluoromethylbenzene yielded statistical mixture of *meta* and *para* product. In order to further optimize their catalytic system, a systematic study of Iridium precursors and series of substituted bipyridine ligands were conducted. The studies revealed that $[Ir(cod)(OMe)]_2$ is the most active precatalyst among $[Ir(cod)Cl]_2$, $[Ir(cod)_2]BF_4$, $[Ir(cod)(OH)]_2$, $[Ir(cod)(OPh)]_2$, $[Ir(cod)(OMe)]_2$, and $[Ir(cod)(OAc)]_2$ and electron donating bipyridine ligands[37] are more reactive than electron withdrawing counterparts.



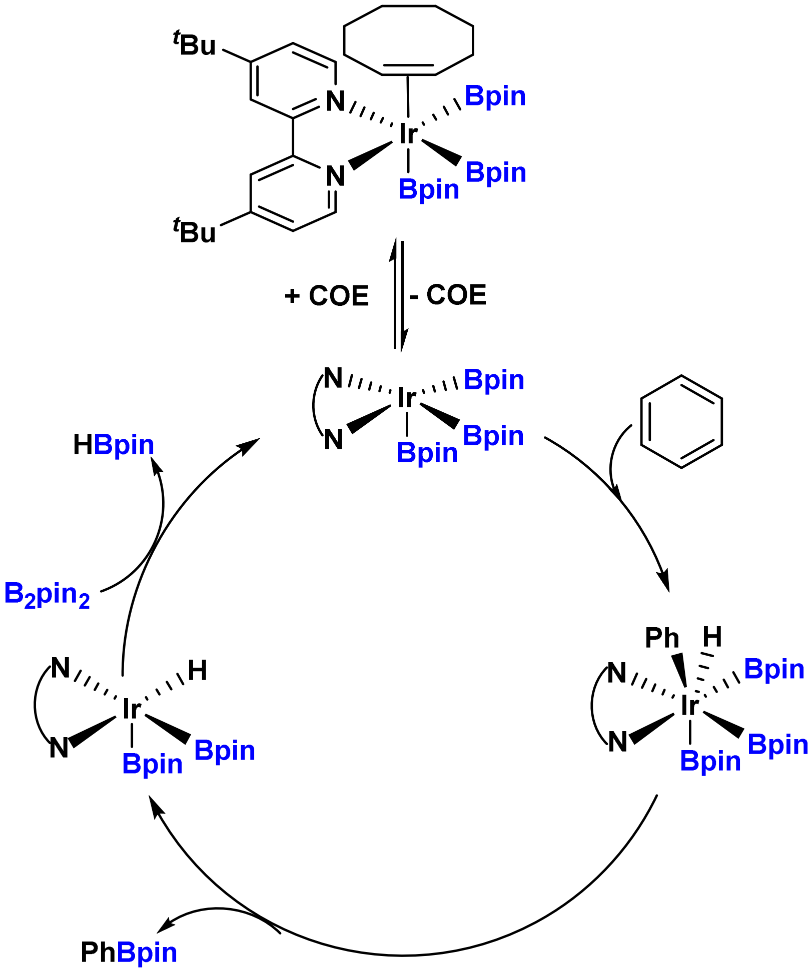
Scheme 1.13. Borylation of arenes catalyzed by the combination of $[Ir(cod)Cl]_2$ and 2,2'-bipyridine

Hartwig and coworkers[38] reported a detailed study for the mechanism of arene C-H borylation catalyzed by dtbpy ligated iridium. Various spectroscopic studies and isolation of the iridium-boryl complexes confirmed that $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ is an active catalytic intermediate. $[Ir(dtbpy)(\eta^2\text{-COE})(Bpin)_3]$ was isolated in 80-95% yield following the sequence that HBpin and COE were added before the bipyridine ligand. The addition of ligand before borane led to low yields of the trisboryl complex as summarized in **Scheme 1.14**.



Scheme 1.14. Synthesis of Iridium-trisboryl complex

On the basis of detailed NMR spectroscopic experiments and kinetic data, Hartwig and coworkers proposed a mechanism represented in **Scheme 1.15**. First after the reversible dissociation of cyclooctene ligand for iridium-trisboryl complex, a 16 electron catalytic intermediate is generated. Coordination of arene to this 16 electron intermediate followed by oxidative addition of arene which is a rate determining step. Reductive elimination of PhBpin from Ir(V) intermediate would produce borylated arene and Ir(III) species. Oxidative addition of B_2pin_2 followed by elimination of HBpin would regenerate active iridium trisboryl complex. Ir (III)/(V) cycle was identified to be consistent with experimental results.



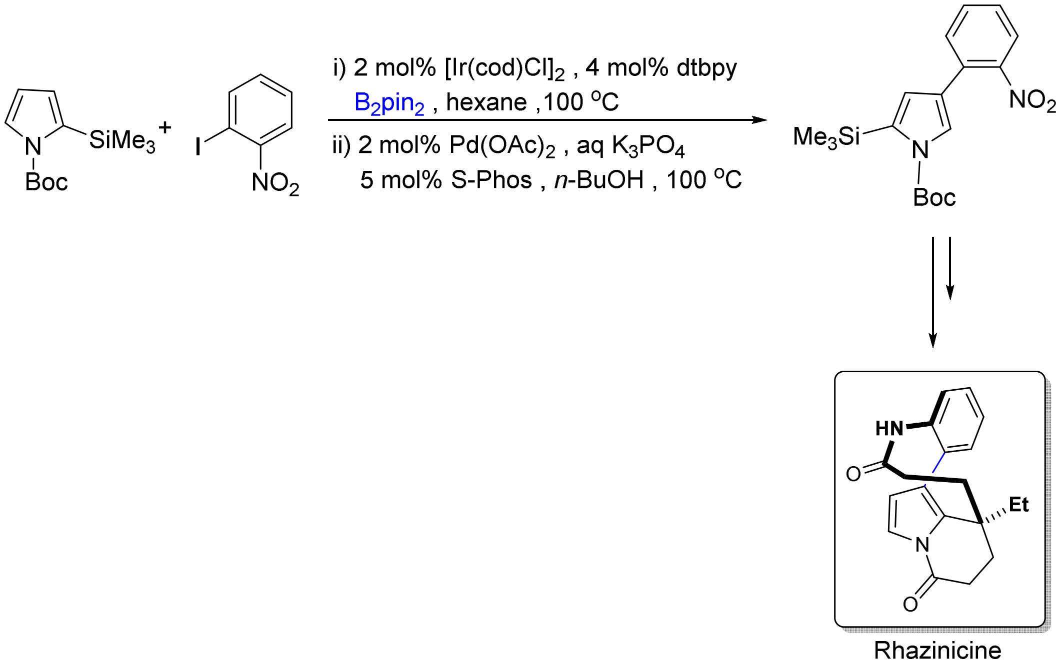
Scheme 1.15. Mechanism for the Iridium-catalyzed borylation of arenes

The field of direct C-H functionalization has been upheaved since after the debut of C-H borylation, it has made tremendous strides towards the goal of selective catalytic functionalization of inert C-H bonds. The fully elucidated mechanism of iridium-catalyzed C-H borylation, its conciliatory characteristics and versatility conferred upon B-C bonds after ensuing borylation event paved the way for its popularity.

Iridium-catalyzed C-H borylation has deciphered organic synthesis puzzle such as synthesis of Verruculogen and Fumitremorgin A, bioactive alkaloids deploying C-H borylation as key step in their total synthesis; achievement of long standing challenges such as introduction of *meta* substitution in phenols bearing o/p directing groups. Some of these prominent examples of appilacability of C-H borylation have been showcased in applications part described below.

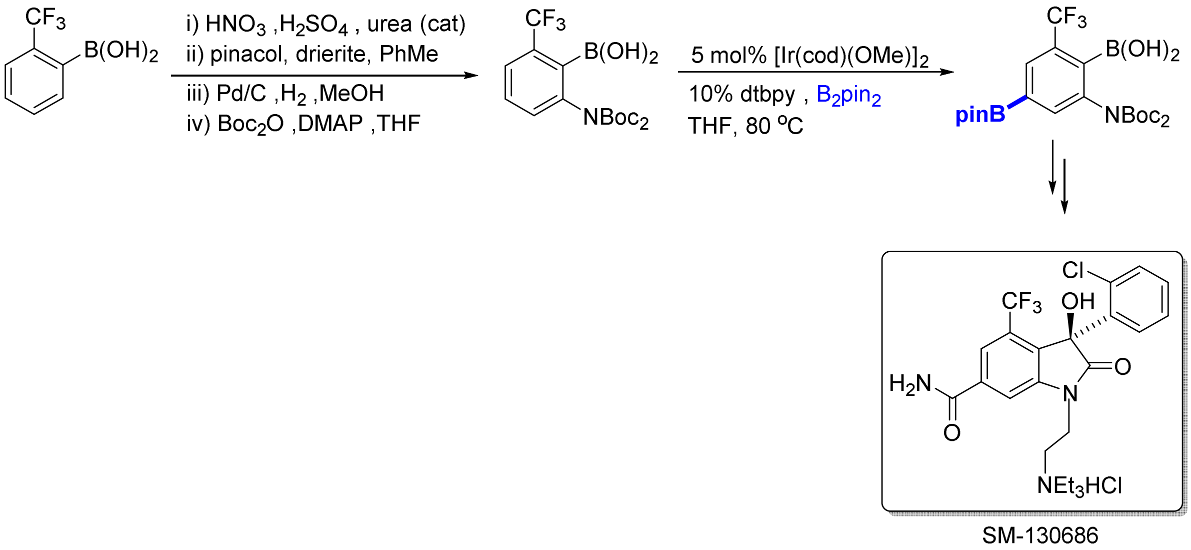
Applications of C-H borylation: Synthetic utility of C-H borylation is exemplified by the total synthesis of various natural products, polysubstituted aromatics, growth hormone secretagogue and pharmaceutically relevant compounds.

Synthesis of Rhazinicine: Gaunt and coworkers have synthesized a pyrrole alkaloid rhazinicine[39] where boc protected 2-trimethylsilyl pyrrole selectively gets borylated at 3-position under Ir-catalyzed borylation condition followed by coupling with 2-iodonitrobenzene as illustrated in **Scheme 1.16**.



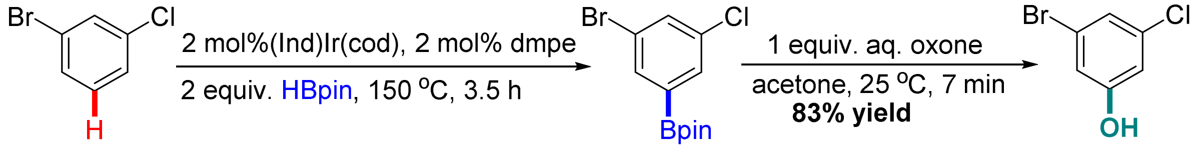
Scheme 1.16. Synthesis of Rhazinicine

Synthesis of SM-130686: Shibasaki and coworkers have demonstrated the applicability of iridium catalyzed C-H borylation by carrying out the synthesis of growth hormone secretagogue SM-130686.[40] One of the key steps employed was C-H borylation (**Scheme 1.17**).

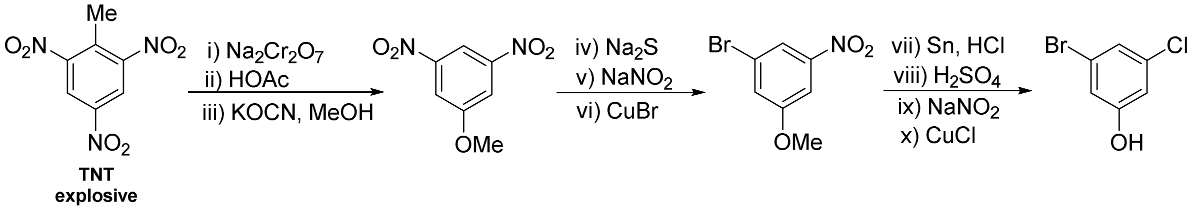


Scheme 1.17. Synthesis of SM-130686

Preparation of 3-chloro-5-bromophenol: Combined steric and electronic effect of substituents governs the synthesis of polysubstituted aromatics.[41] An introduction of *meta* substitution in *ortho*/*para* directing group containing aromatics was a tedious task involving several manipulations and discovery of C-H borylation have resolved this issue as shown in **Scheme 1.18**.

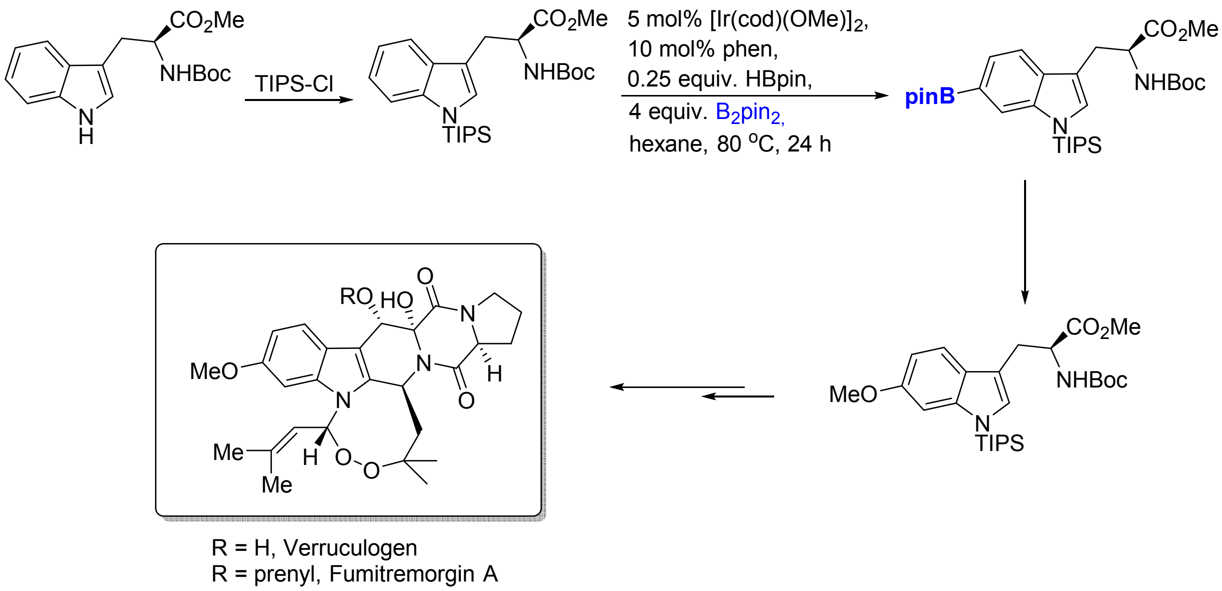


Scheme 1.18. (a) Synthesis of 3-chloro-5-bromophenol



Scheme 1.18. (b) Previous Synthesis of 3-chloro-5-bromophenol

Synthesis of Verruculogen and Fumitremorgin A: Total synthesis of bioactive alkaloids Verruculogen and Fumitremorgin A[42] which is summarized below has been accomplished in 11-12 steps (**Scheme 1.19**) by employing iridium catalyzed C-H borylation accompanied with Chan-Lam procedure to get C6 functionalized N, C3-disubstiuted commercially available tryptophan derivative, 6-methoxytryptophan.

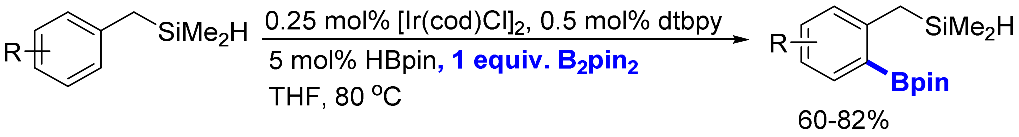


Scheme 1.19. Total synthesis of Verruculogen and Fumitremorgin A

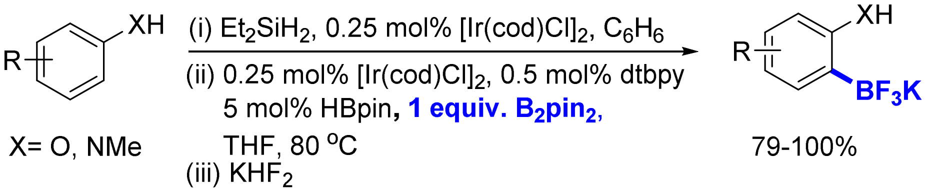
Directed C-H borylation:

Site selective *ortho* C-H functionalization via C-H bond activation was achieved by *DoM* approach but functional group constraints as well as impracticality i.e employment of harsh cryogenic conditions and requirement of strong base limits its utility and thus a method that surpasses these limitations was highly desirable.

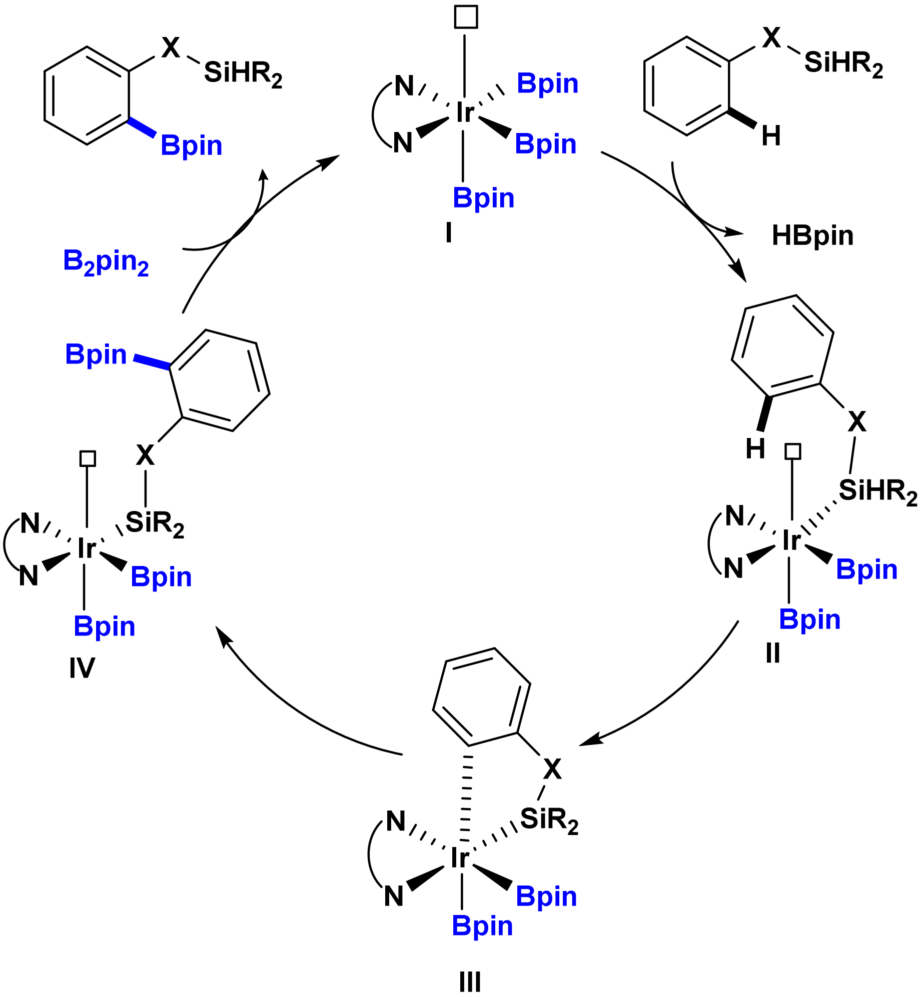
In 2008, Hartwig and coworkers[43] demonstrated *ortho* borylation of arenes, phenols and N-alkyl anilines using dimethyl hydrosilyl as directing group as shown in **Scheme 1.20, 1.21**. The usage of combination of $[Ir(cod)Cl]_2$ and dtbpy led to the selective *ortho*-borylation of arenes providing a milder alternative of *DoM* approach. Final borylated arenes are converted to more stable trifluoroborates by treatment with potassium hydrogen fluoride. The mechanism of this *ortho* borylation was proposed on the basis of deuterium labeling study in which deuterium incorporation occurs 14% at the *ortho* position of recovered starting material indicating selective activation at *ortho* position and 28% D incorporation into Si-H bond. The other experiment in support of proposed mechanism was to prove it is the temporary formation of Ir-Si bond not the silylborane $BnMe_2SiBpin$ that leads to the formation of borylated arenes. The mechanism depicted in **Scheme 1.22**, involves an initial σ-bond metathesis between iridium trisboryl complex and substrate forming bis-boryl silyl Ir complex. Intramolecular *ortho* C-H activation, reductive elimination of product and finally reaction with B_2pin_2 regenerates the catalytic intermediate. In this mechanism of *ortho* borylation, directing group covalently links to the metal catalyst and it is termed as relay directed borylation.



Scheme 1.20. Silyl directed *ortho*-borylation of alkylarenes

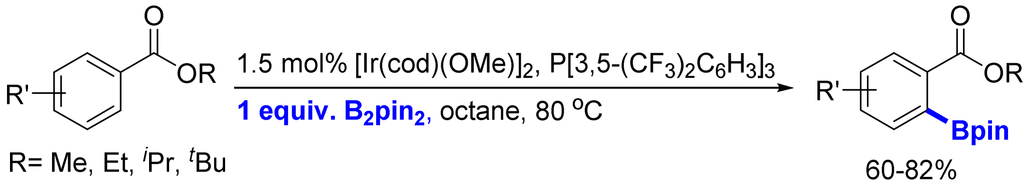


Scheme 1.21. Silyl directed *ortho*-borylation of phenol and arylamines



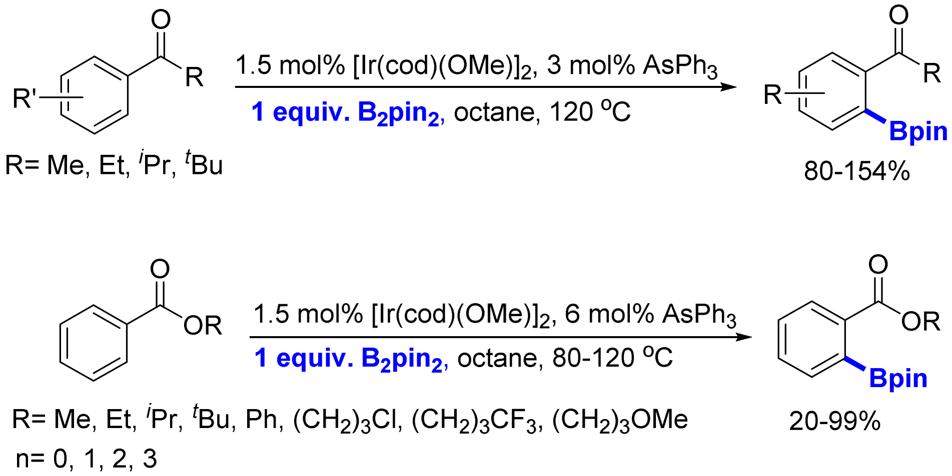
Scheme 1.22. Mechanism of relay directed borylation

In another strategy for directed *ortho*-borylation Lewis basic directing group chelates to the metal. Ishiyama and Miyaura et al[44] developed an *ortho*-borylation procedure for substrates containing oxygen based directing groups, it is illustrated in **Scheme 1.23**. The catalyst system comprises of $[Ir(cod)(OMe)]_2$ and electron poor phosphine $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ as ligand, B_2pin_2 in octane solvent at 80 °C for 16 h.



Scheme 1.23. *Ortho* C-H borylation of aromatic esters

Substituting phosphine ligand with AsPh$_3$[45] as ligand resulted in an increase in catalytic activity and C–H borylation of benzoates and aryl ketones (**Scheme 1.24**), C–H borylation at the vinyl position of α,β-unsaturated esters was also reported.



Scheme 1.24. ***Ortho*** **C-H borylation of aryl ketones and benzoates**

Sawamura et al[46] demonstrated an immobilized catalytic approach to achieve high *ortho* selectivity in various arene possessing oxygenated directing groups such as benzoates, benzamides, sulphonates, benzyl acetals and benzyl methoxymethylethers. Even Cl atom behaves as directing group with isomer ratio *ortho*:others 92:8.

Since, coordination of strongly coordinating bidentate dtbpy ligand generates 16 electron catalytic intermediate, which can only lead to sterically controlled borylation. Thus, suitable ligand modification facilitates the generation of 14 electron catalytic intermediate favouring coordination of basic directing group followed by subsequent C-H activation in the vacant coordination site. These type of borylation are categorized as chelate directed borylation. This silica supported phosphine ligand-Ir system (**Fig 1.1**) resulted in *ortho* borylation under mild condition (25-50 ^{o}C) in excellent yields. The results are summarized in **Scheme 1.25**.

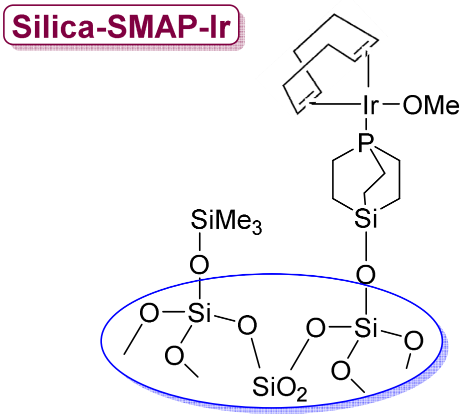
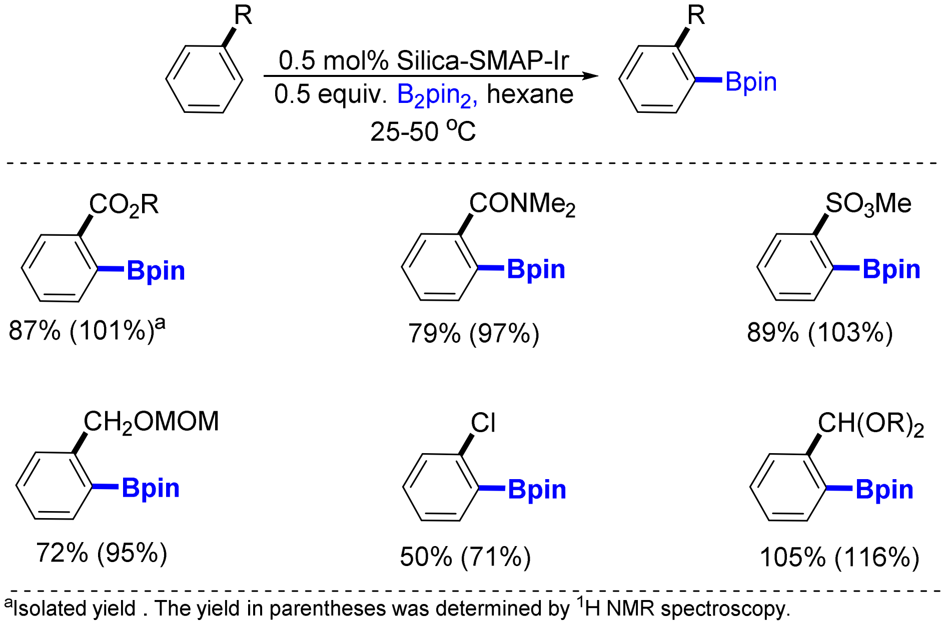


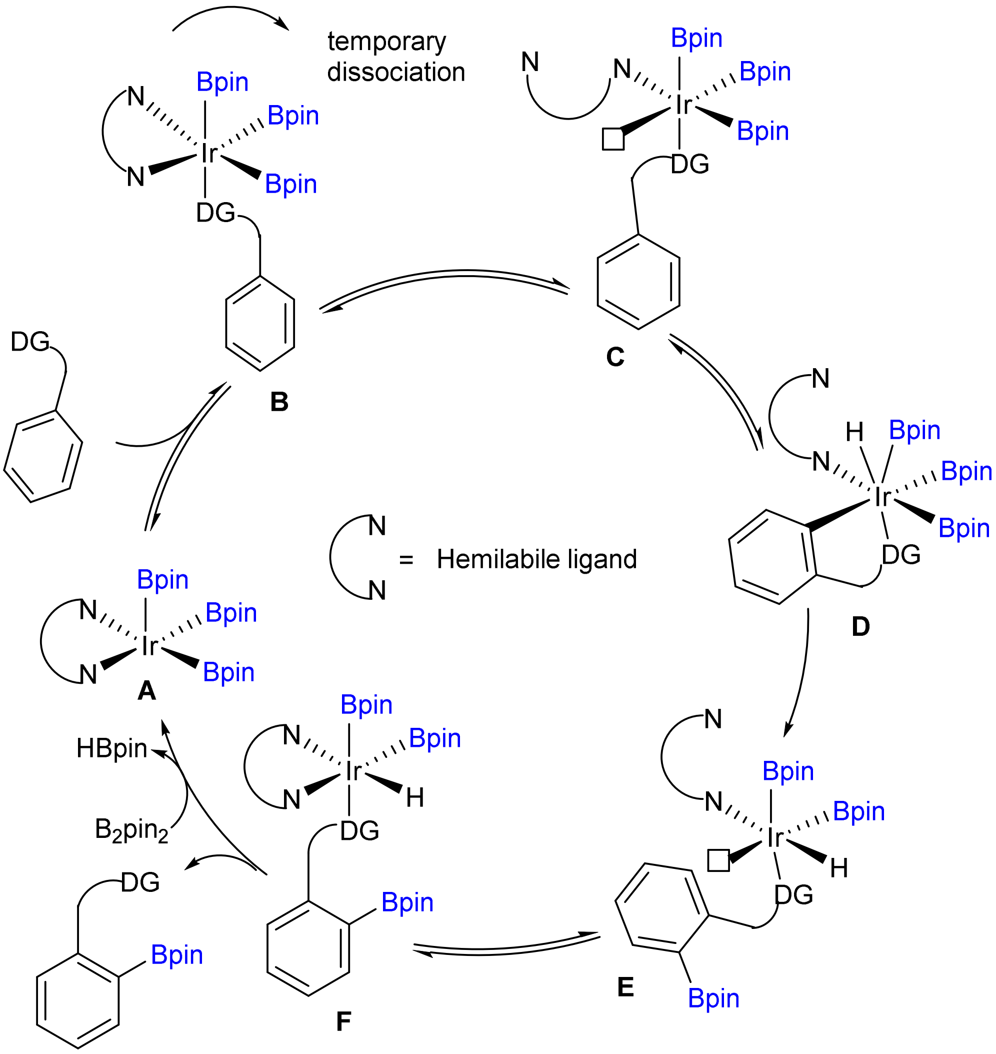
Fig 1.1 Silica supported phosphine ligand



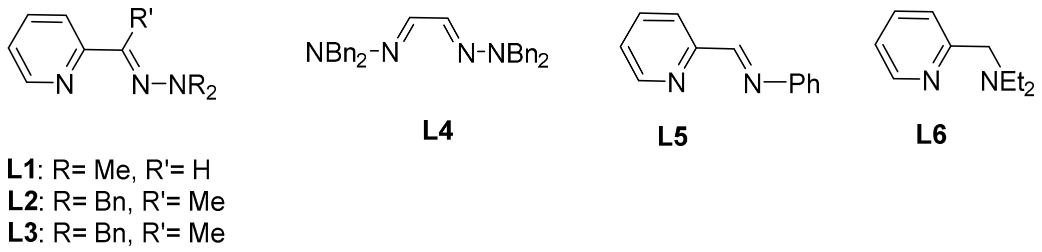
Scheme 1.25. ***Ortho*-borylation of arenes by the Silica-SMAP-Ir System**

Employing the key strategy of ligand modification in chelate directed borylation, Ros, Fernandez, Lassaleta and coworkers[47] envisaged that using hemilabile ligand in place of strongly coordinating ligand will facilitate the generation of vacant coordination site and proposed a mechanism. In the mechanism, as illustrated in **Scheme 1.26**, temporary dissociation of ligand generated vacant coordination site followed by *ortho* C-H activation. Reductive elimination of products followed by recoordination of ligand regenerates the catalytic intermediates.

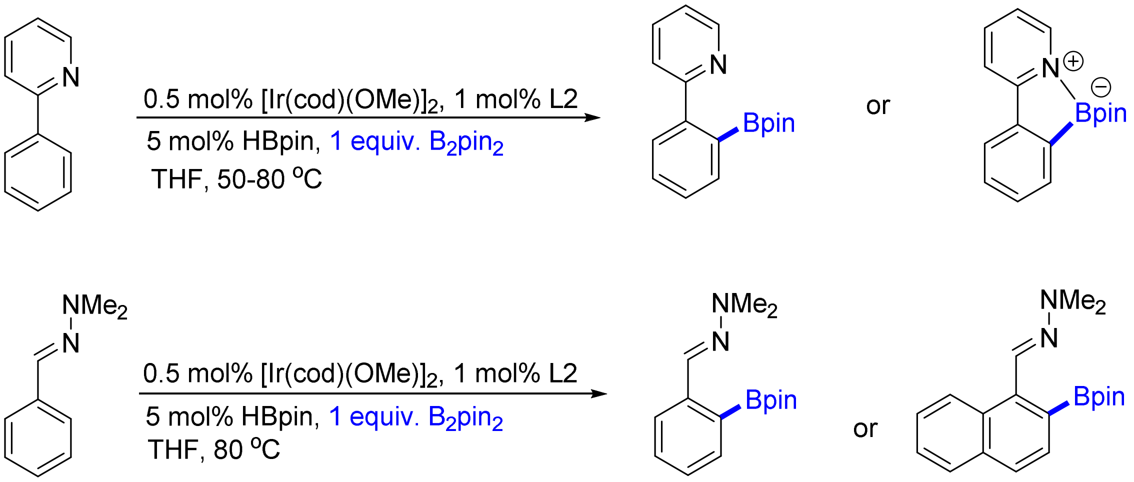
Site-selective *ortho* borylation of aromatic *N,N*-dimethylhydrazones is reported using pyridine dibenzylhydrazone as hemilabile ligand, after screening various similar types of ligands. Out of which L2 shown in **Scheme 1.27** gives highest yield, with these optimized conditions, borylation was performed on a variety of substrates containing 2-pyridyl, 2-isoquinolyl directing groups and aromatic *N,N*-dimethyl hydrazones summarized in **Scheme 1.28**. The methodology worked well for electron donating as well as electron withdrawing substituents on aromatic ring and its synthetic utility is showcased in **Scheme 1.29**.



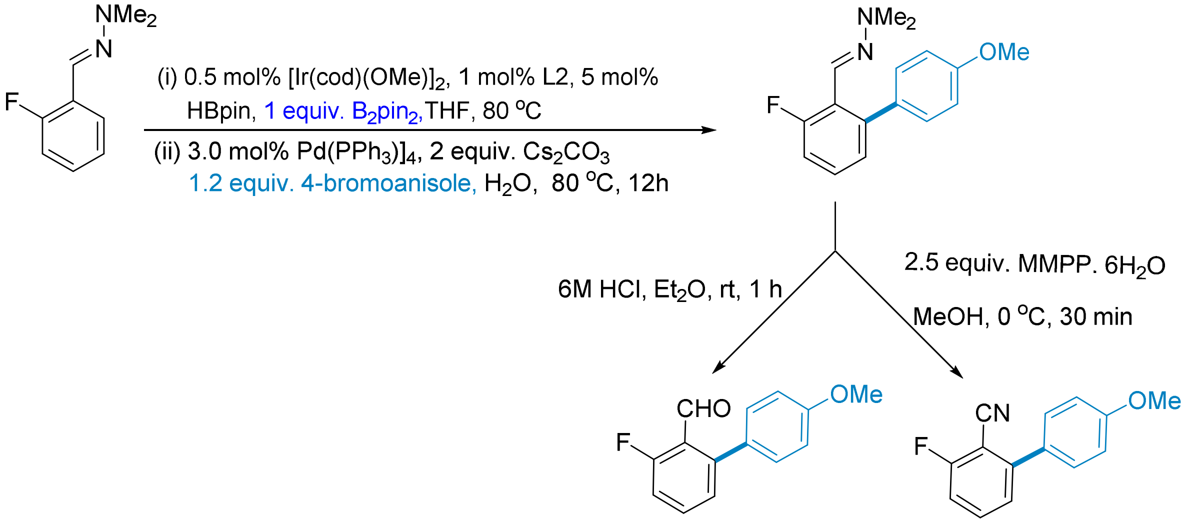
Scheme 1.26. Proposed mechanism with *N,N* hemilabile ligand



Scheme 1.27. ***N,N*** **ligands with hemilabile character**



Scheme 1.28. Directed borylation of aryl pyridines/isoquinolines and aromatic dimethylhydrazones

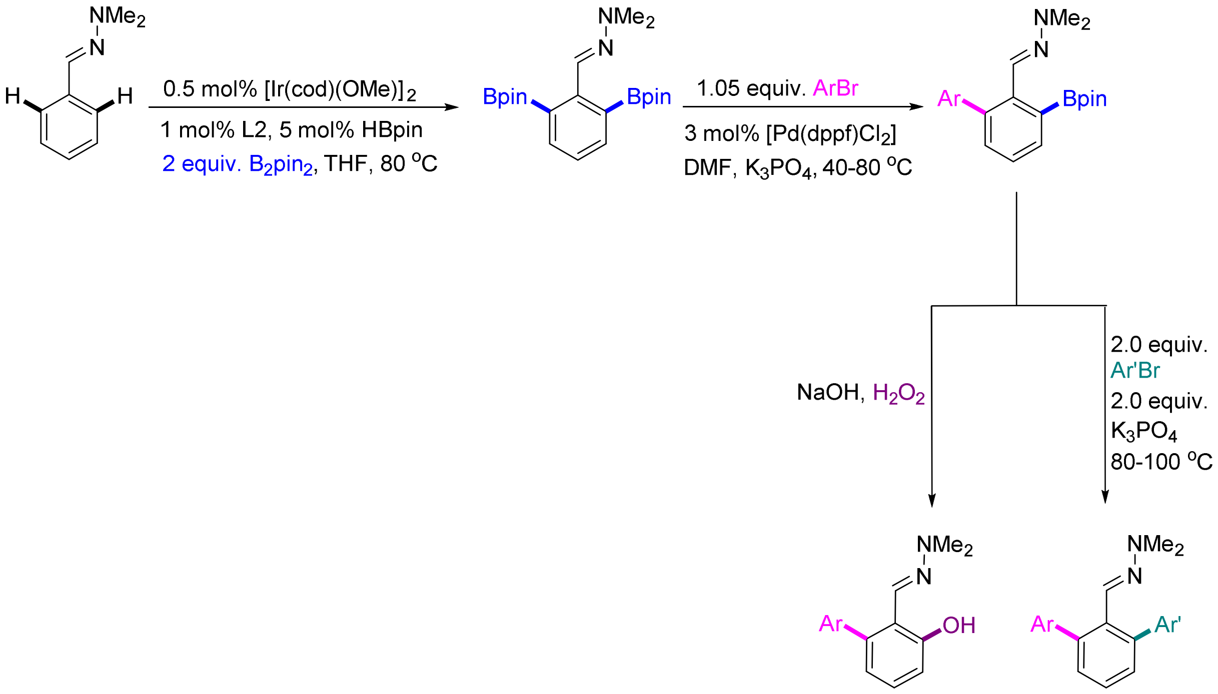


Scheme 1.29. Synthetic utility of developed directed borylation

Regioselective *ortho-ortho'* diborylation[48] of benzaldehyde derivatives was performed on the basis of comparative ^{1}H, ^{11}B NMR and crystallographic studies, of *ortho*-borylated aryl pyridines (S1) and monoborylated aromatic *N,N*-dimethylhydrazones (S2) shown in **Fig 1.2**. The studies revealed that for unhindered substrate S1 exhibited significant intramolecular N-B interaction alongwith other repulsive interactions, whereas substrate S2 lacks such intramolecular N-B interaction due to NMe_2/Me(pinacol) steric repulsion and thus N atom is available for subsequent borylation. Direct *ortho-ortho'* diborylation followed by sequential unsymmetrical functionalization with different electrophiles showcases the immense utility of their developed chemistry as summarized in **Scheme 1.30**.

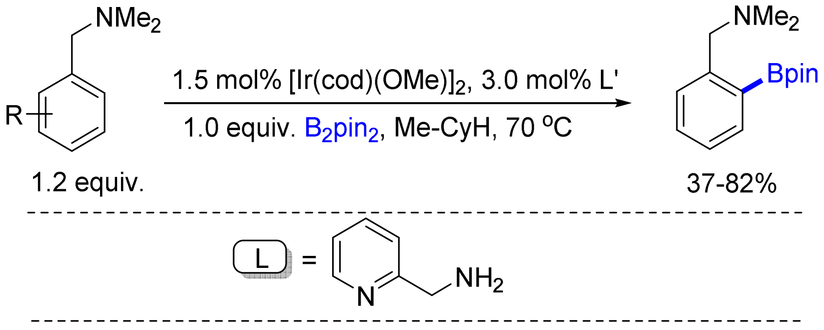
S1 **S2**

Fig 1.2. Preferred conformers of *ortho*-borylated aryl pyridine and aromatic *N,N*-dimethylhydrazones



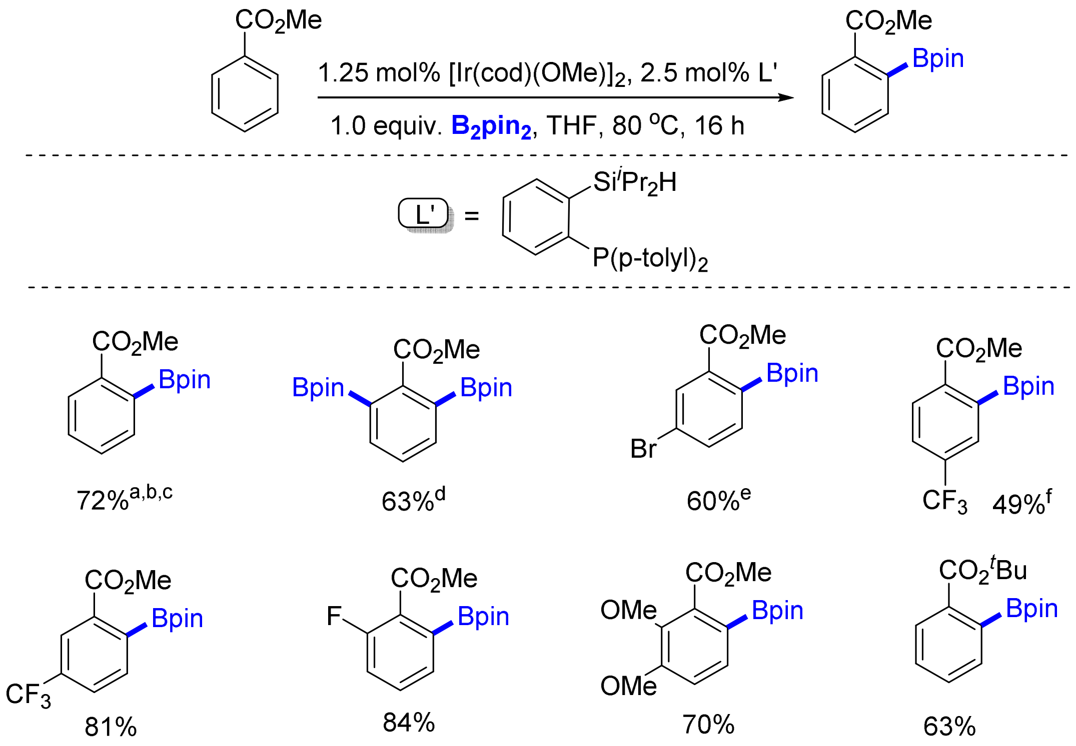
Scheme 1.30. Directed *o,o'*-diborylation of hydrazones and sequential functionalization

Clark et al[49] reported the *ortho* C-H borylation of *N,N*-dimethylbenzylamine using picolylamine as ligand, as shown in **Scheme 1.31**, proposing that H-bonding between N-H bonds of ligands and substrate governs *ortho*-selectivity. But the control experiments using *N,N*-dimethylpicolylamine as ligand yielded the similar selectivity and comparable conversion negating the concept of H-bonding as a governing factor for *ortho*-selectivity.



Scheme 1.31. Substrate directed C-H borylation of benzylic amines

Smith et al[50] disclosed a methodology for the selective *ortho* borylation of a wide range of functional groups employing Si tethered P and N donor ligands. The results are represented in **Scheme 1.32**. Keeping in mind two important considerations, first two vacant coordination site are required for selective *ortho* borylation if the ligand is not hemilabile and second Ir-Si and B-H bond is generated by σ-bond metathesis of Ir-B/Si-H bonds as shown in relay directed borylation. Thus Ir-B/Si-H metathesis between iridium trisboryl complex and synthesized ligand generates the active catalytic intermediate L'.



[a]2.0 mmol substrate was used. [b]0.5 mol %[Ir(cod)(OMe)]$_2$ was used. [c]Reaction was run at 60 °C.
[d]2.0 mmol B$_2$pin$_2$, 0.025 mmol [Ir(OMe)(cod)]$_2$, and 0.050 mmol 5 were used.
[e]0.5 mmol substrate was used. [f]17% diborylated material was isolated.

Scheme 1.32. *Ortho*-borylation of alkylbenzoates with bidentate Si, P ligand

Carbamates and ketones reacted sluggishly with ligand L thus considering that N donor ligands more reactive than P-donor ligand counterparts, Si tethered N donor ligand shown in **Fig 1.3** was also synthesized.

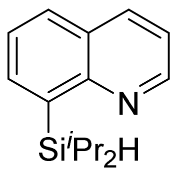
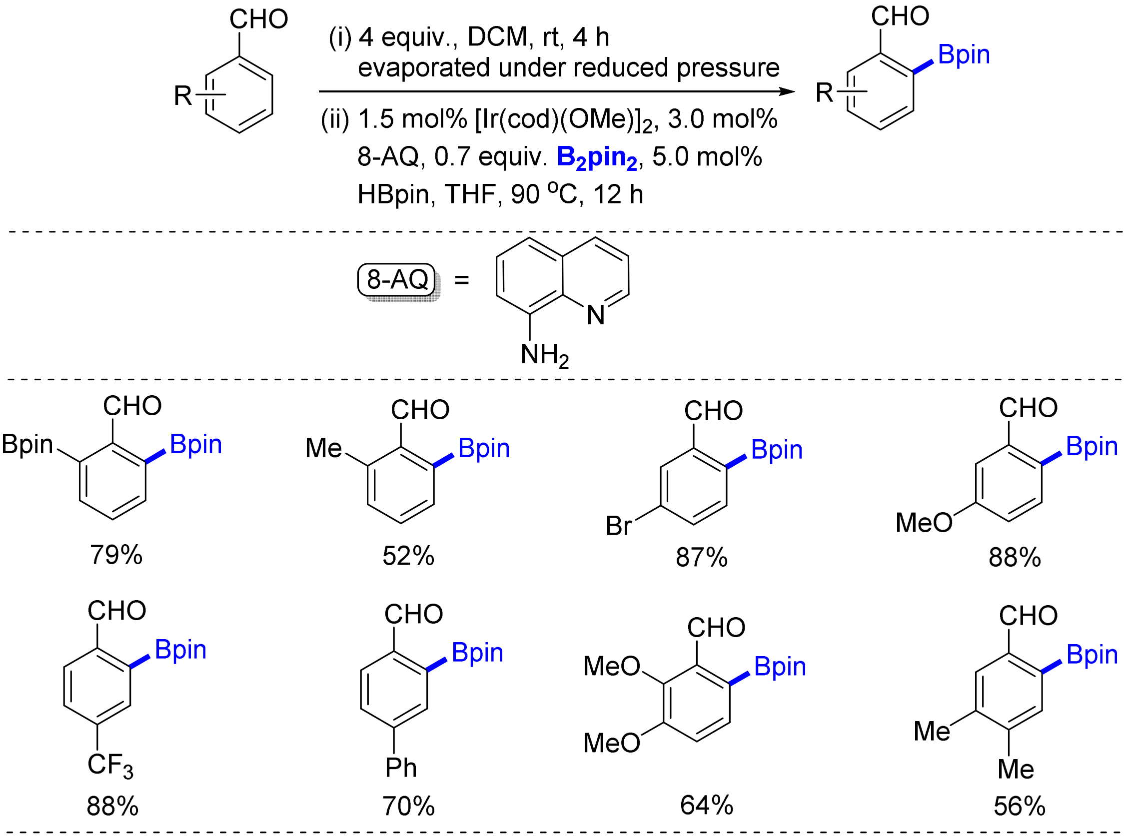


Fig 1.3. Si tethered N donor ligand

Inspired by the results of Fernandez-Lassaletta, Sawamura and Ishiyama's N-directed *ortho* borylation of 2-phenylpyridines and hydrazones, our group demonstrated N-directed *ortho* borylation of aromatic imines serving as traceless protecting and directing group. 8-AQ was identified as suitable hemilabile ligand,[51] which undergoes temporary dissociation and opens a vacant coordination site with *tert*-butyl imine directing group containing substrates not with isopropyl amd methylimines. Wide range of differently substituted benzaldehydes, electron-rich as well as electron deficient ones afforded *ortho* borylated product in appreciable yields, summarized in **Scheme 1.33**.



Scheme 1.33. *Ortho*-borylation of benzaldehydes via in situ generated imines

The finesse of iridium-catalyzed C-H borylation has reached to a fascinating level. Site-selectivity is no longer governed only by covalent forces and steric factors instead weaker non-covalent interaction like H-bonding, electrostatic interaction, O-K interaction[52] are becoming the torchbearer of regioselectivity.

Metal catalyzed C-H activation rely on cyclometalation approach for proximal *ortho* functionalization and for remote C-H activation and functionalization, bulky linkers and templates are required which are undoubtedly unique tools for remote functionalization but their bulkiness and long synthetic routes for their synthesis limits its practicality and utility.

Nature judiciously employ noncovalent interactions in the action of its catalyst, enzymes. Vital role is played by NCI's in organocatalysis such as hydrophobic-hydrophobic interaction between cyclodextrins and steroids in C-H hydroxylation,[53] H-bond governed hydroformylation of alkenes[54] and hydrometalation of unsymmetrical alkynes, host guest size differentiated C-H functionalization[54] and many more.

Thus unification of NCI's and transition metal catalysis to exert site-selectivity through rational catalyst-substrate designing in C-H activation and functionalization holds tremendous potential and would allow possible development of new technologies C-H activation/borylation chemistry. Integration of mild and synthetically versatile iridium catalyzed C-H borylation with NCI's is an emerging field which has prominent pathbreaking examples.

Smith, Maleckza, Singleton et al[55] discovered that H-bonding between N-Boc protected aniline and boryl O-atom governs *ortho* selectivity, represented in **Fig 1.4.** Mechanistic investigations and theoretical calculations were fully in agreement with the proposed hypothesis. The authors categorized it as outer-sphere direction as ligand on the catalyst is responsible for recognition of functionality on substrate. High *ortho* selectivity is achieved for 4-substituted substrate but doesnot works well with 3-substituted and 2-substituted substrates (**Scheme 1.34**).

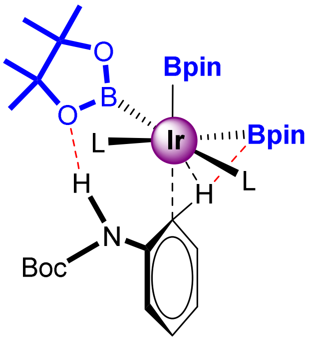
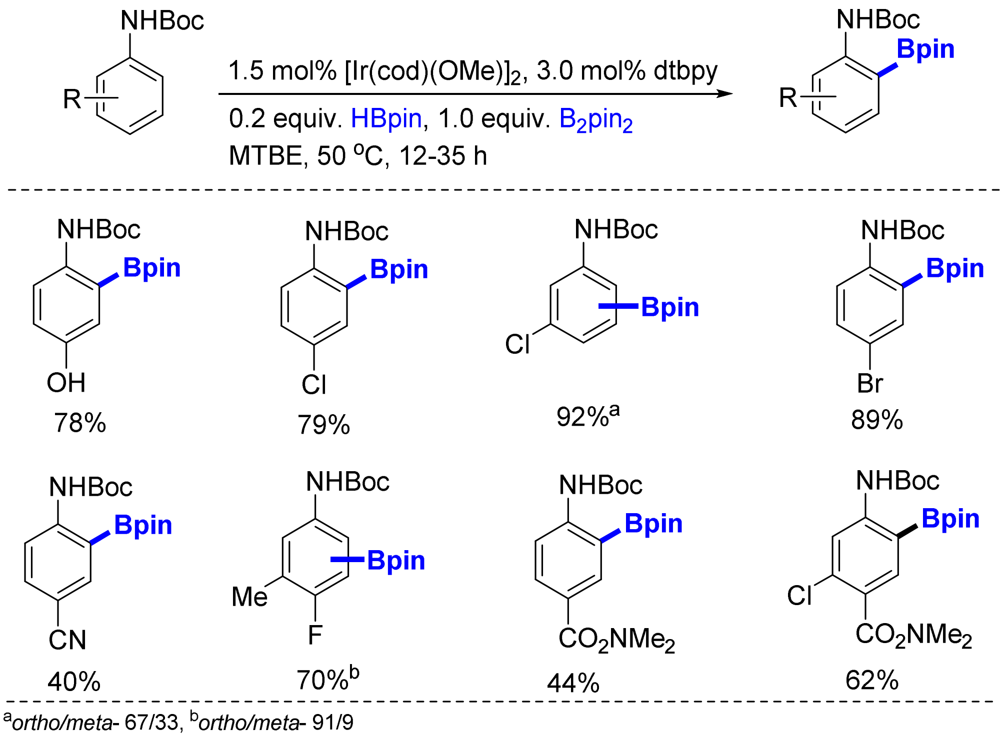


Fig 1.4. Proposed transition state for regioselective *ortho*-borylation



Scheme 1.34. ***Ortho*-borylation of N-Boc anilines**

The same group later revisited their chemistry and overcame the disadvantage of requirement of extra steps for installation and removal of directing groups. Bpin[56] acts as a traceless directing group for *ortho* borylation of anilines, proposed transition state is shown in **Fig 1.5**, but the chemistry remained limited to 4-substituted and disubstituted anilines (**Scheme 1.35**).

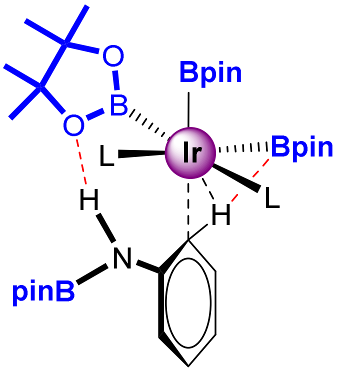
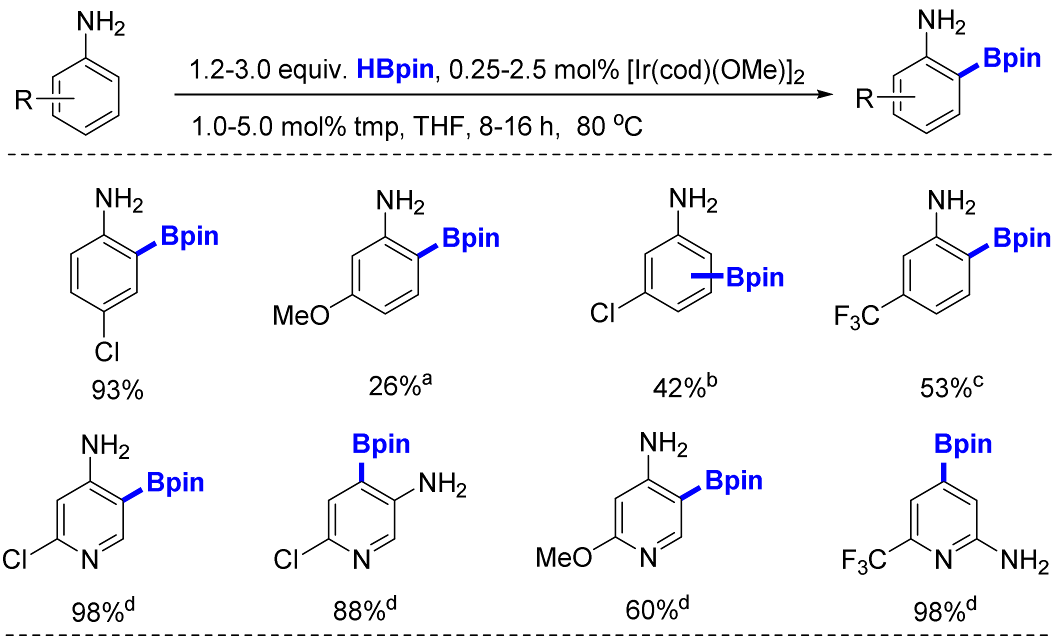


Fig 1.5. Proposed transition state for regioselective *ortho*-borylation



[a] 5-borylated product (47%). [b] 5-borylated product (21%). [c] 5-borylated product(17%).
[d] 0.5 equiv. B_2pin_2 used

Scheme 1.35. *Ortho*-borylation of anilines and aminopyridines by traceless Bpin group

Very recently our group in collaboration with Smith and Maleczka developed an approach for *ortho* borylation of anilines using Beg[57] as traceless protecting and directing group. The developed chemistry overcame all the previous limitations encountered in *ortho* C-H borylation of aniline. The methodology is equally efficient for *para*, *meta*, *ortho* as well as disubstituted anilines. The proposed transition state and substrate scope is depicted in **Fig 1.6** and **Scheme 1.36**.

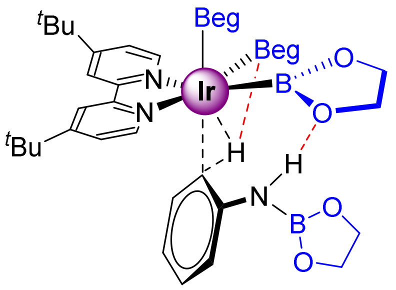
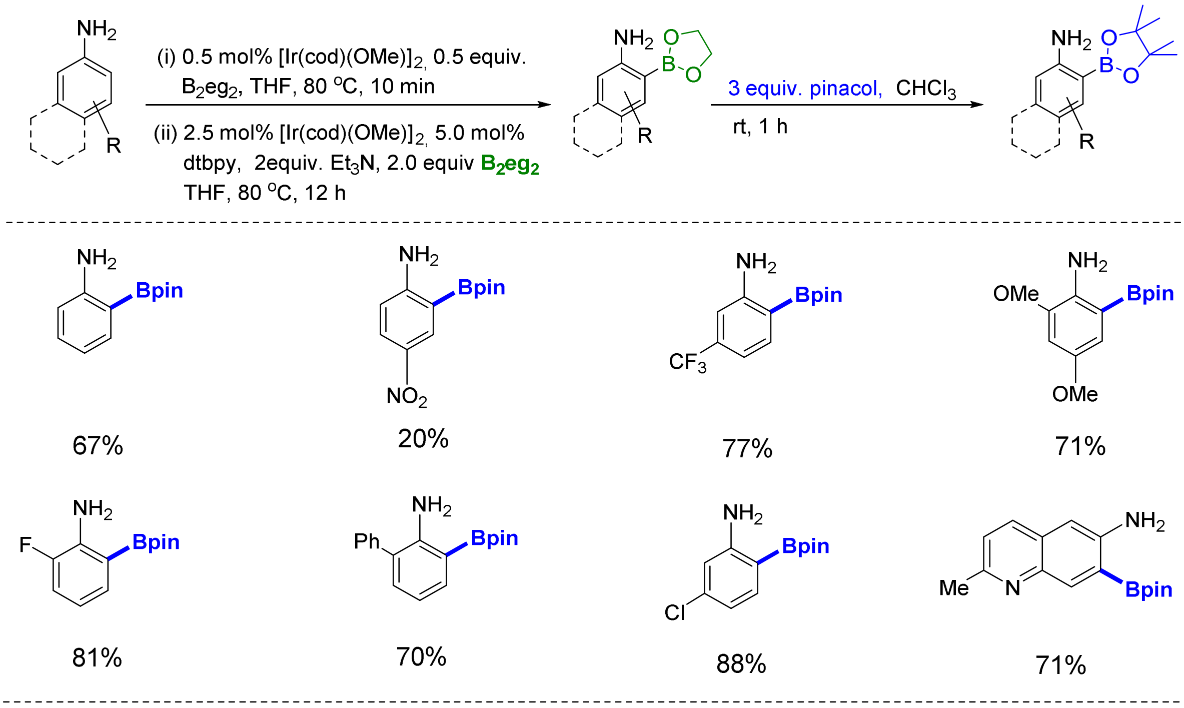


Fig 1.6. Proposed transition state for regioselective *ortho*-borylation



Scheme 1.36. Traceless Beg directed borylation of anilines and heterocycles

Kanai, Kuninobu and coworkers[58] employed a novel Lewis acid-base controlled NCI between S atom of substrate and boryl group of ligand realizing the *ortho* borylation of aryl sulphides depicted in **Fig 1.7**. Introduction of CF$_3$ group resulted in an excellent *ortho* selectivity 30:1. *Meta*- and *para* substituted substrates exhibited good *ortho* selectivity but increasing the steric on S atom reduces the selectivity and heterocycles shown in **Scheme 1.37** didn't underwent borylation.

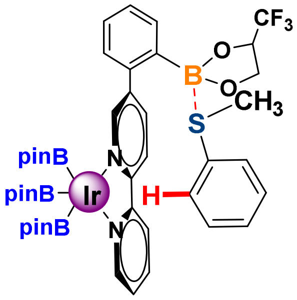
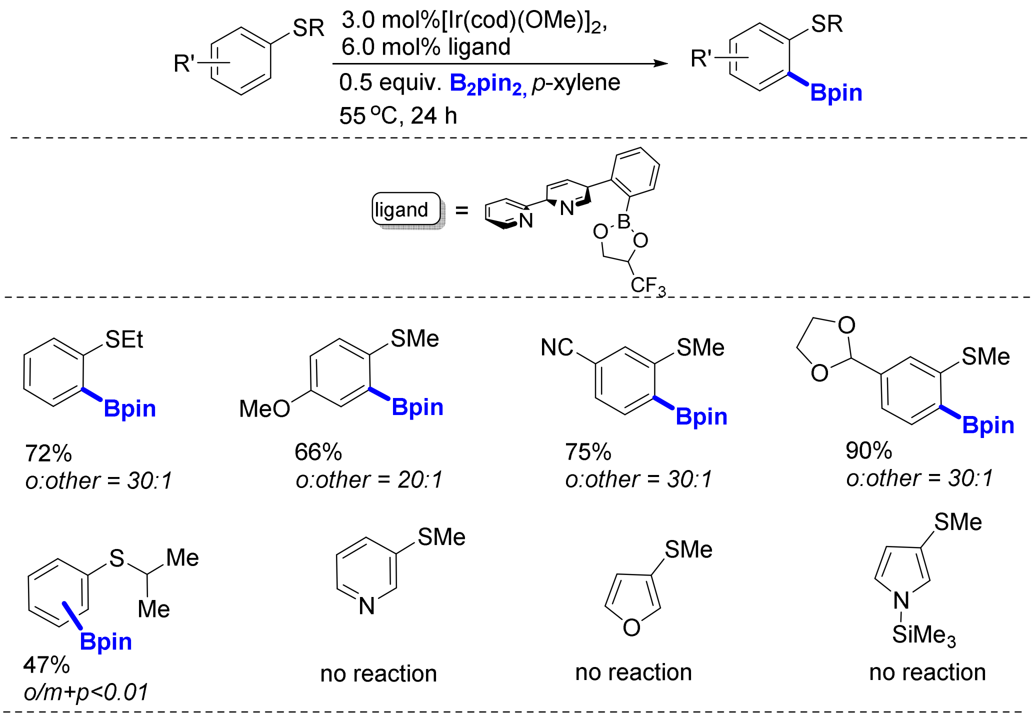
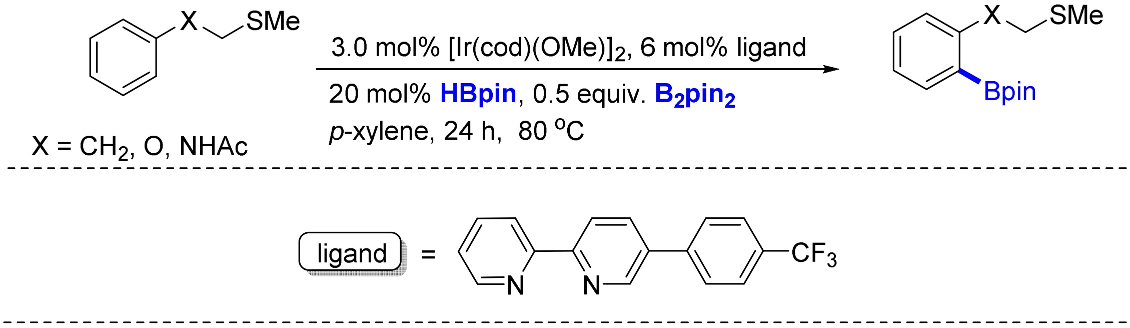


Fig 1.7. Proposed transition state for regioselective *ortho* borylation



Scheme 1.37. *Ortho*-borylation of aryl sulphides

The same group extended their strategy for *ortho*-borylation of phenols and anilines by modification of their ligand, represented in **Scheme 1.38.**[59]



Scheme 1.38. *Ortho*-borylation of phenol and aniline

Very recently Smith, Maleczka et al[60] devised an electrostatic interaction between partially negatively charged OBpin group and positively charged bipyridine ring (**Fig 1.8**) as a governing factor for *ortho* C-H activation and borylation of phenol. However requirement of substituent larger than CN or F is a major issue to achieve high *ortho* selectivity. Moreover higher level calculations while studying TS's suggested methyl group of Bpin brings significant distortions in arene geometry thus alleviating *ortho* selectivity. To prove their hypothesis they prepared OBeg protected phenols and by simply changing boron source from sterically demanding Bpin to sterically less demanding Beg, excellent *ortho* selectivity was achieved. The results are summarized in **Scheme 1.39 and 1.40**.

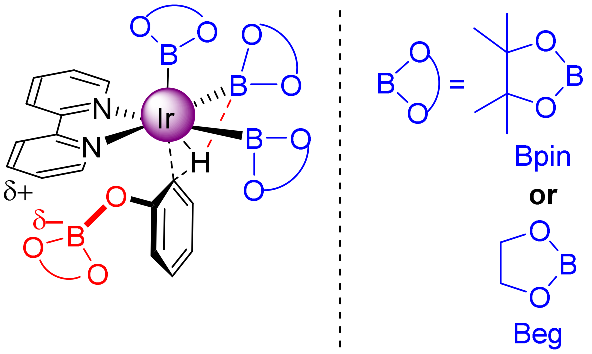
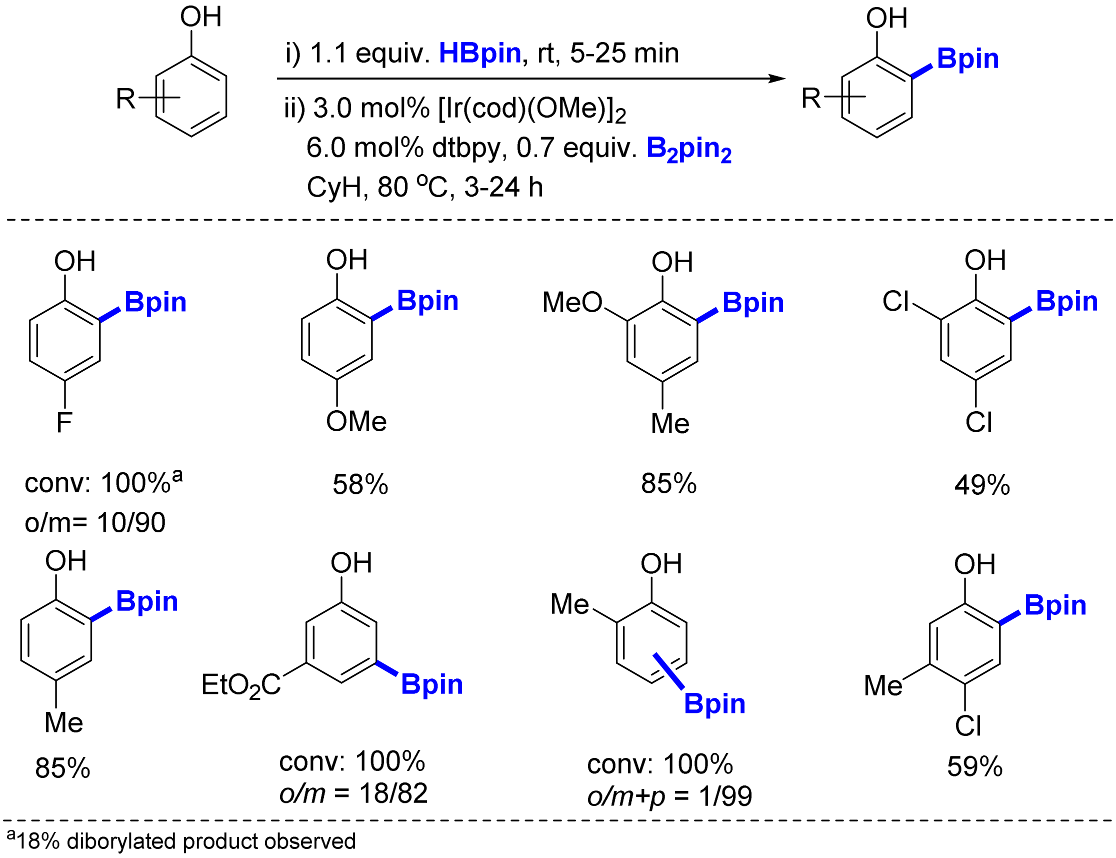
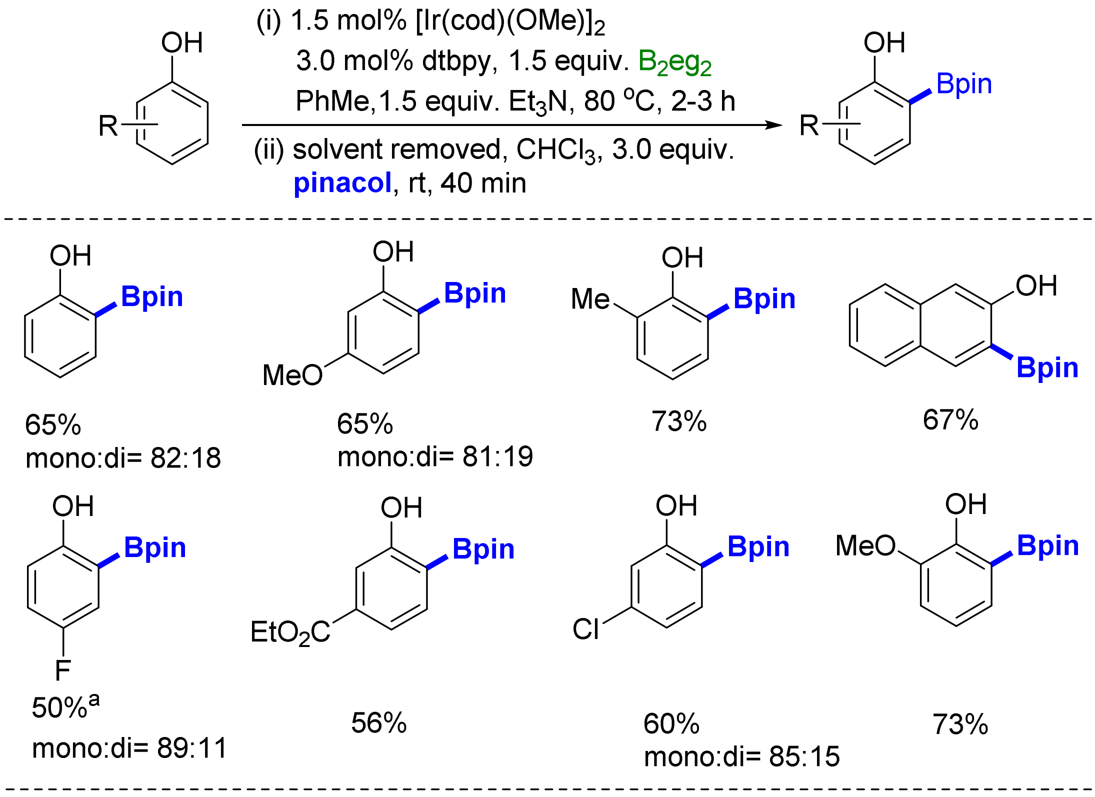


Fig 1.8. Proposed transition state for regioslective *ortho* borylation



Scheme 1.39. Traceless Bpin-directed borylation of phenols



[a] B_2eg_2 used as 1.2 equiv

Scheme 1.40. Traceless Beg-directed borylation of phenols

Iridium catalyzed *meta* borylation of arenes- The pioneering example of *meta* borylation of arenes is exemplified in H-bonding interaction shown in **Fig 1.9**, between pendant urea moiety covalently linked to bipyridine core unit and H-bonding acceptor group present on aromatic amides, aryl phosphonates and phosphonic diamides and phosphine by Kanai, Kuninobu et al.[61] NMR experiments confirmed the involvement of H-bonding interaction which brings the Ir metal in proximity of distal *meta* C-H bond of substrate. While examining substrate scope (**Scheme 1.41**), *ortho* monosubstituted substrates yielded *meta*-selective products in moderate to excellent yields. In addition to this aryl phosphonates, phosphonic diamide and phosphine oxides also exhibited *meta*-selective borylation. C-H borylation also proceeded with heteroaromatic amides. With benzaldehyde, acetophenone, nitrobenzene, *N,N*-Dihexyl-2-naphthamide, *N,N*-dihexyl-2-(methylthio)benzamide and *N,N*-dihexyl-4-(trifluoromethyl)benzamide no borylated products were obtained.

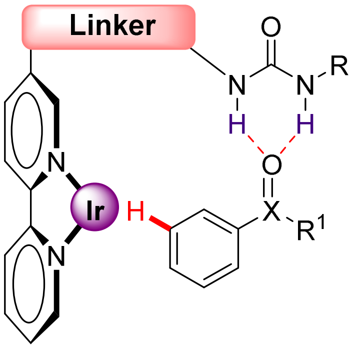
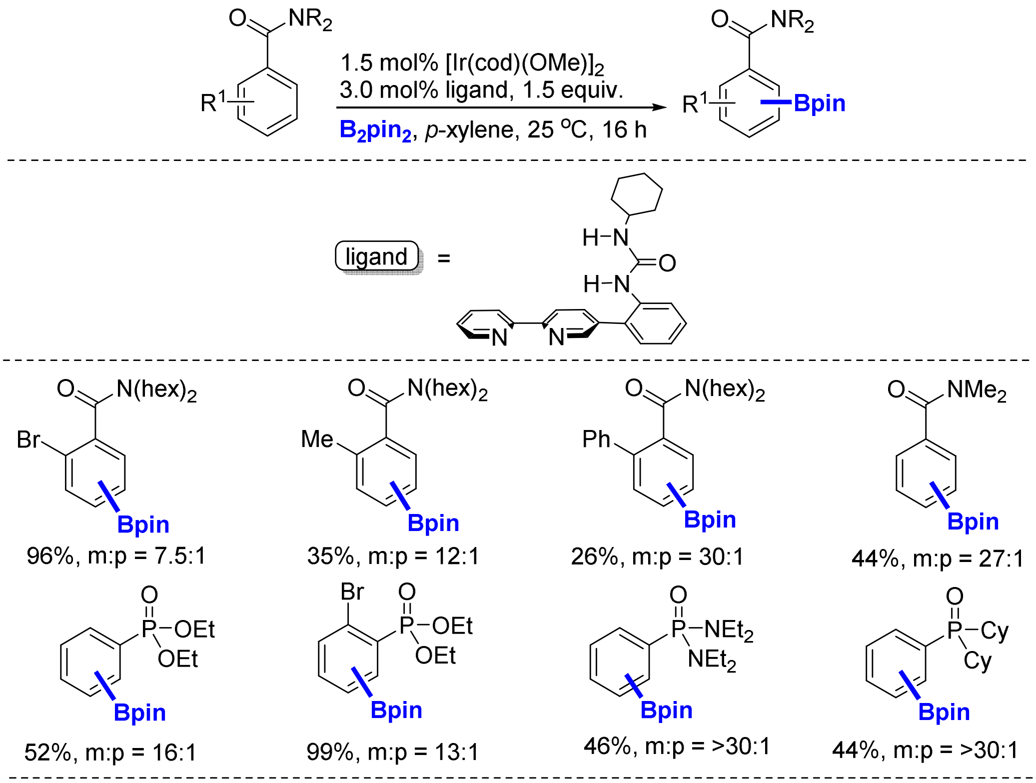


Fig 1.9. Proposed transition state for regioselective *meta*-borylation



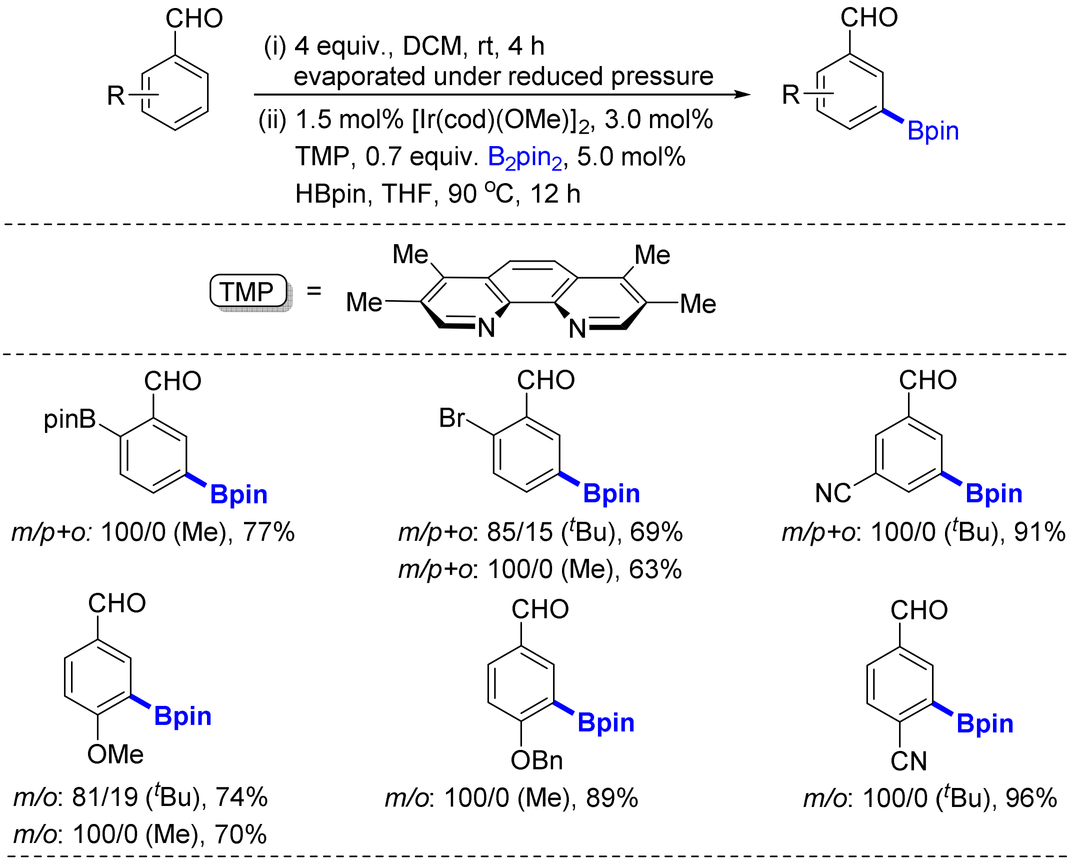
Scheme 1.41. H-bond controlled *meta*-borylation

Concurrently our group disclosed the concept of noncovalent electrostatic interaction arising due to encapsulation of electron rich ligand into the cavity of trisboryl complex and B-N noncovalent interaction between ligand of catalyst and substrate for regioselective *meta*-borylation of aromatic aldehydes. Experimental findings supports electrostatic interaction and B-N interaction[62] for the origin of high *meta* selectivity, as switching imine substituent from ^{t}Bu to ^{i}Pr to Me imine resulted in an enormous enhancement in *meta*-selectivity indicating the involvement of TS 1 instead of TS 2 (**Fig 1.10**). Wide range of methylamine substituted benzaldehyde were tested with optimized condition and afforded excellent *meta*-selectivity in all cases, even bulky substituent at 4- position afforded *meta*-borylated product, summarized in **Scheme 1.42**.

TS 1

TS 2

Fig 1.10 Possible transition states



Scheme 1.42 Electrostatic and B-N bond directed *meta*-borylation of aromatic aldehydes

Phipps and coworkers[63] introduced a novel ion-pairing noncovalent interaction between two classes of aromatic quarternary ammonium salts and an anionic sulphonate containing bipyridine shown in **Fig 1.11**. The designed anionic ligand exhibits ion-pairing interaction with substrate enabling *meta* C-H borylation of quarternary ammonium salts of benzylamine and aniline. The results are summarized in **Scheme 1.43**. The scope of substrates is wide as benzylamine derived quarternary ammonium salts containing halogen functionality as well as electron donating and withdrawing groups are compatible under reaction conditions. Aniline derived quarternary ammonium salts follows the similar trend with respect to the electron donating as well as withdrawing groups and halogen functionality, in all cases high *meta* selectivity was obtained.

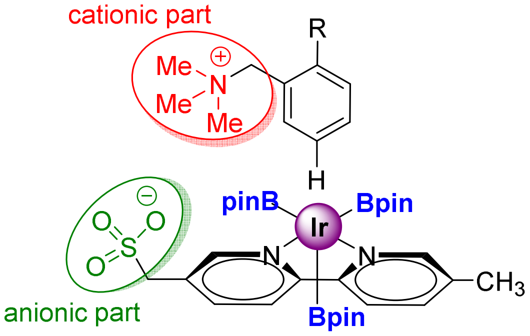
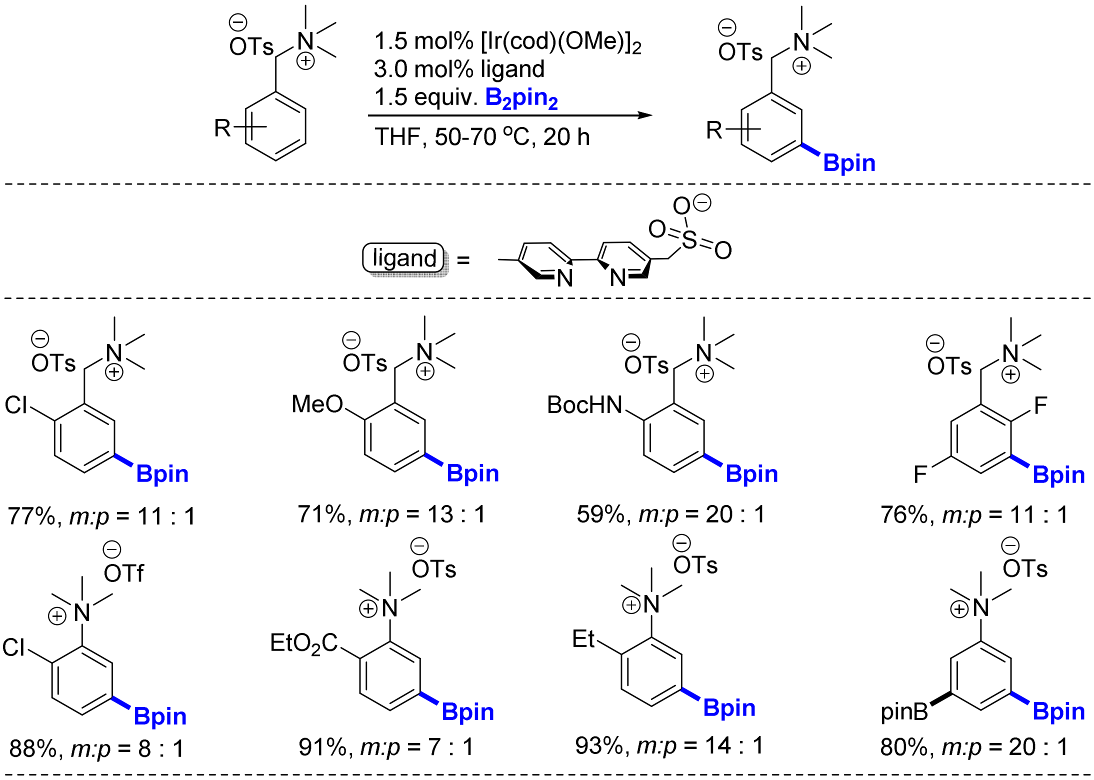


Fig 1.11. Proposed transition state for regioselective *meta*-borylation



Scheme 1.43 Ion-pair directed *meta*-borylation of aromatic quarternary ammonium salts

The same group[64] have shown that single anionic sulphonate bearing ligand engages in H-bonding interaction with the amides derived from benzylamines, phenethylamines and phenylpropylamines allowing *meta*-selective borylation (**Fig 1.12**). Control experiments are in full agreement with the proposed H-bonding interaction. The scope of substrates is broad as electron withdrawing groups like ester, trifluoromethyl, electron donating group, halides all afforded *meta*-selective products in good to high yield. *Meta* diborylated products are obtained with unsubstituted arenes and even increasing chain length upto 3 carbons lead to *meta*-selective products in good yields, in addition to this pyridine derived amides also underwent borylation smoothly (**Scheme 1.44**).

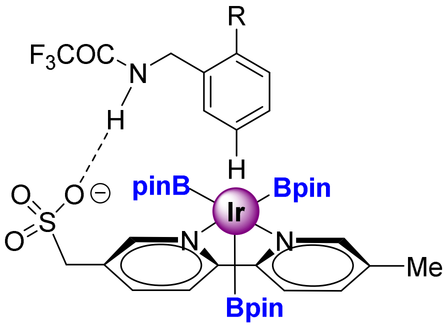
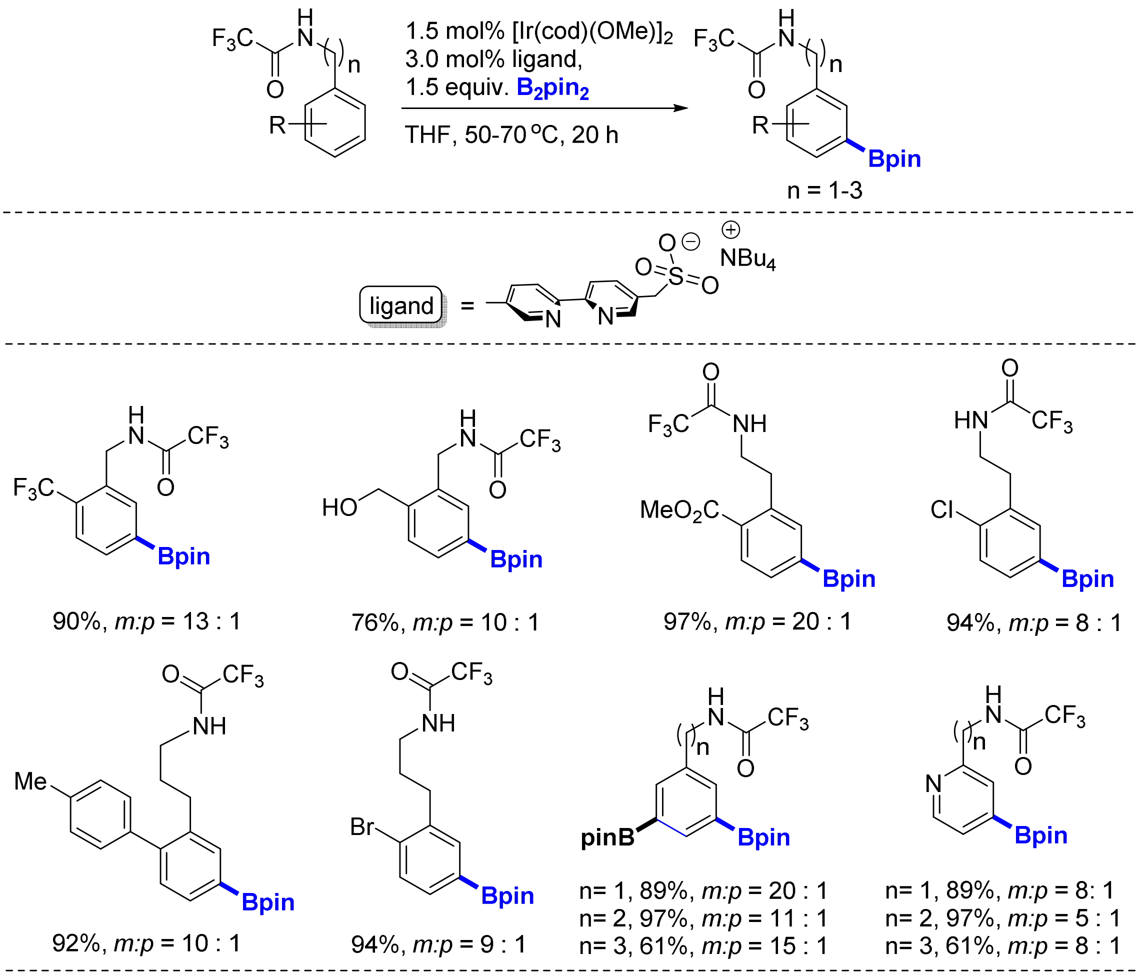


Fig 1.12. Proposed transition state for regioselective *meta*-borylation



Scheme 1.44. *Meta*-selective C-H borylation of benzylamine-, phenethylamine-, and phenylpropylamine-derived amides

The same group has demonstrated the viability of ion-pairing approach even in flexible quarternized phenethylamine and phenylpropylamine substrate with single anionic sulphonate bearing tether onto bipyridine ring realizing *meta*-borylation of three different classes of substrate. The proposed transition state is represented in **Fig 1.13**.[65] In contrast to their previous approaches electron donating groups bearing quarternized phenethylamine and phenylpropylamine didn’t underwent reaction, electron withdrawing groups, halides and an aromatic substituents led to *meta*-selective products (**Scheme 1.45**). Remoteness of ammonium ion from aryl ring weakens its –I effect that’s why electron donating groups are not compatible under reaction conditions as the ring did not get sufficiently activated.

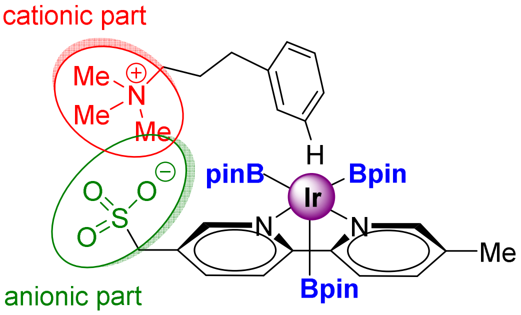
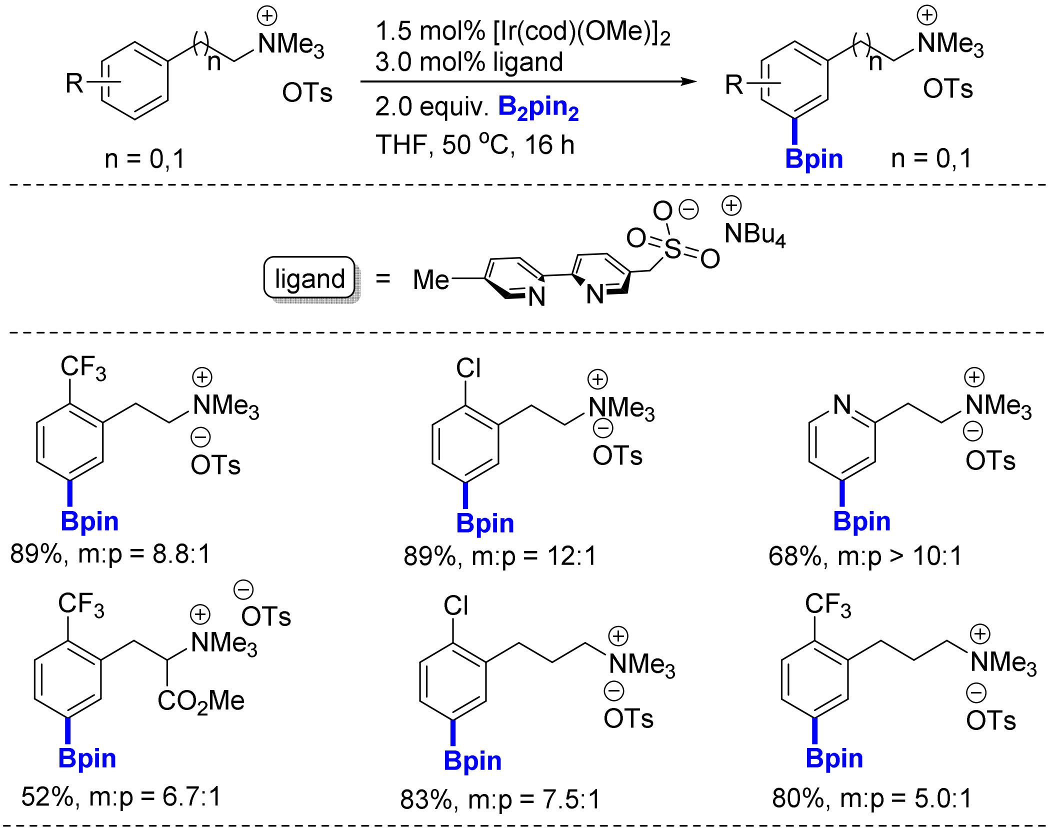


Fig 1.13. Proposed transition state for regioselective *meta*-borylation

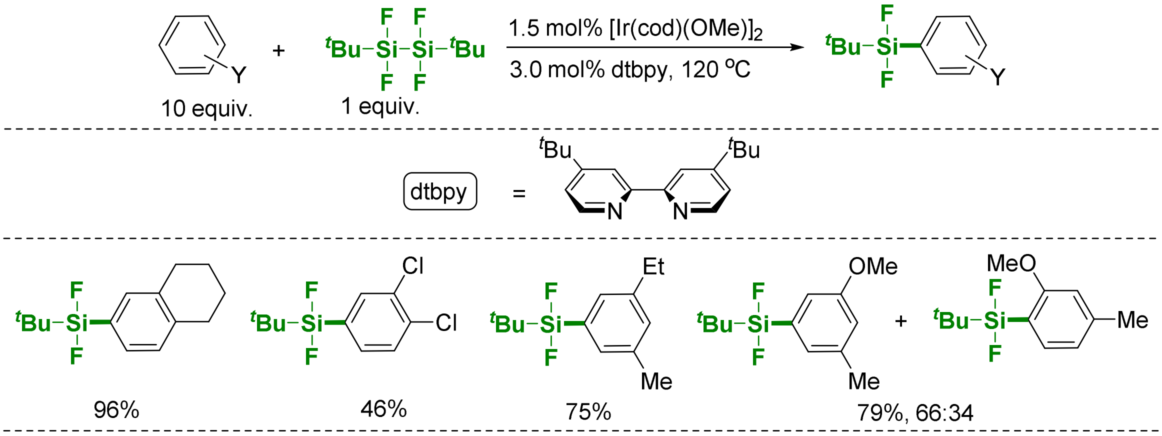


Scheme 1.45. *Meta*-selective borylation of quaternized phenethylamines and phenylpropylamines

C-H Silylation

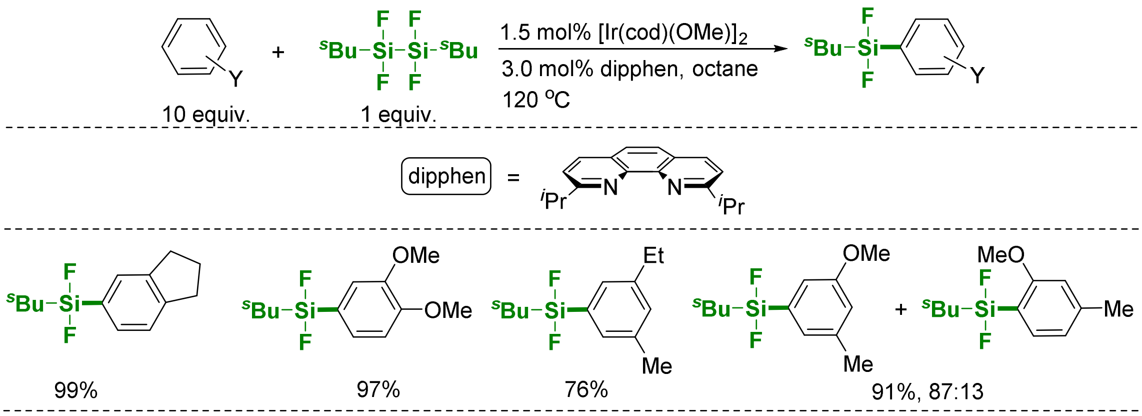
The inceptive report on C-H silylation surfaced in 1982 by Curtis[66] and co-workers who performed C-H silylation of benzene which gave phenylsiloxanes along with other redistribution products, although nonselective but it laid foundation for transition metal catalyzed C-H silylation reaction.

Twenty years later Ishiyama, Miyaura and others have achieved the first direct synthesis of arylhalosilanes[67] from arenes using $[Ir(cod)(OMe)]_2$, dtbpy and 1,2-di-*tert*-butyl-1,1,2,2-tetrafluorodisilane ($^tBuF_2Si_2$) represented in **Scheme 1.46**, previously other metals such as Pt, Rh, Ru were employed for direct C-H activation and silylation. Limited substrate scope, low regioselectivity for functionalized arenes and impractical ratio of arene to silane (60:1) were the major limitations of this work.



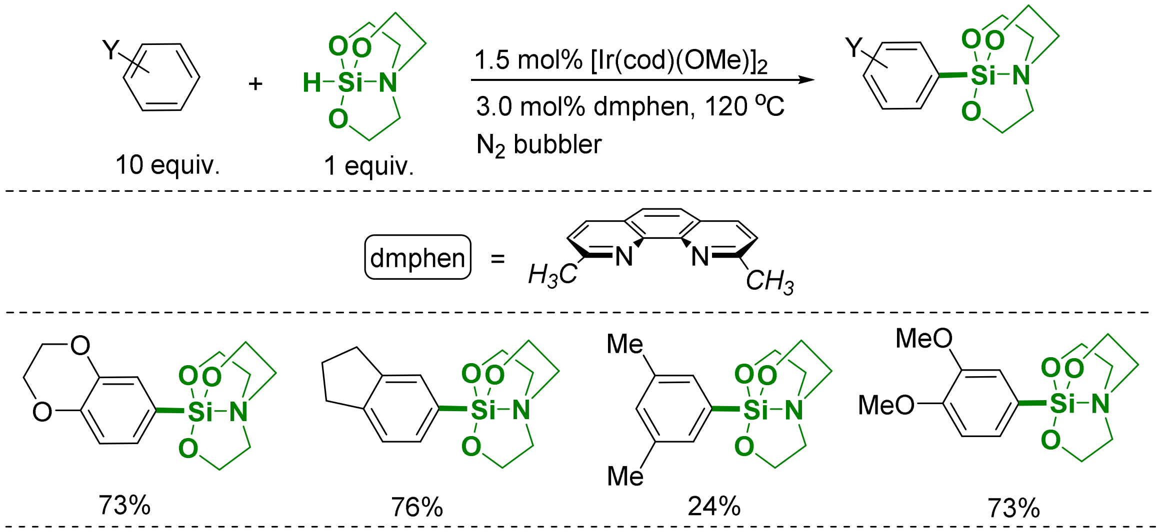
Scheme 1.46. Synthesis of aryl halosilanes by ($^tBuF_2Si)_2$

Later the same group improved their previously developed protocol where 2,9-diisopropyl1,10-phenanthroline (dipphen) was used as a ligand and 1,2-di-sec-butyl1,1,2,2-tetrafluorodisilane[68] (s-$BuF_2Si)_2$ as a silylation reagent as depicted in **Scheme 1.47**. The amount of arene (60 equiv.) has been reduced to 10 equiv. but from disilane only one silyl group gets incorporated into the product as prolonged reaction time doesnot lead to increase in yield of the reaction.



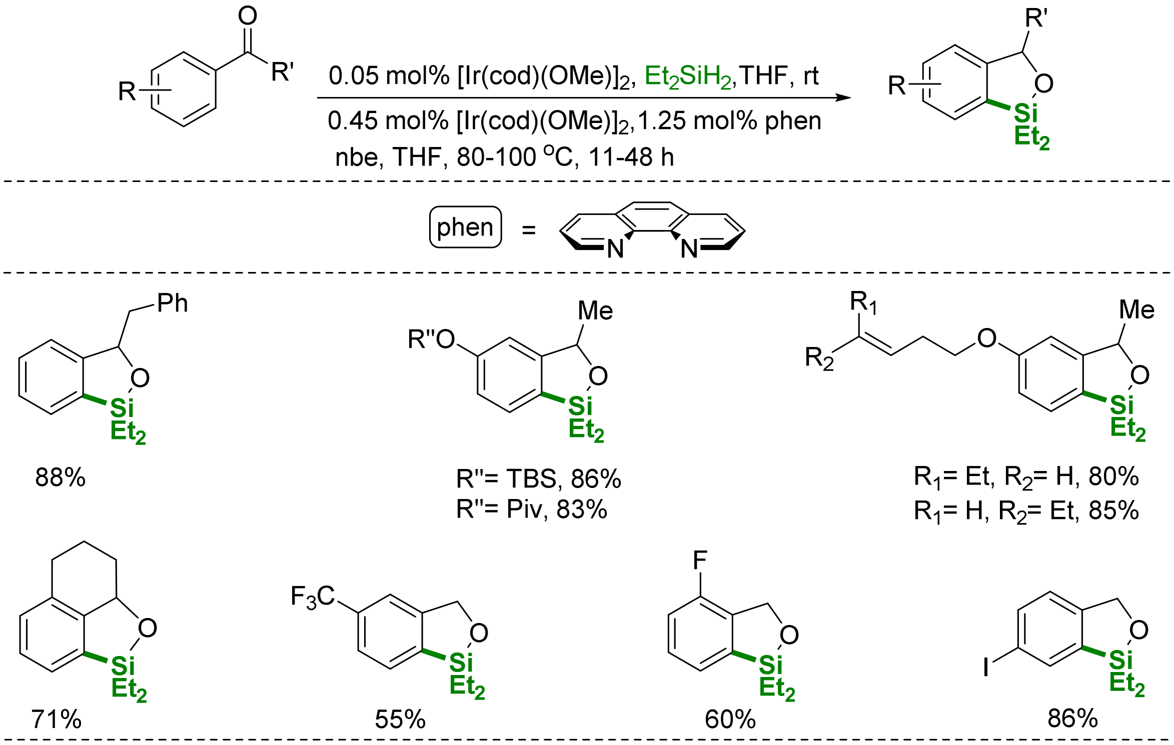
Scheme 1.47. Aromatic C-H silylation of arenes with (^{s}BuF$_2$Si)$_2$

To avoid the multistep synthesis of fluorodisilanes and resolve the introduction of only one silyl group from disilanes into the arylsilylated product and to increase the economic efficiency of reaction, Ishiyama et al devised a strategy for the synthesis of arylsilatranes[69] utilising 1-hydrosilatrane as silylating agent which can be easily synthesized in one step by treatment of triethoxysilane with boratrane which are easily commercially available as illustrated in **Scheme 1.48**.



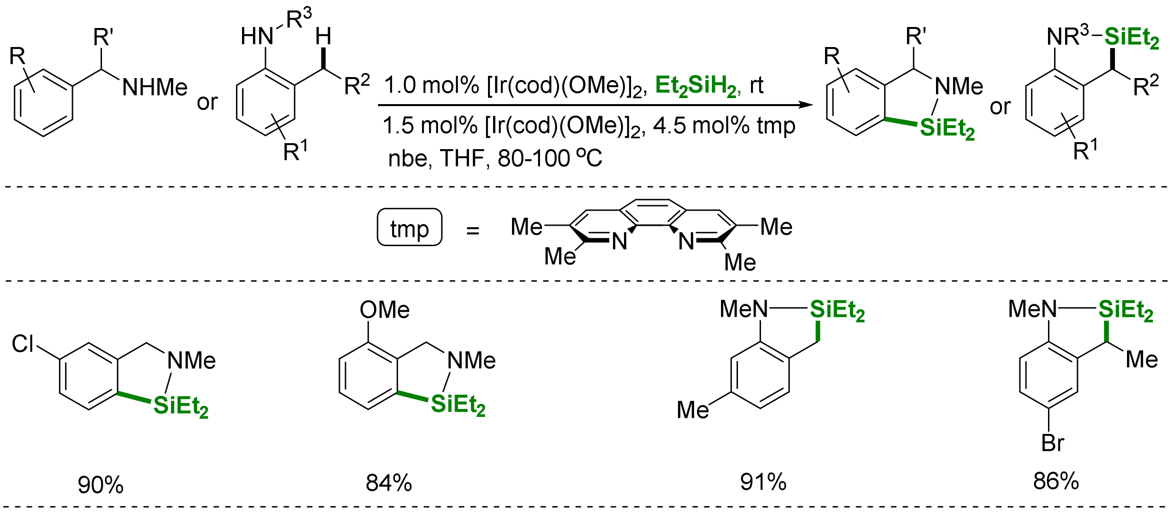
Scheme 1.48. Aromatic C–H silylation of arenes with 1-hydrosilatrane

Applying their strategy of silyl directed C-H borylation[70] to C-H silylation, Hartwig et al[71] developed a 2 step process where first hydrosilylation of ketone or dehydrogenative silylation of alcohol generated free Si-H bond in arene followed by dehydrogenative silylation of aryl C-H bonds through the formation of six membered iridacycle. They have designed their strategy so as to subjugate the limitations existing at that time such as difficulty in the removal of installed directing groups and formation of mono and bis-silylated products, their strategy utilizes hydroxy group as a directing group after the formation of dihydrosilyl ether and as the reaction is intramolecular, no possibility of bis-silylation as represented in **Scheme 1.49**.



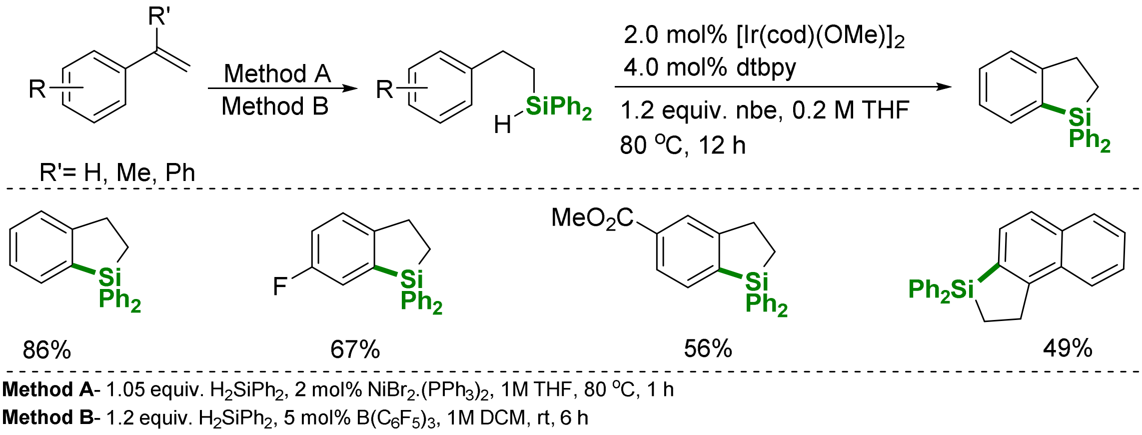
Scheme 1.49. (Hydrido)silyl-directed *ortho*-silylation of arenes

In addition to this, they developed a methodology where a secondary amine[72] directing group accomplishes *ortho* C-H silylation of benzmethylamine and N-alkyl anilines through the formation of diethyl hydrido silyl amines (**Scheme 1.50**).



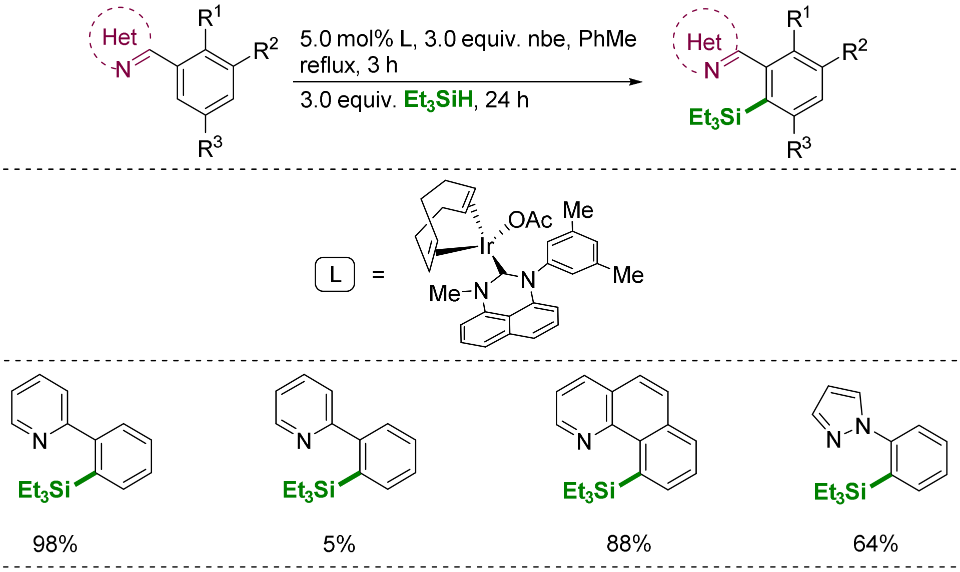
Scheme 1.50. Secondary amine directed silylation of aromatic and benzylic C-H bonds

Later a one pot synthesis of dihydrobenzosiloles was reported by Gevorgyan et al[73,74] through Ni-catalyzed hydrosilylation of styrenes with diphenylsilane, subsequently Ir-catalyzed dehydrogenative cyclization leading to dihydrobenzosiloles summarized in **Scheme 1.51**. The developed protocol shows good functional group tolerance and dihydrobenzosiloles can be transformed to benzosiloles and 2-hydroxyphenethylalcohols. They then extended this strategy for the silylation of heteroarenes.



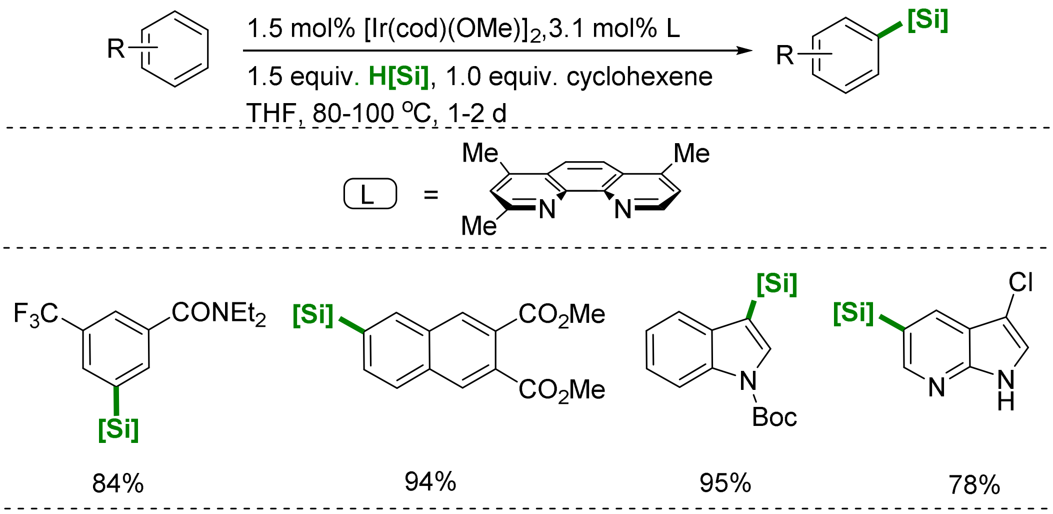
Scheme 1.51. Hydrosilylation and dehydrocyclization reaction for synthesis of dihydrobenzosiloles from styrenes

Mashima et al have achieved an Ir carbene-catalyzed[75] silylation of pyridyl and iminyl substrates, this is the first example where during catalytic cycle carbanion site (N-xylyl ring of perimidine based carbene ligand) acts as labile coordination site of hemilabile ligation via cyclometalation /demetalation reaction as shown in **Scheme 1.52**. This work provided a detailed mechanistic insight on the C-H silylation reaction.



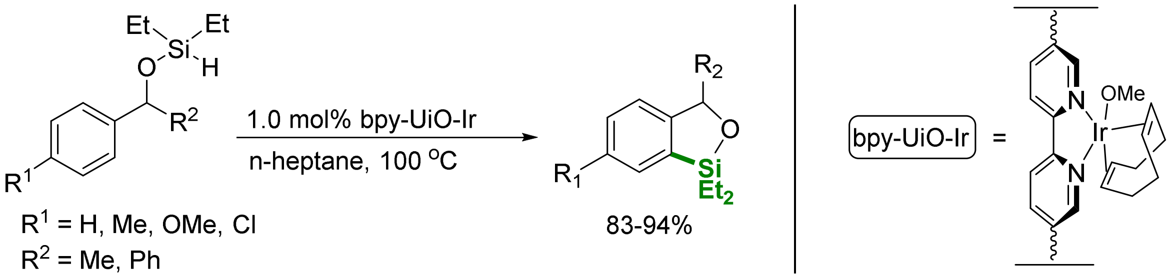
Scheme 1.52. Pyridyl and Iminyl directed dehydrogenative ortho-C-H silylation of arenes

Hartwig and Cheng[76] have demonstrated the first undirected, intermolecular Rh-catalyzed silylation of aryl C-H bonds under mild conditions with arene as limiting reagent. To circumvent limitations encountered in their present approach like moderate functional group tolerance as heavy halides and basic N atom of nitriles and heteroarenes chelates with catalyst, leading to poisoning and employed chiral phosphine ligand is expensive which affects the utility of reaction on large scale, they developed economically efficient and high functional group compatible approach as depicted in **Scheme 1.53**. Suitably substituted phenanthroline ligand (2,4,7 trimethylphenanthroline) and $[Ir(cod)(OMe)]_2$ catalyst overcame the shortcomings in Rh-catalyzed approach. Its utility is showcased by the reaction of series of active pharmaceutical reagents.



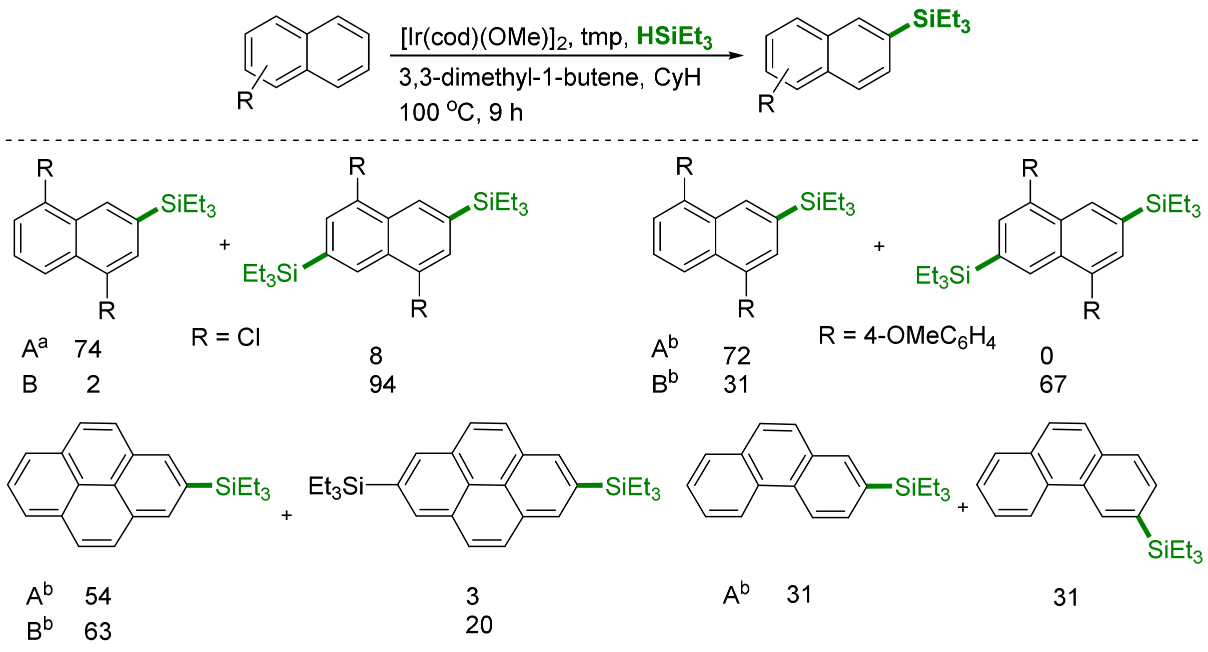
Scheme 1.53. Silylation of aryl and heteroaryl C-H bonds

Metal–organic frameworks (MOFs) are a new class of porous molecular materials that acts as a single-site solid catalysts and stabilize catalytic species that could undergo deactivation in solution. Lin et al[77] have designed a stable and recyclable single-site solid catalysts. The iridium containing 2,2’- bipyridyl-derived metal-organic framework (MOF) has a UiO structure. The designed MOF not only carries out aromatic C-H borylation but also *ortho*-silylation of benzylicsilyl ethers and activity is at least 3 orders of magnitude to homogenous counterparts as shown in **Scheme 1.54**.



Scheme 1.54. *Ortho*-silylation of benzylicsilyl ethers catalyzed by bipy-UiO-Ir

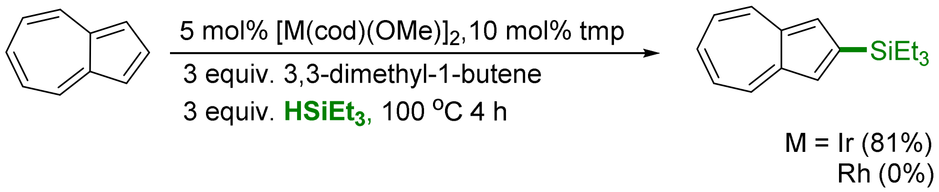
Takai and their co-workers[78] have disclosed a method for C-H silylation of polycyclic hydrocarbons in which regioselectivity is governed by steric factors and is contrast to the site selectivity observed in electrophilic functionalizations. The reaction is favoured by more electron deficient hydrocarbons. Selective synthesis of mono- and bis-silylated arenes has been achieved by applying two sets of conditions, by changing ratio of arene/silane. The results are depicted in **Scheme 1.55**.



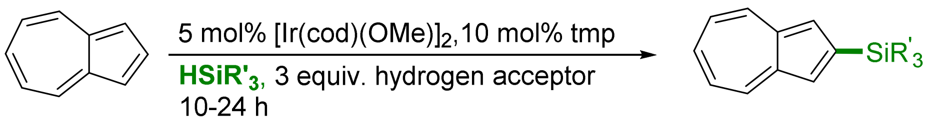
^{a}Reaction time 4 h, ^{b}Dioxane as solvent, **Method A**- arene/silane = 2:1, 2.5 mol% $[Ir(cod)(OMe)]_2$,5 mol% tmp, 2.0 equiv. 3,3-dimethyl-1-butene, **Method B**- arene/silane = 1:3, 5.0 mol% $[Ir(cod)(OMe)]_2$,10 mol% tmp, 3.0 equiv. 3,3-dimethyl-1-butene

Scheme 1.55. Dehydrogenative silylation of polycyclic aromatic hydrocarbons

Azulenes show unique photophysical and redox properties owing to the unusual dipolar and electron polarization. Simple and efficient methods for their skeleton modification are desirable. Previous methods[79] for C-H functionalization of azulenes yields regioisomeric mixture. Takai et al have devised a strategy for the regioselective dehydrogenative silylation of azulenes at 2-position[80] without requirement of any directing group. Scope of the silane was limited to monohydrosilanes, dihydrosilanes Et_2SiH_2, Ph_2SiH_2, and $PhMeSiH_2$, were not suitable. Steric factors predominate site selectivity leading to functionalization at sterically least hindered position as shown in **Scheme 1.56** and **1.57**.



Scheme 1.56. Dehydrogenative silylation of azulene

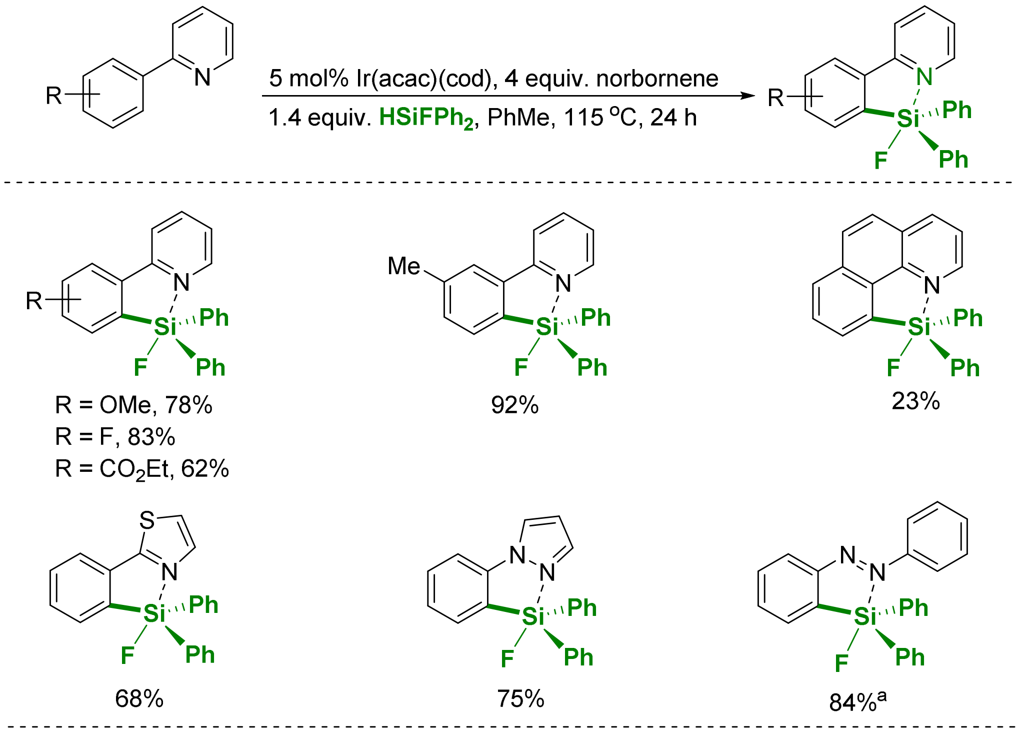


#	Method[a]	Temp (°C)	SiR'$_3$	Yield (%)
1	A	125	SiMe$_2$Ph	67
2	A	125	SiMe$_2$(4-MeOC$_6$H$_4$)	66
3	A	125	SiMe$_2$(4-CF$_3$C$_6$H$_4$)	61
4	B	100	SiMe$_2$Bn	79

Method A: Norbornene (hydrogen acceptor) and octane as solvent.
Method B: 3,3'Dimethyl-1-butene (hydrogen acceptor) and CyH as solvent.

Scheme 1.57. Dehydrogenative silylation of azulene with different silanes

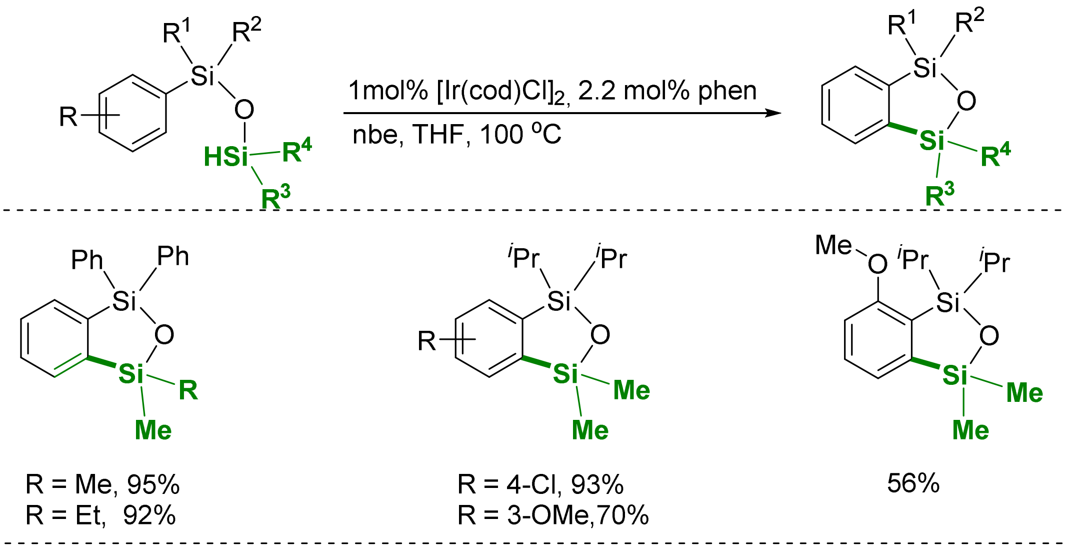
Kuninobu, Kanai and Wakaki have demonstrated *ortho* C-H silylation of aromatic compounds such as as 2-phenylpyridines, benzo[h]-quinoline, pyridylferrocene, 2-phenylpyrimidine, 2-phenylpyrazine, 1-phenyl-1H-pyrazole, 2-phenylthiazole, 2-phenylimidazole, and azobenzene[81] towards the synthesis of π-conjugated molecules controlled by Lewis acid-base interaction between Lewis acidic silicon atom of fluorinated hydrosilanes and Lewis basic N-atom of substrate. Electronic properties of substituents on *para, meta* position of substrate does not affects the reaction outcome, similarly silylated product formation is unaltered by the electronic nature of substituents on fluorinated hydrosilanes summarized in **Scheme 1.58**. Chemical shifts of ^{29}Si NMR spectra, evidences Lewis acid–base interactions between the silicon and nitrogen atoms.



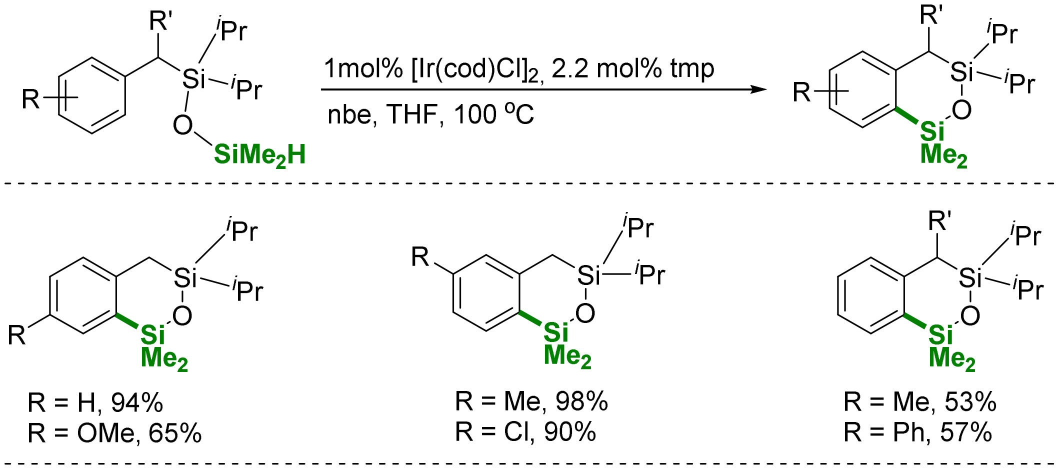
^{a}E/Z= 1:1

Scheme 1.58. ***Ortho*-selective C-H silylation of arenes through Lewis acid-base Interaction**

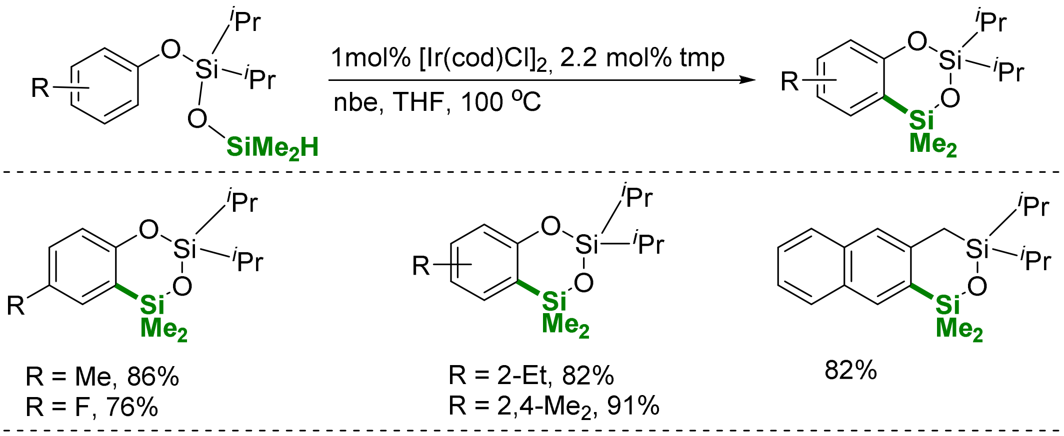
Xu et al[82] have developed a strategy for *ortho*-silylation of siloxane tethered aryl, benzyl and phenoxysilanols in which silanol acts as a directing group for the straightforward and efficient synthesis of unsymmetrical cyclic disiloxanes. Final disiloxanes containing unequal and modifiable multiple Si atom possess vast synthetic potential for further modification. In the intramolecular dehyrogenative silylation of arylsilanols, functional group compatibility is good as *meta* and *para* substituents delivered disiloxanes in excellent yield whereas *ortho* substituents lowered the yield. Two silicon atom show different effect on cyclization on changing substituent attached to them as on increasing the size of substituents on silicon atom of hydrosilyl and decreasing the size of substituents on silicon atom of silanol has detrimental effect on product yield. By changing ligand from phenanthroline to tetramethylphenanthroline they have achieved cyclization in other cyclic variants such as benzyl and phenoxysilanols. The results are illustrated in **Schemes 1.59**, **1.60** and **1.61**.



Scheme 1.59. Intramolecular C-H silylation with arylsilanols



Scheme 1.60. Intramolecular C-H silylation with benzylsilanols



Scheme 1.61. Intramolecular C-H silylation with phenoxysilanols

Conclusion:

Undoubtedly C-H borylation has expanded the horizon of transition metal-catalyzed C-H functionalization. The introductory part of iridium-catalyzed C-H borylation describes these advancements concisely. Numerous examples of proximal and *ortho*-borylation are present but only few examples of remote C-H borylation are there, which need to be explored more by engineering suitable catalyst-ligand-substrate assembly. Some promising examples of *meta*-selective functionalization by other metals[83] have been developed, but are not discussed here.

Recent years have witnessed the seminal advances made in this field as discussed in this introduction. However for further development of C-H silylation methodology, more reactive catalyst systems should be developed as the silylation of C–H bonds proceeds with slow rates and high temperatures and high catalyst loadings. Directing group assisted as well as undirected C-H silylation activates and functionalizes the proximal C-H bond and sterically least hindered C-H bond respectively. Pertinent designing of ligand system needs to be done to access the distal C-H bonds to achieve remote C-H silylation of arenes.

References:

1. Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 48.
2. Kalyani, D.; Sanford, M. S. *Top. Organomet. Chem.* **2007**, *24*, 85.
3. Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437.
4. Activation and Functionalization of C-H Bonds; Goldberg, K. I.,Goldman, A. S., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 2004; Vol. 885.
5. Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544.
6. Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843.
7. Murai, S.; Kakiuchi, F .; Sekine, S.;Tanaka, Y.; Kamatani, A.; Sonoda, M. ; Chatani, N. *Nature* **1993**, *366*, 529.
8. Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.
9. David, L. ; Keith, F. *Chem. Lett.* **2010**, *39*, 1118.
10. Gilman, H.; Young, R. V. *J. Am. Chem. Soc.* **1934**, *56*, 1415.
11. Wittig, G.; Fuhrmann, G., *Ber. Dtsch. Chem. Ges. B* **1940,** *73B*, 1197.
12. Snieckus, V., Directed *ortho* metalation. *Chemical Reviews* **1990,** *90*, 879.
13. I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890.
14. Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III *J Org Chem*. **2015**, *80*, 8341.
15. Srinivasan, R.; Coyne, A.G.; Abell, C. *Chem. Eur. J.* **2014**, *20*, 11680.
16. Chu, L.; Qing, F. L. *Org. Lett*., **2010**, 12, 21.
17. Konig, W.; Scharrnbeck, W. *Journal Fur Praktische Chemie-Leipzig* **1930**, *128*, 153.
18. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
19. Zhang, L.; Jiao, L. *J. Am. Chem. Soc.*, **2017**, *139*, 607.
20. Lickiss, P. D. *Adv. Inorg. Chem*. **1995**, *42*, 147.
21. Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221.
22. Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843.
23. Manoso, A. S.; DeShong, P. *J. Org. Chem*. **2001**, *66*, 7449.
24. Denmark, S. E.; Smith, R. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc*. **2009**, *131*, 3104.
25. Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 15958.
26. Murata, M.; Fukuyama, N.; Wada, J.-i.; Watanabe, S.; Masuda, Y. *Chem. Lett.* **2007**, *36*, 910.
27. Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600.
28. Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853.
29. Cox, P. A. The Elements: Their Origin, Abundance, and Distribution; Oxford Science Publications: Oxford, 1989.
30. Rablen, P. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4648.
31. Sakaki, S.; Kikuno, T. *Inorg. Chem.* **1997**, *36*, 226.
32. Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329.
33. Waltz, K. M.; He, X.; Muhoro, C.; Hartwig, J. F. *J. Am. Chem. Soc.***1995**, *117*, 11357.
34. Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696.
35. Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305..

36. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.

37. Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem.,Int. Ed.* **2002**, *41*, 3056.

38. Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc*. **2005**, *127*, 4263.

39. Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**,*47*, 3004.

40. Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem.Soc.* **2009**, *131*, 6946.

41. Hodgson, H. H.; Wignall, J. S. *J. Chem. Soc.* **1926**, 2077.

42. Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. S. *J. Am. Chem. Soc.*, **2015**, *137*, 10160.

43. Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534.

44. T. Ishiyama, H. Isou, T. Kikuchi and N. Miyaura, *Chem.Commun*., **2010**, *46*, 159.

45. I. Sasaki, H. Doi, T. Hashimoto, T. Kikuchi, H. Ito ;T. Ishiyama, *Chem. Commun*., **2013**, *49*, 7546.

46. Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.

47. Ros, A.; Estepa, B.; Lopez-Rodríguez, R.; Alvarez, E.; Ferna´ ndez, R.;´ Lassaletta, J. M. *Angew. Chem., Int. Ed*. **2011**, *50*, 11724.

48. Ros, A.; Lopez-Rodrıguez, R.; Estepa, B.; Alvarez, E.; Ferna´ndez, R.; Lassaletta, J. M. *J. Am. Chem. Soc*., **2012**, *134*, 4573.

49. Roering, A. J.; Hale, L. V. A.; Squier, P. A.; Ringgold, M. A.; Wiederspan, E. R.; Clark, T. B. *Org. Lett*., **2012**, *42*, 3558.

50. Ghaffari,B.; Preshlock,S.M.; Plattner, D.L.; Staples, R.J.; Maligres, P.E.; Krska, S.W.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc*. **2014**, *136*, 14345.

51. Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2016**, *138*, 84.

52. Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. J. Am. Chem. Soc. 2017, 139, 7745.

53. Breslow, R.; Zhang, X.; Huang, Y. J. Am. Chem. Soc. 1997, 119, 4535.

54. Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. Chem. Rev. 2015, 115, 3012.

55. Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E.; Smith, M. R., III *J. Am. Chem. Soc*. **2012**, *134*, 11350.

56. Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R., III *Angew. Chem., Int. Ed*. **2013**, *52*, 12915.

57. Smith, M. R.; Bisht, R.; Haldar, C.; Pandey, G.; Dannatt, J. E.; Ghaffari, B.; Maleczka, R. E.; Chattopadhyay, B. *ACS Catalysis* **2018**, *8,* 6216.

58. Li, H. L.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed*. **2017**, *56*, 1495.

59. Li, H. L.; Kanai, M.; Kuninobu, Y. *Org. Lett.* **2017**, *19*, 5944..

60. Chattopadhyay, B.; Dannatt, J. E.; Sanctis, I. L. A.-de.; Gore, K. A.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R. *J. Am. Chem. Soc.* **2017**, *139*, 7864.

61. Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem*. **2015**, *7*, 712.

62. Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc*. **2016**, *138*, 84.

63. Davis, H. J.; Mihai, M. T.; Phipps, R. J. *J. Am. Chem. Soc.* **2016**, *138*, 12759.

64. Davis, H. J.; Genow, G. R.; Phipps, R. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 13351.

65. Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J. *ACS Catal*. **2018**, *8*, 3764.

66. Gustavson, W. A.; Epstein, P. S.; Curtis, M. D. *Organometallics* **1982**, *1*, 884.

67. Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346.

68. Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068.

69. Ishiyama, T.; Saiki, T.; Kishida, E.; Sasaki, I.; Ito, H.; Miyaura, N. *Org. Biomol. Chem.* **2013**, *11*, 8162.

70. Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 7534.

71. Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092.

72. Li, Q.; Driess, M.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2014**, *53*, 8471.

73. Kuznetsov, A.; Gevorgyan, V. *Org. Lett*. **2012**, *14*, 914.

74. Kuznetsov, A.; Onishi, Y.; Inamoto, Y.; Gevorgyan, V. *Org. Lett*. **2013**, *15*, 2498.

75. Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149.

76. Cheng, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 592.

77. Manna K, Zhang T, Lin W. *J Am Chem Soc*, **2014**, *136*, 6566.

78. Murai, M.; Takami, K.; Takai, K. *Chem. Eur. J*. **2015**, *21*, 4566.

79. (a) Kurotobi, K.; Miyauchi, M.; Takakura, K.; Murafuji, T.; Sugihara, Y. *Eur. J. Org. Chem*. **2003**, 3663. (b) Fujinaga, M.; Murafuji, T.; Kurotobi, K.; Sugihara, Y. *Tetrahedron* **2009**, *65*, 7115. (c) Zhao, L.; Bruneau, C.; Doucet, H. *Chem. Commun*. **2013**, *49*, 5598. (d) Dyker, G.; Borowski, S.; Heiermann, J.; Ko□ rning, J.; Opwis, K.; Henkel, G.; Ko□ckerling, M. *J. Organomet. Chem.* **2000**, *606*, 108.

80. Murai, M.; Takami, K.; Takeshima, H.; Takai, K. *Org Lett*. 2015, *17*, 1798.

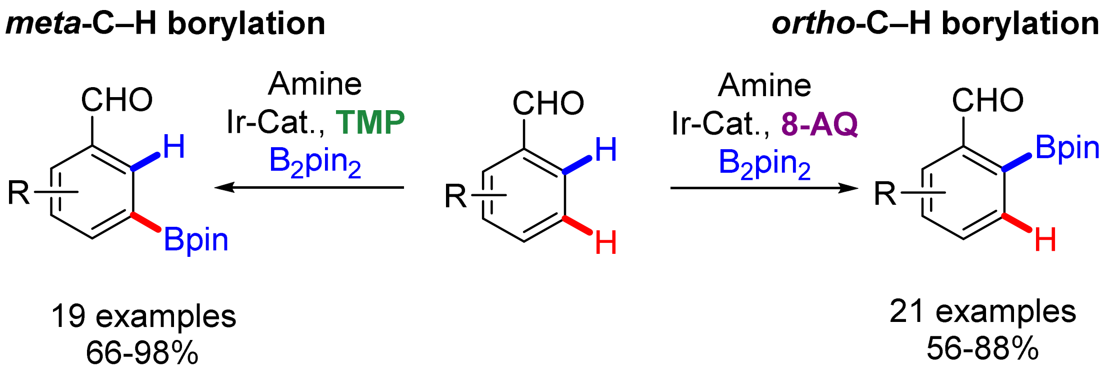
81. Wakaki, T.; Kanai, M.; Kuninobu, Y. *Org. Lett.* **2015**, *17*, 1758.

82. Lin, Y.; Jiang, K-Z.; Cao, J.; Zheng, Z-J.; Xu, Z.; Cui, Y-M.; Xu, L-W. *Adv.Synth.Catal.* **2017**, *359*, 2247.

83.(a) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E., *Angew. Chem., Int. Ed*. **2006,** *45*, 3775. (b) Obligacion, J. V.; Semproni, S. P.; Chirik, P. J., *J. Am. Chem. Soc.* **2014,** *136*, 4133. (c) Fan, Z.; Ni, J.; Zhang, A., *J. Am. Chem. Soc.* **2016,** *138*, 8470. (d) Zhou, Y.; Zhao, J.; Liu, L., *Angew. Chem., Int. Ed*. **2009,** *48*, 7126. (e) Dey, A.; Agasti, S.; Maiti, D., *Organic & Biomolecular Chemistry* **2016,** *14*, 5440.

Chapter 2

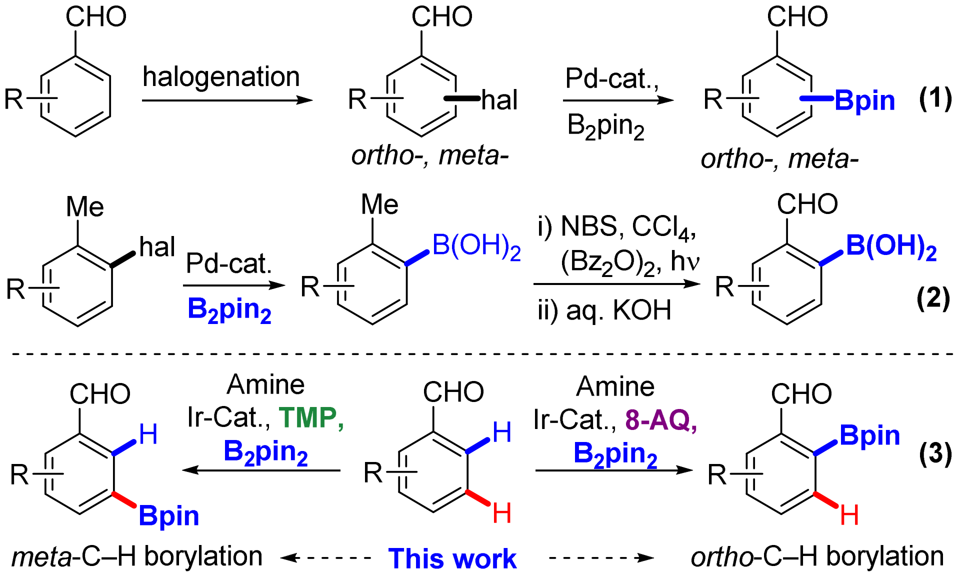
Formal Ir-catalyzed ligand-enabled ortho- and meta-borylation of aromatic aldehydes via in situ generated imines



Objective: To investigate the role played by nature of ligand in determination of regioselectivity of C-H borylation of benzaldehydes.

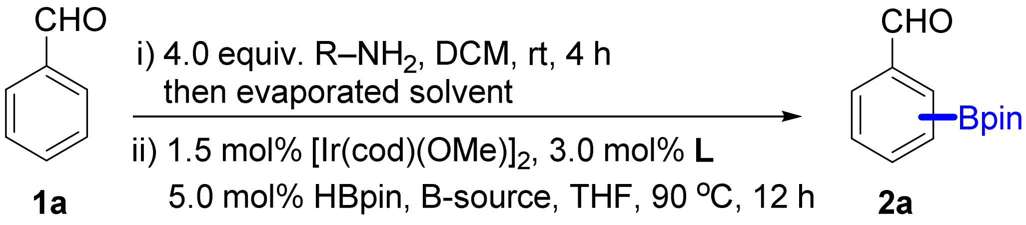
Discussion:

Over the past decade, C–H bond functionalizations have emerged as competent and ideal reactions.[1] Among various protocols, the C–H bond borylation has shown its utility attributed to the synthetic versatility for which B–C bonds are well-known. Control over regioselectivity is a major challenge in C–H borylations. Generally, steric effects are the governing factor for regioselectivity of aromatics,[2] and it is thus a complementary methodology over widely used directed *ortho* metalations (*DoMs*).[3] However, the inherent functional group incompatibility and harsh reaction condition employed in *DoMs*, (for example, groups like esters are incompatible with *DoM* and require low temperature) have deepened the requisite to develop efficient method for *ortho* C–H borylations. Few methods for the functional group[4] directed *ortho* borylations[5] have been developed.

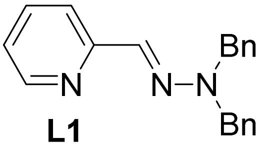


On the contrary, *meta*-selective C–H bond borylation of arenes is a challenging task. Literature precedents states that only one type of *meta* C–H borylation of 1,3-disubstituted arenes is developed by Smith-Maleczka[6] and Hartwig[7]. Sterics was the governing factor for the regiochemistry of this *meta* borylation.[8] Although synthetically beneficial, this sterically controlled *meta* borylation, its applicability is mostly limited to 1,3-disubstituted arenes. In addition to this, the arenes with reactive functional groups such as aldehydes, ketones etc. are not well compatible.[9] It deserves mentioning that, when this manuscript was in preparation, a communication ellucidating an innovative concept of a *meta*-selective C–H borylation by a secondary interaction between ligand and substrate was published.[10] Undoubtedly, this method is one of the most efficacious strategy for *meta* borylation. Thus, it is a great challenge to develop catalytic processes for the selective *ortho* and *meta* borylation of benzaldehydes. Conventionally, *ortho* and *meta* borylated benzaldehydes were synthesized via a Miyaura cross-coupling reaction with bis(pinacolato)diborane subsequent to the halogenation of benzaldehydes (**eq. 1 & eq. 2**).[11,12] Herein, a ligand enabled one-pot unified strategy for the *ortho*- and *meta*-selective C–H borylation of benzaldehydes using iridium-catalyzed C–H activation is reported (**eq. 3**).

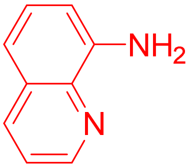
Table 2.1. Evaluation and optimization of reaction conditions[a]



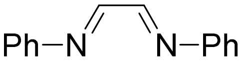
#	R	L	B-source	Ratio(*o*/*m*/*p*)[b]	Yield
1	Me	L1	B_2pin_2 (0.7 eq.)	-	0
2	^{i}Pr	L1	B_2pin_2 (0.7 eq.)	-	0
3	^{t}Bu	L1	B_2pin_2 (1.5 eq.)	33/37/30	53
4	^{t}Bu	L1	B_2pin_2 (0.7 eq.)	86/8/6	57[c]
5	^{t}Bu	8-AQ	HBpin (1.5 eq.)	-	0
6	**^{t}Bu**	**8-AQ**	**B_2pin_2 (0.7 eq.)**	**100/0/0**	**87**[d]
7	Me	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	7
8	^{t}Bu	L2	B_2pin_2 (0.7 eq.)	100/0/0	66[e]
9	^{t}Bu	L3	B_2pin_2 (0.7 eq.)	95/3/2	72[f]
10	^{t}Bu	L4	B_2pin_2 (0.7 eq.)	97/2/1	62[g]



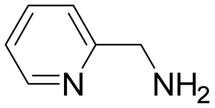
L1



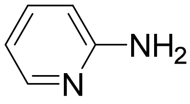
8-AQ



L2



L3



L4

Reactions were run with 1.0 mmol substrate, yields are for isolated *ortho*-isomer after column chromatography. [b]Ratios are calculated by GC-FID analysis from crude reaction mixture; in GC/MS no imine borylated products were found, only aldehyde borylated products were observed. [c]mono/*o*,*o*-di = 90/10. [d]mono/*o*,*o*-di = 89/11. [e]mono/*o*,*o*-di = 80/20. [f]mono/*o*,*o*-di = 87/13. [g]mono/*o*,*o*-di = 85/15.

Fernández-Lassaletta[13] Sawamura,[14] and Ishiyama[15] devised a nitrogen-directed *ortho* borylation of 2-phenylpyridines and hydrazones recently. Keeping their findings in mind, we hypothesized that imines might acts as an easily removable directing groups[16] for *ortho* borylation of benzaldehydes. For this, benzaldehyde-derived imines were treated with B_2pin_2 under the standard borylation conditions using hydrazone-derived ligand (L1) designed[13a] by Fernández and Lassaletta (entry 1, **Table 2.1**). Initial screening revealed that no borylation was observed for methyl and isopropyl imines, but the *tert*-butyl imine gave good *ortho* selectivity (86%, entry 4).[17] During monitoring of crude reaction mixtures by GC/MS, the products appeared as aldehyde borylated products, the imine borylated products can be seen in the crude proton NMR (**Fig 2.1**). We assumed that in the GC/MS, the imine borylated products are hydrolyzed. Likewise, during silica gel column chromatography, the products are hydrolyzed. Appeasingly, the combination of *tert*-butylamine, 8-AQ and B_2pin_2 yielded 100% *ortho* selectivity with excellent isolated yield (87%, entry 6). Notably, using 8-AQ as ligand system methylamine resulted in 7% yield only (entry 7), presumably the less sterics of methylimine compared to the *tert*-butylimine is incapable to open a vacant coordination site to accomplish *ortho* borylation.[18] Results with other ligand systems such as L2, L3 and L4 which were less effective than 8-AQ ligand system are represented in **Table 2.1** (entries 8-10).

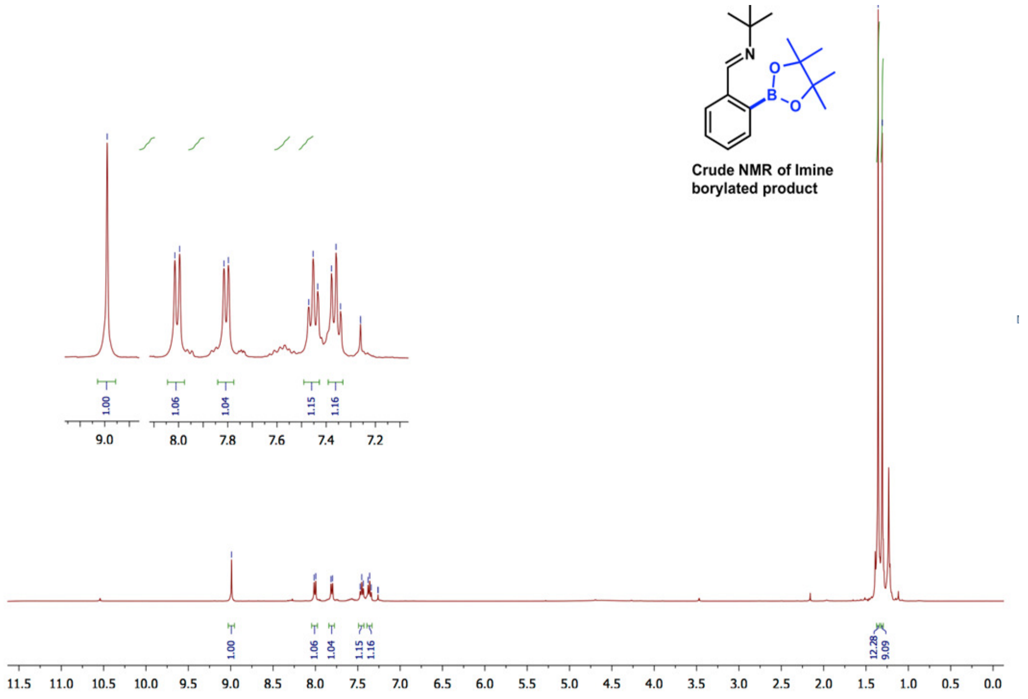
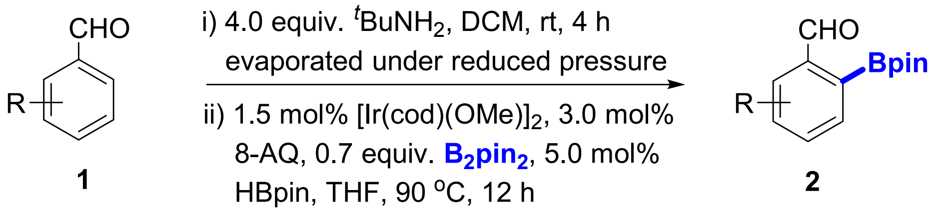


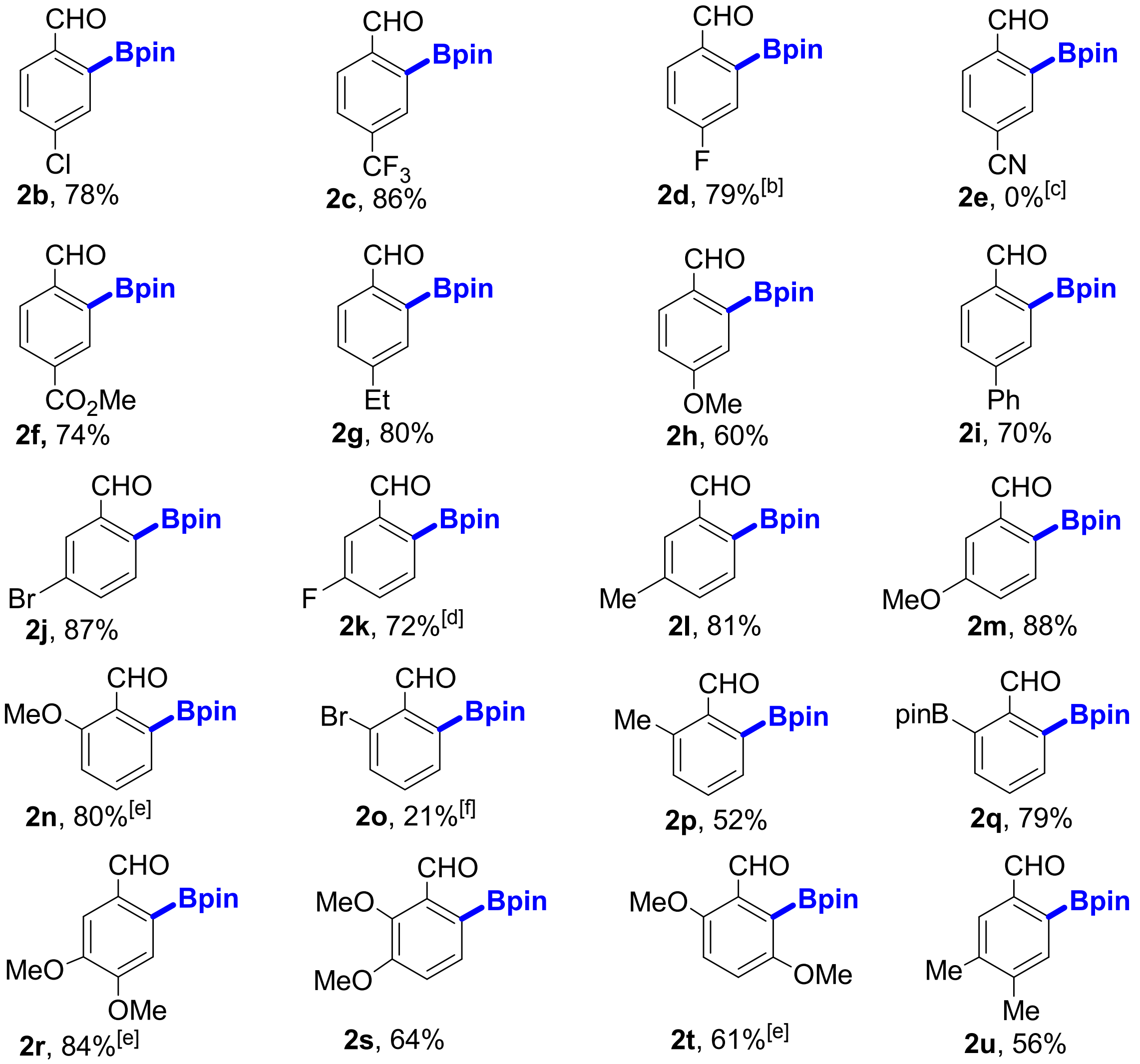
Fig 2.1. NMR spectra representing crude reaction mixture of imine-borylated material

With these optimized condition, borylations were performed for a range of aldehydes and the results are depicted in **Table 2.2**. Regardless of the substituent present in the aryl ring such as halogens (Cl, F, Br), alkyl groups (Me, Et, CF_3), phenyl, methoxy, benzaldehydes underwent C–H borylations smoothly affording the *ortho* directed products in good to excellent yields without any diborylations (entries 2b–2d & 2f-2i), except entry 2d (7% meta isomer). No C–H borylation was observed in case of 4-cyanobenzaldehyde (entry 2e).

Notably, for 4-phenylbenzaldehyde borylation, the Ph C–H bonds remain unchanged under borylation conditions yielding exclusively *ortho* directed product (entry 2i). Moreover, *meta*-substituted benzaldehydes (entries 2j-2m) reacted regioselectively at the sterically less hindered *ortho* C–H bond. In the case of 3-fluorobenzaldehyde, the most acidic proton flanked in between CHO and F being the most susceptible site for borylation, didn't undergo borylation exclusively (only 25% borylation) under the developed conditions (entry 2k), instead, *ortho* borylation occurred at the position which is less acidic compared to the another *ortho* proton. Notably, electronic nature of *ortho* substituents didn't impeded the reaction efficiency producing exclusively *ortho* borylated products (entries 2n, 2p & 2q). In case of 2-bromobenzaldehyde reaction didn't underwent smoothly (21% conversion, entry 2o). Furthermore, the developed protocol is electronically unbiased, wide range of differently substituted benzaldehydes are well tolerated under developed borylation conditions (entries 2r-2u).

Table 2.2. ***Ortho*-borylation of substituted benzaldehydes**[a]





2b, 78%

2c, 86%

2d, 79%[b]

2e, 0%[c]

2f, 74%

2g, 80%

2h, 60%

2i, 70%

2j, 87%

2k, 72%[d]

2l, 81%

2m, 88%

2n, 80%[e]

2o, 21%[f]

2p, 52%

2q, 79%

2r, 84%[e]

2s, 64%

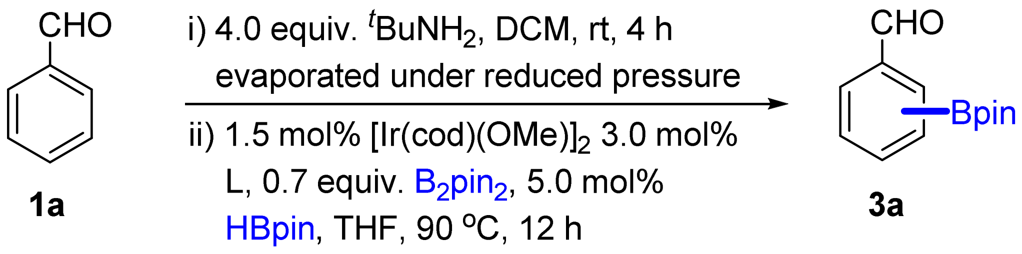
2t, 61%[e]

2u, 56%

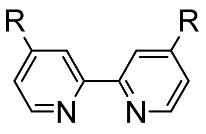
[a] Reactions were run with 1.0 mmol substrate, yields are for isolated aldehyde borylated products after column chromatography. [b] Ortho/meta = 93/07. [c] No reaction occurred even with ligand L1. [d] o,o' di = 75/25. [e] Reactions were conducted using L1 ligand. [f] 21% conversion, failed to isolate due to rapid protodeborylation.

Next, attention shifted towards the ligand screening for the *meta*-selective C–H activation/borylation. Benzaldehyde was chosen as our model system and borylation was performed with various electronically variable bipyridines **L5-L7**. Results in **Table 2.3** clearly indicates an increase in *meta* selectivity as the more electron rich bipyridine ligand is employed (entries 1-3). With these encouraging initial results, we then executed borylation using TMP ligand (**L8**). Gratifyingly, improved *meta* selectivity alongwith with excellent conversion (66% *meta*-borylated aldehyde product) was observed (entry 4). To probe out the reason for enhancement in selectivity, we proposed that there might be two governing factors, such as i) an electrostatic interaction,[19] arising after the encapsulation[20] of imine substrate into the cavity of iridium trisboryl complex attached with electron rich ligand and, and ii) the substrate showing the secondary interaction via either H-bonding[21] between the imine hydrogen atom and boryl oxygen atom of the catalyst (**Fig 2.2**, **TS-1**), or the imine N atom interacting with the boryl B atom of the catalyst (**TS-2**).

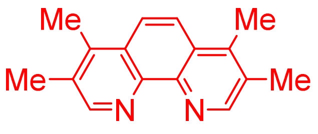
Table 2.3. Ligand screening for *meta*-borylation[a]



#	L	(*meta/para/ortho*)[b]	mono/di	Conv. (%)[c]
1	L5	11/61/28	89/11	63
2	L6	33/46/21	82/18	83
3	L7	47/37/16	88/12	88
4	**L8**	**66/23/11**	**97/03**	**93(67)**[d]



L5, R = CF_3
L6, R = H
L7, R = ^tBu



TMP (L8)

[a]Reactions were run with 1.0 mmol substrate. [b]GC ratios. [c]GC conversion was measured using dodecane as internal standard. [d]In parentheses isolated yield for aldehyde *meta*-borylated product.

In both cases (**TS-1** & **TS-2**) the electrostatic interaction is present which is enhancing the *meta*-selectivity, but the question still persists which **TS** (**TS-1** or **TS-2**) is actually governing the *meta*-selectivity? In case of (**TS-1**) the H-bond directed approach, the imine substituent (R) is not in the vicinity of reaction centre and thus, the size of the R group should not control the outcome of the *meta* borylation. On the contrary, in case of **TS-2**, due to the close proximity of the R group and the boryl group of the catalyst, the outcome should get affected by the size of the R group, i.e on altering the sterics of the imine substituent (R) from ^{t}Bu→^{i}Pr→Me, there should be an enhancement in *meta*-selectivity.

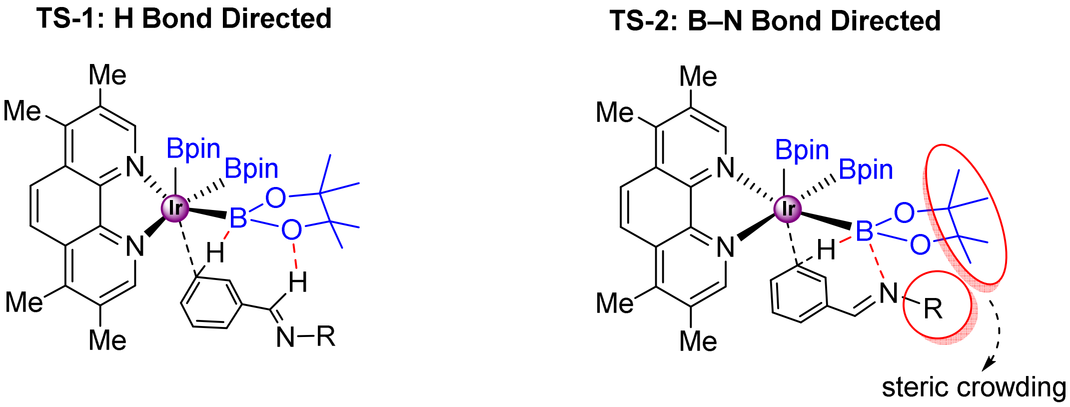
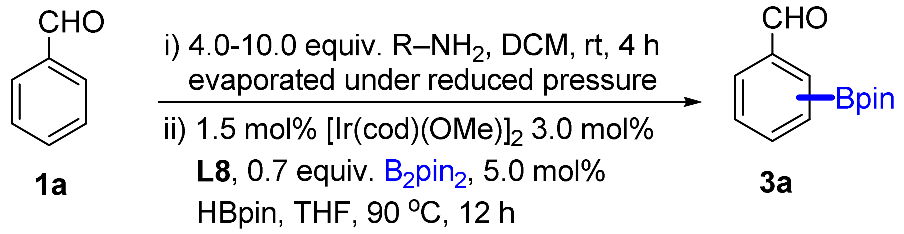


Fig 2.2. Hypothesis for the origin of *meta*-selectivity

When we tested our hypothesis by performing borylations with isopropyl imine and methyl imine of the benzaldehyde, notably, succesive enhancement of the *meta*-selectivity as the imine substituent (R) is made small was observed (**Table 2.4**). We propounded that due to the reduced steric crowding from small imine substituent, the secondary interaction through the imine N atom and boryl B atom of the catalyst (**TS-2**) gets facilitated leading to an enhanced *meta* selectivity (100% for R = Me). However, the detailed mechanism remains to be ascertained and is open for discussion.

Table 2.4. Effect of imine substituent: Proof of hypothesis for *meta*-borylation[a]



#	R	(*meta/para+ortho*)[b]	mono/di	Conv. (%)[c]
1	^{t}Bu	66/34	93/07	78 (57)
2	^{i}Pr	84/16	90/10	73
3	**Me**	**97/03**	**97/03**	**80 (73)**[d]

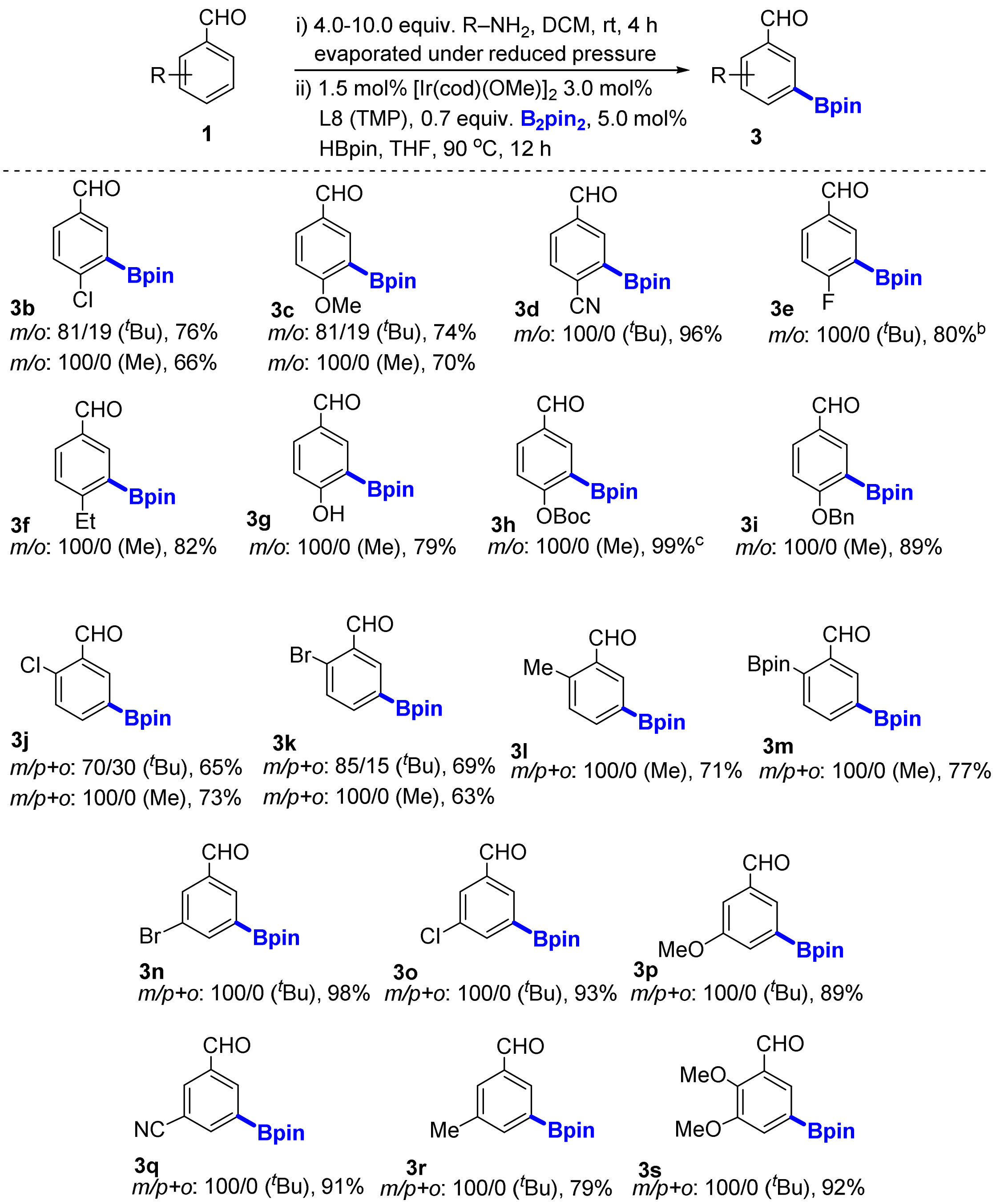
[a]Reactions were run with 1.0 mmol substrate, see experimental part for details. [b]GC ratios. [c]GC conversion; in GC/MS no imine borylated products were found, only aldehyde borylated products were observed. [d]In parentheses isolated yield of the aldehyde borylated product.

The results of examination of substrates scope for the *meta* borylations are summarized in **Table 2.5**. Diverse range of substituents are compatible under the borylation conditions yielding exclusive *meta*-selectivity with excellent isolated yields. For example, with *tert*-butylamine, 4-chlorobenzaldehyde gave 81/19 *meta*/*ortho* selectivity (entry 3b), whereas with methylamine as the protecting/directing group 100% *meta*-selectivity was obtained. Similarly 4-methoxybenzaldehyde gave 81/19 and 100/0 *meta*/*ortho* selectivity on switching from *tert*-butylamine to methylamine respectively (entry 3c). Likewise, 4-cyano-, 4-fluoro-, 4-ethyl-, 4-hydroxy-benzaldehydes, afforded complete *meta*-selectivity (entry 3d-3g). Remarkably even use of very bulky substituents at the 4-position of the benzaldehyde such as OBoc[22] and OBn group (entries 3h & 3i) resulted *meta* isomer as the sole products. Thus, these observations are in agreement with proposed hypothesis of existence of an electrostatic interaction and secondary interaction between the imine N atom and the boryl B atom of the catalyst.

Challenging 2-substituted substrates with several open reactive sites for C–H activation/borylation such as, 2-Bpin-, 2-bromo-, 2-chloro-, and 2-methyl-benzaldehydes could have given a regioisomeric mixture. Remarkably, they resulted complete *meta*-selectivity (entry 3j-3m). *Meta*-substituted benzaldehydes (entries 3n-

3r), as well as highly electron-rich 2,3-dimethoxybenzaldehyde yielded excellent *meta* borylated product with excellent yield (entry 3s).

Table 2.5 *Meta*-borylation of substituted benzaldehydes[a]



1 → **3**: i) 4.0-10.0 equiv. R–NH_2, DCM, rt, 4 h evaporated under reduced pressure; ii) 1.5 mol% $[Ir(cod)(OMe)]_2$ 3.0 mol% L8 (TMP), 0.7 equiv. B_2pin_2, 5.0 mol% HBpin, THF, 90 °C, 12 h

3b *m/o*: 81/19 (^{t}Bu), 76%; *m/o*: 100/0 (Me), 66%

3c *m/o*: 81/19 (^{t}Bu), 74%; *m/o*: 100/0 (Me), 70%

3d *m/o*: 100/0 (^{t}Bu), 96%

3e *m/o*: 100/0 (^{t}Bu), 80%[b]

3f *m/o*: 100/0 (Me), 82%

3g *m/o*: 100/0 (Me), 79%

3h *m/o*: 100/0 (Me), 99%[c]

3i *m/o*: 100/0 (Me), 89%

3j *m/p+o*: 70/30 (^{t}Bu), 65%; *m/p+o*: 100/0 (Me), 73%

3k *m/p+o*: 85/15 (^{t}Bu), 69%; *m/p+o*: 100/0 (Me), 63%

3l *m/p+o*: 100/0 (Me), 71%

3m *m/p+o*: 100/0 (Me), 77%

3n *m/p+o*: 100/0 (^{t}Bu), 98%

3o *m/p+o*: 100/0 (^{t}Bu), 93%

3p *m/p+o*: 100/0 (^{t}Bu), 89%

3q *m/p+o*: 100/0 (^{t}Bu), 91%

3r *m/p+o*: 100/0 (^{t}Bu), 79%

3s *m/p+o*: 100/0 (^{t}Bu), 92%

---

[a] Reactions were run with 1.0 mmol substrate, for details see experimental part for details, yields are for isolated aldehyde meta-borylated products after column chromatography. [b] 2.0 mmol substrate was used. [c] 99% conversion.

In conclusion, complementary methods for the *ortho-* and *meta*-selective C-H bond activation/borylation of aromatic aldehydes have been developed. *Ortho*-borylation is achieved through directed C-H activation/borylation where *tert*-butylamine acts as traceless protecting/directing group, an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate enables *meta*-borylation. The developed methods exhibits very broad substrate scope and functional group tolerance. Working hypothesis for *meta*-selective C–H activation/borylation is still not entirely certain at this stage, thus further studies are underway and will be reported in due course.

Experimental:

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBPin) and bis(pinacolato)diboron (B_2Pin_2) were procured from A. K. Scientific. 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). 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). Ligands L1,[23] L2[24] and L5[25] were prepared according to the reported procedure.

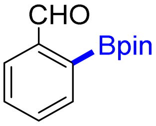
^1H, ^{13}C, ^{11}B and 2D-NMR spectra were recorded on Bruker 400 MHz and 800 MHz NMR spectrometers. The boron bearing carbon atom was not observed due to quadrupolar relaxation. All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet). 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.

General procedure for the preparation of authentic borylated compounds:

In the glovebox, a 5 mL wheaton microreactor was charged with $PdCl_2$•dppf (18.2 mg, 2.5 mol%), KOAc (196.0 mg, 2.0 equiv.), B_2pin_2 (254.0 mg, 1.0 equiv.), corresponding bromobenzaldehyde (185.0 mg, 1.0 mmol) and dry THF (3 mL). The microreactor was sealed and heated at 100 °C for 3 h. After completion (judged by GC), the reaction mixture was cooled to room temperature and filtered through a short pad of celite, which was then evaporated under reduced pressure to afford the crude product. Chromatographic separation with silica gel (chloroform as eluent) gave the borylated product.

Synthesis of *ortho*-borylated benzaldehyde by cross-coupling:

The *ortho*-borylated benzaldehyde is prepared according to the general procedure for the preparation of authentic borylated compounds using 2-bromobenzaldehyde (185.0 mg, 1.0 mmol). Chromatographic separation with silica gel (chloroform as eluent) gave 188.0 mg of the *ortho*-borylated product (81%) as oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 1H), 7.95 (d, J = 6.8 Hz, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.54-7.61 (m, 2H), 1.39 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 141.4, 135.6, 133.1, 130.9, 128.0, 84.6, 25.0.

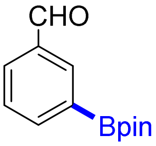
^{11}B NMR (128 MHz, $CDCl_3$): δ 33.5.

HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BO_3$ $[M+Na]^+$ 255.1168, found 255.1159.

Synthesis of *meta*-borylated benzaldehyde by cross-coupling:

The *meta*-borylated benzaldehyde is prepared according to the general procedure for the preparation of authentic borylated compounds using 3-bromobenzaldehyde

(185.0 mg, 1.0 mmol). Chromatographic separation with silica gel (chloroform as eluent) gave 195.0 mg of the *meta*-borylated product (84%) as colourless oil.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.04 (s, 1H), 8.30 (s, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 1.36 (s, 12H).

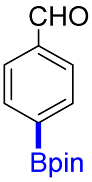
^{13}C NMR (100 MHz, CDCl$_3$): δ 192.7, 140.8, 137.4, 135.9, 131.4, 128.5, 84.4, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BO_3$ [M+Na]$^+$ 255.1168, found 255.1141.

Synthesis of *para*-borylated benzaldehyde by cross-coupling:

The *para*-borylated benzaldehyde is prepared according to the general procedure for the preparation of authentic borylated compounds using 4-bromobenzaldehyde (185.0 mg, 1.0 mmol). Chromatographic separation with silica gel (chloroform as eluent) gave 188.0 mg of the para-borylated product (81%) as oil.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.03 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 7.6 Hz, 2H), 1.35 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 192.7, 138.2, 135.3, 128.8, 84.4, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.4.

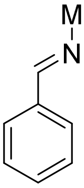
HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BO_3$ [M+Na]$^+$ 255.1168, found 255.1145.

General procedure for the synthesis of intermediate imines from benzaldehydes:

To a solution of benzaldehydes (1.0 mmol) in dry dichloromethane (3.0 mL) and *tert*-butylamine (420.3 µL, 4.0 mmol) was added slowly by a syringe and the mixture was stirred for 4-6 h at room temperature. The reaction mixture was evaporated under reduced pressure to afford imines quantitatively. The products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

Preparation of *N*-methyl-1-phenylmethanimine:

The *N*-methyl-1-phenylmethanimine was prepared as described in the general procedure using the benzaldehyde (106.0 mg, 1.0 mmol), aqueous methylamine (137.7 µL, 4.0 mmol) and dichloromethane (3.0 mL) at room temperature for 6 h.

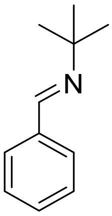


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.65-7.67 (m, 2H), 7.31-7.33 (m, 3H), 3.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 136.7, 130.8, 128.9, 128.3, 48.5

Preparation of *N*-*tert*-butyl-1-phenylmethanimine (1a):

The *N*-*tert*-butyl-1-phenylmethanimine (**1a**) was prepared as described in the general procedure using the benzaldehyde (106.1 mg, 1.0 mmol).

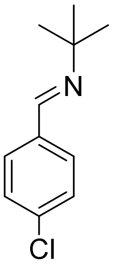


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.78-7.80 (m, 2H), 7.41-7.42 (m, 3H), 1.34 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 137.2, 130.2, 128.5, 127.9, 57.3, 29.8.

Preparation of *N-tert*-butyl-1-(4-chlorophenyl)methanimine (1b):

The *N-tert*-butyl-1-(4-chlorophenyl)methanimine (**1b**) was prepared as described in the general procedure using the 4-chlorobenzaldehyde (140.5 mg, 1.0 mmol).



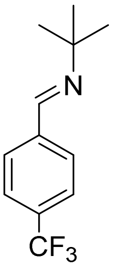
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 136.1, 135.8, 129.2, 128.9, 57.5, 29.8.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}ClN$ $[M+H]^+$ 196.0893, found 196.0879.

Preparation of *N-tert*-butyl-1-(4-(trifluoromethyl)phenyl)methanimine (1c):

The *N-tert*-butyl-1-(4-(trifluoromethyl)phenyl)methanimine (**1c**) was prepared as described in the general procedure using the 4-trifluoromethylbenzaldehyde (174.1 mg, 1.0 mmol).



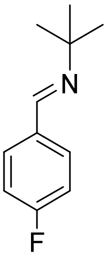
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 153.8, 140.5, 131.9 (q, J_{C-F} = 32.1 Hz), 128.2, 125.9 (q, J_{C-F} = 3.8 Hz), 122.8 (q, J_{C-F} = 266.8 Hz), 57.9, 29.7.

HRMS (ESI) *m/z* calcd for $C_{12}H_{14}F_3N$ [M+H]$^+$ 230.1157, found 230.1145.

Preparation of *N-tert*-butyl-1-(4-fluorophenyl)methanimine (1d):

The *N-tert*-butyl-1-(4-fluorophenyl)methanimine (**1d**) was prepared as described in the general procedure using the 4-fluorobenzaldehyde (124.1 mg, 1.0 mmol).



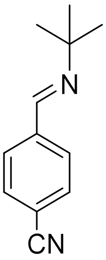
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.23 (s, 1H), 7.72-7.75 (m, 2H), 7.08 (t, J = 8.4 Hz, 2H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 164.1 (d, J_{C-F} = 248.1 Hz), 153.8, 133.5, 129.8, 115.6 (d, J_{C-F} = 21.6 Hz), 57.3, 29.8.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}FN$ [M+H]$^+$ 180.1189, found 180.1176.

Preparation of 4-((*tert*-butylimino)methyl)benzonitrile (1e):

The 4-((*tert*-butylimino)methyl)benzonitrile (**1e**) was prepared as described in the general procedure using the 4-cyanobenzaldehyde (131.1 mg, 1.0 mmol).



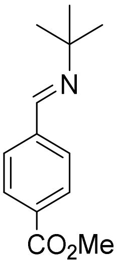
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 1.26 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 153.2, 140.9, 132.2, 128.3, 118.6, 113.2, 57.9, 29.5.

HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2$ $[M+H]^+$ 187.1235, found 187.1221.

Preparation of methyl-4-((*tert*-butylimino)methyl)benzoate (1f):

The methyl-4-((*tert*-butylimino)methyl)benzoate (**1f**) was prepared as described in the general procedure using the methyl-4-formylbenzoate (164.2 mg, 1.0 mmol).



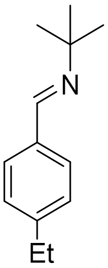
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.31 (s, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 3.93 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.0, 154.4, 141.2, 131.5, 129.9, 127.9, 57.9, 52.3, 29.8.

HRMS (ESI) *m/z* calcd for $C_{13}H_{17}NO_2$ $[M+H]^+$ 220.1338, found 220.1327.

Preparation of *N*-*tert*-butyl-1-(4-ethylphenyl)methanimine (1g):

The *N*-*tert*-butyl-1-(4-ethylphenyl)methanimine (**1g**) was prepared as described in the general procedure using the 4-ethylbenzaldehyde (134.2 mg, 1.0 mmol).

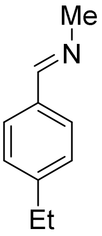


^{1}H NMR (400 MHz, CDCl$_3$): δ 8.26 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.30 (s, 9H), 1.24 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 146.8, 134.9, 128.2, 128.1, 57.2, 29.9, 29.0, 15.7.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}N$ $[M+H]^+$ 190.1596, found 190.1585.

The corresponding methylamine was prepared according to the same procedure.

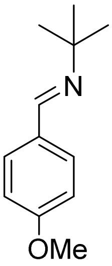


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 3.60 (s, 3H), 2.73 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 147.5, 134.3, 128.5, 128.3, 48.6, 29.2, 15.9.

Preparation of *N-tert*-butyl-1-(4-methoxyphenyl)methanimine (1h):

The *N-tert*-butyl-1-(4-methoxyphenyl)methanimine (**1h**) was prepared as described in the general procedure using the 4-methoxybenzaldehyde (136.2 mg, 1.0 mmol).



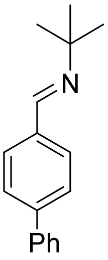
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 154.6, 130.3, 129.5, 114.0, 57.0, 55.4, 29.9.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $[M+H]^+$ 192.1388, found 192.1377.

Preparation of 1-([1,1'-biphenyl]-4-yl)-*N*-(*tert*-butyl)methanimine (1i):

The 1-([1,1'-biphenyl]-4-yl)-*N*-(*tert*-butyl)methanimine (**1i**) was prepared as described in the general procedure using the 4-phenylbenzaldehyde (182.2 mg, 1.0 mmol).



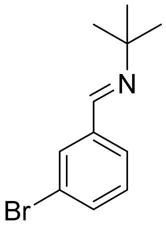
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.33 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 7.6 Hz, 4H), 7.46 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.9, 143.0, 140.7, 136.2, 128.9, 128.5, 127.7, 127.4, 127.3, 57.5, 29.9.

HRMS (ESI) *m/z* calcd for $C_{17}H_{19}N$ $[M+H]^+$ 238.1596, found 238.1586.

Preparation of (3-bromophenyl)-*N*-(*tert*-butyl)methanimine (1j):

The (3-bromophenyl)-*N*-(*tert*-butyl)methanimine (**1j**) was prepared as described in the general procedure using the 3-bromobenzaldehyde (185.0 mg, 1.0 mmol).



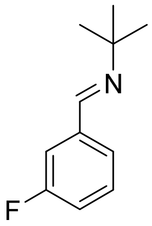
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (s, 1H), 7.97 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 153.7, 139.3, 133.1, 130.5, 130.1, 126.9, 123.0, 57.7, 29.7.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}BrN$ $[M+H]^+$ 240.0388, found 240.0372.

Preparation of *N-tert*-butyl-1-(3-fluorophenyl)methanimine (1k):

The *N-tert*-butyl-1-(3-fluorophenyl)methanimine (**1k**) was prepared as described in the general procedure using the 3-fluorobenzaldehyde (124.1 mg, 1.0 mmol).



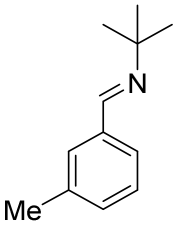
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.54 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.31-7.36 (m, 1H), 7.07 (dt, J = 8.4 Hz, J = 2.0 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3 (d, $J_{C\text{-}F}$ = 244.6 Hz), 153.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 139.6 ($J_{C\text{-}F}$ = 7.1 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.1 (d, $J_{C\text{-}F}$ = 2.6 Hz), 117.0 (d, $J_{C\text{-}F}$ = 21.6 Hz), 113.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 57.5, 29.6.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}FN$ $[M+H]^+$ 180.1189, found 180.1176.

Preparation of *N-tert*-butyl-1-(*m*-tolyl)methanimine (1l):

The *N-tert*-butyl-1-(*m*-tolyl)methanimine (**1l**) was prepared as described in the general procedure using the 3-methylbenzaldehyde (120.2 mg, 1.0 mmol).



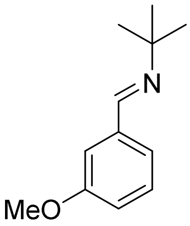
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.62 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 2.39 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 138.4, 137.2, 131.1, 128.5, 128.1, 125.7, 57.3, 29.9, 21.4.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}N$ $[M+H]^+$ 176.1439, found 176.1431.

Preparation of *N-tert*-butyl-1-(3-methoxyphenyl)methanimine (1m):

The *N-tert*-butyl-1-(3-methoxyphenyl)methanimine (**1m**) was prepared as described in the general procedure using the 3-methoxybenzaldehyde (136.2 mg, 1.0 mmol).



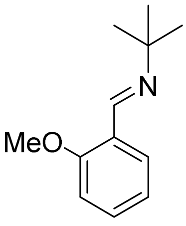
^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.37 (d, J = 1.6 Hz, 1H), 7.29-7.37 (m, 2H), 6.94-6.97 (m, 1H), 3.86 (s, 3H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 155.0, 138.7, 129.5, 121.1, 116.8, 111.7, 57.3, 55.3, 29.8.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $[M+H]^+$ 192.1388, found 192.1374.

Preparation of *N-tert*-butyl-1-(2-methoxyphenyl)methanimine (1n):

The *N-tert*-butyl-1-(2-methoxyphenyl)methanimine (**1n**) was prepared as described in the general procedure using the 2-methoxybenzaldehyde (136.2 mg, 1.0 mmol).



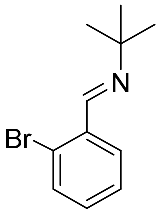
^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.00 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H), 7.32-7.37 (m, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 151.2, 131.3, 127.0, 125.6, 120.8, 110.8, 57.4, 55.4, 29.9.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $[M+H]^+$ 192.1388, found 192.1375.

Preparation of (2-bromophenyl)-*N*-(*tert*-butyl)methanimine (1o):

The (2-bromophenyl)-*N*-(*tert*-butyl)methanimine (**1o**) was prepared as described in the general procedure using the 2-bromobenzaldehyde (185.0 mg, 1.0 mmol).



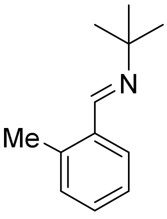
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.00 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.55 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.23 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 135.6, 132.9, 131.4, 128.7, 127.7, 125.2, 58.1, 29.8.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}BrN$ $[M+H]^+$ 240.0375, found 240.0375.

Preparation of *N-tert*-butyl-1-(o-tolyl)methanimine (1p):

The *N-tert*-butyl-1-(o-tolyl)methanimine (**1p**) was prepared as described in the general procedure using the 2-methylbenzaldehyde (120.2 mg, 1.0 mmol).

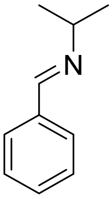


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.27-7.31 (m, 2H), 7.19 (d, J = 6.8 Hz, 1H), 2.54 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 136.9, 135.0, 130.4, 129.5, 127.0, 126.0, 57.3, 29.6, 19.1.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}N$ [M+H]$^+$ 176.1439, found 176.1425.

Using the same procedure corresponding methylimine was prepared.

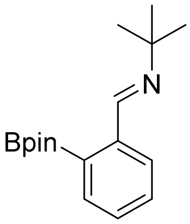


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.31-7.40 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 3.64 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 137.3, 134.2, 130.8, 130.1, 127.1, 126.2, 48.8, 19.2.

Preparation of *N-tert*-butyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanimine (1q):

The *N-tert*-butyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanimine (**1q**) was prepared as described in the general procedure using the 2-borylatedbenzaldehyde (232.0 mg, 1.0 mmol).



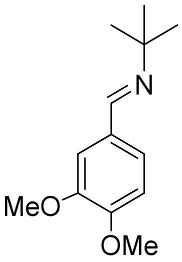
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 6.8 Hz, 1H), 1.34 (s, 12H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 143.4, 135.9, 131.4, 129.3, 126.3, 84.1, 57.9, 30.2, 25.3.

HRMS (ESI) *m/z* calcd for $C_{17}H_{26}BNO_2$ [M+H]$^+$ 288.2135, found 288.2111.

Preparation of *N-tert*-butyl-1-(3,4-dimethoxyphenyl)methanimine (1r):

The *N-tert*-butyl-1-(3,4-dimethoxyphenyl)methanimine (**1r**) was prepared as described in the general procedure using the 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol).



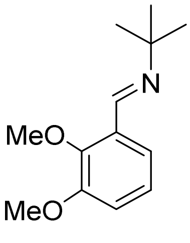
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (s, 1H), 7.44 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.8, 151.0, 149.4, 130.6, 122.6, 110.5, 108.9, 57.1, 56.1, 30.0.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_2$ [M+H]$^+$ 222.1494, found 222.1482.

Preparation of *N-tert*-butyl-1-(2,3-dimethoxyphenyl)methanimine (1s):

The *N-tert*-butyl-1-(2,3-dimethoxyphenyl)methanimine (**1s**) was prepared as described in the general procedure using the 2,3-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol).



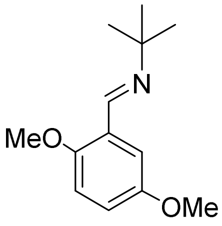
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.63 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 152.5, 151.1, 149.0, 130.7, 124.0, 118.5, 113.6, 61.4, 57.4, 55.6, 29.7.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_2$ $[M+H]^+$ 222.1494, found 222.1482.

Preparation of *N*-*tert*-butyl-1-(2,5-dimethoxyphenyl)methanimine (1t):

The *N*-*tert*-butyl-1-(2,5-dimethoxyphenyl)methanimine (**1t**) was prepared as described in the general procedure using the 2,5-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol).



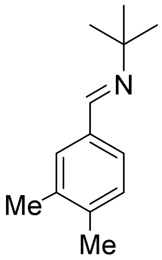
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.53 (d, J = 3.2 Hz, 1H), 6.91 (dd, J = 8.8 Hz, J = 3.2 Hz, 1H), 6.83 (d, J = 9.2 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 153.2, 151.3, 126.4, 117.9, 112.6, 110.9, 57.6, 56.3, 56.0, 30.0.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_2$ $[M+H]^+$ 222.1494, found 222.1483.

Preparation of *N*-*tert*-butyl-1-(3,4-dimethylphenyl)methanimine (1u):

The *N*-*tert*-butyl-1-(3,4-dimethylphenyl)methanimine (**1u**) was prepared as described in the general procedure using the 3,4-dimethylbenzaldehyde (134.2 mg, 1.0 mmol).



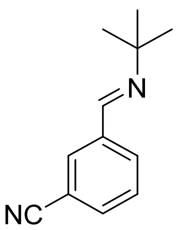
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.62 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 139.0, 136.7, 134.9, 129.7, 128.5, 125.9, 57.0, 29.8, 19.8, 19.7.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}N$ $[M+H]^+$ 190.1596, found 190.1587.

Preparation of 3-((*tert*-butylimino)methyl)benzonitrile (1v):

The 3-((*tert*-butylimino)methyl)benzonitrile (**1v**) was prepared as described in the general procedure using the 3-cyanobenzaldehyde (131.2 mg, 1.0 mmol).



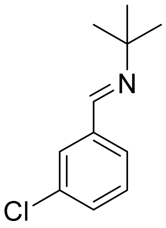
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.06 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 138.3, 133.3, 132.2, 131.4, 129.4, 118.6, 112.9, 57.9, 29.6.

HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2$ $[M+H]^+$ 187.1235, found 187.1221.

Preparation of *N-tert*-butyl-1-(3-chlorophenyl)methanimine (1w):

The *N-tert*-butyl-1-(3-chlorophenyl)methanimine (**1w**) was prepared as described in the general procedure using the 3-chlorobenzaldehyde (140.5 mg, 1.0 mmol).



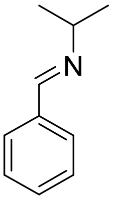
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.79 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.29-7.36 (m, 2H), 1.30 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 139.0, 134.8, 130.2, 129.8, 127.6, 126.4, 57.6, 29.7.

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}ClN$ $[M+H]^+$ 196.0893, found 196.0881.

Preparation of *N*-isopropyl-1-phenylmethanimine:

The *N*-isopropyl-1-phenylmethanimine was prepared as described in the general procedure using the benzaldehyde (106.0 mg, 1.0 mmol), isopropylamine (339.6 μL, 4.0 mmol) and dry dichloromethane (3.0 mL) at room temperature for 6 h.



^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.76-7.78 (m, 2H), 7.40-7.42 (m, 3H), 3.555 (septet, J = 6.3 Hz, 1H), 1.31 (d, J = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 136.9, 130.8, 129.0, 128.5, 62.1, 24.7.

General procedure for optimization of reaction conditions for *ortho*-borylation:

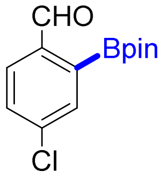
A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**) (106.0 mg, 1.0 mmol), $^tBuNH_2$ (420.3 μL, 4.0 mmol) and dry dichloromethane (3.0 mL) and stirred for 4 h at room temperature. The crude mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol%), appropriate amount of ligand (**L1**: 9.03 mg; **8-AQ**: 4.32 mg, **L2**: 6.24 mg; **L3**: 3.24 mg; **L4**: 2.82 mg; 3.0 mol%), HBpin (7.25 μL, 5.0 mol%), B_2pin_2 (177.8 mg, 0.7 equiv) and dry THF (2.5 mL, 0.4M). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 °C. The reaction mixture was stirred for 12 h and the results are summarized in the **Table 2.1**.

Ortho-borylation and isolation of imine borylated benzaldehyde:

A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**) (106.0 mg, 1.0 mmol), ^{t}BuNH$_2$ (420.3 µL, 4.0 mmol) and dry dichloromethane (3.0 mL) and stirred for 4 h at room temperature. The crude mixture was dried under reduced pressure. In a glove box, this crude imine was charged with [Ir(cod)(OMe)]$_2$ (10.0 mg, 1.5 mol%), 8-AQ (4.32 mg, 3.0 mol%), HBpin (7.25 µL, 5.0 mol%), B$_2$pin$_2$ (177.8 mg, 0.7 equiv) and dry THF (2.5 mL, 0.4M). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 °C. The reaction mixture was stirred for 12 h and the solvent was evaporated under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave *ortho*-borylated benzaldehydes.

Ortho-borylation of 4-chlorobenzaldehyde (2b):

The *ortho*-borylated of 4-chlorobenzaldehyde was prepared as described in the general procedure using the 4-chlorobenzaldehyde (**1b**) (140.5 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 208.0 mg of **2b** (78%) as solid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.50 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.51 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 1.39 (s, 12H).

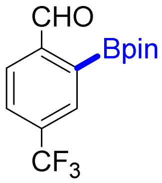
^{13}C NMR (100 MHz, CDCl$_3$): δ 193.5, 140.0, 139.6, 135.7, 131.2, 129.4, 84.9, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.4.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BClO_3$ $[M+Na]^+$ 289.0779, found 289.0772.

Ortho-borylation of 4-trifluoromethylbenzaldehyde (2c):

The *ortho*-borylated 4-trifluoromethylbenzaldehyde was prepared as described in the general procedure using 4-trifluoromethylbenzaldehyde (**1c**) (174.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 258.0 mg of **2c** (86%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.65 (s, 1H), 8.15 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 1.41 (s, 12H).

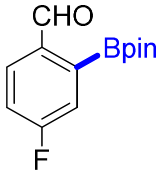
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 143.9, 132.7, 128.0, 127.8, 127.0, 125.1, 85.1, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.6.

HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BF_3O_3$ $[M+HCOOH]^-$ 345.1121, found 345.1118.

Ortho-borylation of 4-fluorobenzaldehyde (2d):

The *ortho*-borylated 4-fluorobenzaldehyde was prepared as described in the general procedure using 4-fluorobenzaldehyde (**1d**) (124.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 198.0 mg of **2d** (79%) as colourless liquid. The ratio of *ortho*/*meta* borylated product was found to be 93/07 by the GC-FID.



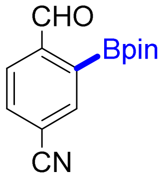
^{1}H NMR (400 MHz, CDCl$_3$): δ 10.47 (s, 1H), 8.00 (dd, J = 8.4 Hz, J = 5.2 Hz, 1H), 7.51 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.22 (dt, J = 8.0 Hz, J = 2.4 Hz, 1H), 1.39 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.1, 148.7, 137.9, 131.0 (d, $J_{C\text{-}F}$ = 9.9 Hz), 122.3 (d, $J_{C\text{-}F}$ = 21.6 Hz), 118.0 (d, $J_{C\text{-}F}$ = 21.8 Hz), 84.9, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.6.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BFO_3$ $[M+Na]^+$ 273.1074, found 273.1068.

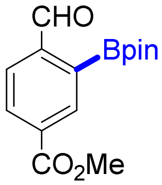
Ortho-borylation of 4-cyanobenzaldehyde:



The 4-cyanobenzaldehyde (**1e**) (131.1 mg, 1.0 mmol) was subjected under conditions as described in the general procedure. By GC and crude NMR analysis, the reaction didn’t work, entire starting imine left unreacted. Employment of other ligand systems such as **L1**, **L2**, **L3** and **L4** were also unsuccessful for borylation.

Ortho-borylation of 4-carbomethoxybenzaldehyde (2f):

The *ortho*-borylated 4-carbomethoxybenzaldehyde was prepared as described in the general procedure using 4-carbomethoxybenzaldehyde (**1f**) (164.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 214.6 mg of **2f** (74%) as solid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.62 (s, 1H), 8.51 (d, J = 1.6 Hz, 1H), 8.19 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 1.40 (s, 12H).

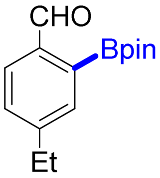
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 166.4, 144.3, 136.9, 133.7, 131.9, 127.8, 84.9, 52.6, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.6.

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}BO_5$ $[M+H]^+$ 291.1404, found 291.1401.

***Ortho*-borylation of 4-ethylbenzaldehyde** (**2g**):

The *ortho*-borylated 4-ethylbenzaldehyde was prepared as described in the general procedure using 4-ethylbenzaldehyde (**1g**) (134.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 208.0 mg of **2g** (80%) as colourless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 2.71 (q, J = 7.6 Hz, 2H), 1.40 (s, 12H), 1.25 (t, J = 4.4 Hz, 3H).

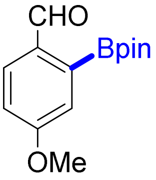
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 150.1, 139.3, 135.2, 130.4, 128.4, 84.5, 29.2, 25.0, 15.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.5.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_3$ $[M+Na]^+$ 283.1481, found 283.1449.

***Ortho*-borylation of 4-methoxybenzaldehyde** (**2h**):

The *ortho*-borylated 4-methoxybenzaldehyde was prepared as described in the general procedure using 4-methoxybenzaldehyde (**1h**) (136.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 157.0 mg of **2h** (60%) as colourless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 3.90 (s, 3H), 1.39 (s, 12H).

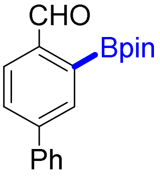
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 163.5, 134.8, 130.8, 120.0, 116.3, 84.6, 55.7, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 32.0.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_4$ $[M+H]^+$ 263.1455, found 263.1442.

Ortho-borylation of 4-phenylbenzaldehyde (2i):

The *ortho*-borylated 4-phenylbenzaldehyde was prepared as described in the general procedure using 4-phenylbenzaldehyde (**1i**) (182.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 215.0 mg of **2i** (70%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.41 (d, J = 7.2 Hz, 1H), 1.39 (s, 12H).

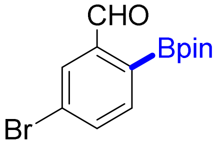
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 145.7, 140.2, 140.0, 134.4, 129.5, 129.0, 128.6, 128.4, 127.6, 84.6, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.6.

HRMS (ESI) *m/z* calcd for $C_{19}H_{21}BO_3$ [M+Na]$^+$ 331.1481, found 331.1475.

Ortho-borylation of 3-bromobenzaldehyde (2j):

The *ortho*-borylated 3-bromobenzaldehyde was prepared as described in the general procedure using 3-bromobenzaldehyde (**1j**) (185.0 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 270.5 mg of **2j** (87%) as solid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.55 (s, 1H), 8.09 (d, J = 1.2 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 1.38 (s, 12H).

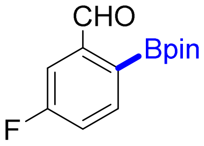
^{13}C NMR (100 MHz, CDCl$_3$): δ 193.5, 143.0, 137.6, 135.9, 130.5, 126.3, 84.8, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BBrO_3$ [M+Na]$^+$ 333.0274, found 333.0263.

Ortho-borylation of 3-fluorobenzaldehyde (2k):

The *ortho*-borylated 3-fluorobenzaldehyde was prepared as described in the general procedure using 3-fluorobenzaldehyde (**1k**) (124.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 180.0 mg of **2k** (72%) as colourless liquid. Crude GC/MS analysis showed that the ratios between two *ortho* isomers are: 75/25. During isolation, it underwent rapid protodeborylation.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.62 (d, $J_{H\text{-}F}$ = 3.2 Hz, 1H), 7.92 (q, J = 6.0 Hz, 1H), 7.64 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 7.27 (dt, J = 8.0 Hz, J = 2.4 Hz, 1H), 1.37 (s, 12H).

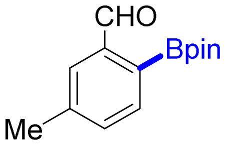
^{13}C NMR (100 MHz, CDCl$_3$): δ 193.7, 164.8 (d, $J_{C\text{-}F}$ = 251.3 Hz), 144.2 (d, $J_{C\text{-}F}$ = 6.3 Hz), 138.6 (d, $J_{C\text{-}F}$ = 7.6 Hz), 120.1 (d, $J_{C\text{-}F}$ = 20.6 Hz), 113.7 (d, $J_{C\text{-}F}$ = 21.3 Hz), 84.7, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.3.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BFO_3$ [M+Na]$^+$ 273.1074, found 273.1063.

Ortho-borylation of 3-methylbenzaldehyde (**2l**):

The *ortho*-borylated 3-methylbenzaldehyde was prepared as described in the general procedure using 3-methylbenzaldehyde (**1l**) (120.2 mg, 1.0 mmol). The reaction mixture was stirred for 12 h. After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 199.0 mg of **2l** (81%) as colourless liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.57 (s, 1H), 7.77 (d, J = 6.8 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 2.42 (s, 3H), 1.38 (s, 12H).

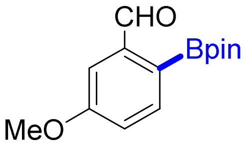
^{13}C NMR (100 MHz, CDCl$_3$): δ 195.2, 141.6, 141.3, 136.0, 133.9, 128.1, 84.4, 25.0, 21.6.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.1.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_3$ [M+Na]$^+$ 269.1325, found 269.1325.

Ortho-borylation of 3-methoxybenzaldehyde (2m):

The *ortho*-borylated 3-methoxybenzaldehyde was prepared as described in the general procedure using 3-methoxybenzaldehyde (**1m**) (136.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 231.0 mg of **2m** (88%) as colourless liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.67 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 3.87 (s, 3H), 1.36 (s, 12H).

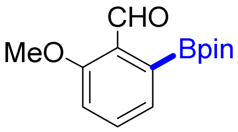
^{13}C NMR (100 MHz, CDCl$_3$): δ 195.0, 162.0, 143.7, 138.1, 120.1, 110.4, 84.3, 55.5, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 33.2.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_4$ [M+Na]$^+$ 285.1274, found 285.1265.

Ortho-borylation of 2-methoxybenzaldehyde (2n):

The *ortho*-borylated 2-methoxybenzaldehyde was prepared as described in the general procedure using 2-methoxybenzaldehyde (**1n**) (136.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 210.0 mg of **2n** (80%) as sticky liquid.



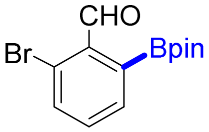
^{1}H NMR (400 MHz, CDCl$_3$): δ 10.43 (s, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 1.43 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 161.6, 135.5, 128.2, 124.5, 112.3, 84.1, 55.7, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 32.8.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_4$ $[M+Na]^+$ 285.1274, found 285.1263.

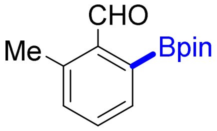
Ortho-borylation of 2-bromobenzaldehyde (2o):



The *ortho*-borylated 2-bromobenzaldehyde was prepared as described in the general procedure using 2-bromobenzaldehyde (**1o**) (185.0 mg, 1.0 mmol). The reaction mixture was stirred for 12 h. GC/MS analysis showed that conversion was 21% and during column chromatography rapid protodeborylation occurred.

Ortho-borylation of 2-methylbenzaldehyde (2p):

The *ortho*-borylated 2-methylbenzaldehyde was prepared as described in the general procedure using 2-methylbenzaldehyde (**1p**) (120.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 128.0 mg of **2p** (52%) as colourless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 7.50 (d, J = 6.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.26 (d, overlapped with $CDCl_3$, J = 6.8 Hz, 1H), 2.65 (s, 3H), 1.41 (s, 12H).

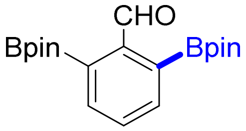
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 140.2, 138.4, 133.0, 132.9, 131.7, 84.3, 25.0, 19.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.5.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_3$ $[M+Na]^+$ 269.1325, found 269.1315.

Ortho-borylation of 2-borylatedbenzaldehyde (2q):

The *ortho*-borylated 2-borylatedbenzaldehyde was prepared as described in the general procedure using 2-borylatedbenzaldehyde (**1q**) (232.0 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 282.0 mg of **2q** (79%) as sticky liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.71 (s, 1H), 7.78 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 1.42 (s, 24H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 136.2, 132.3, 84.5, 25.3.

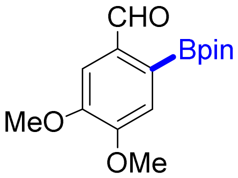
^{11}B NMR (128 MHz, $CDCl_3$): δ 34.3.

HRMS (ESI): This compound didn't ionize well in HRMS.

GCMS for $C_{19}H_{28}B_2O_5$ 358.21, found: 358.21

Ortho-borylation of 3,4-dimethoxybenzaldehyde (2r):

The *ortho*-borylated 3,4-dimethoxybenzaldehyde was prepared as described in the general procedure using 3,4-dimethoxybenzaldehyde (**1r**) (166.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 245.0 mg of **2r** (84%) as colourless sticky liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 7.55 (s, 1H), 7.35 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 1.37 (s, 12H).

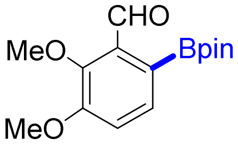
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 152.9, 151.3, 136.4, 117.3, 108.7, 84.5, 56.3, 56.1, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.1.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_5$ $[M+H]^+$ 293.1560, found 293.1553.

***Ortho*-borylation of 2,3-dimethoxybenzaldehyde (2s)**:

The *ortho*-borylated 2,3-dimethoxybenzaldehyde was prepared as described in the general procedure using 2,3-dimethoxybenzaldehyde (**1s**) (166.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 187.0 mg of **2s** (64%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 1.42 (s, 12H).

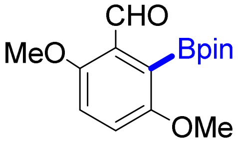
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 153.9, 152.2, 133.9, 128.9, 117.3, 84.1, 62.5, 56.1, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 32.2.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_5$ $[M+H]^+$ 293.1560, found 293.1555.

Ortho-borylation of 2,5-dimethoxybenzaldehyde (2t):

The *ortho*-borylated 2,5-dimethoxybenzaldehyde was prepared as described in the general procedure using 2,5-dimethoxybenzaldehyde (**1t**) (166.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 178.0 mg of **2t** (61%) as sticky liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.03 (d, J = 9.2 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 1.44 (s, 12H).

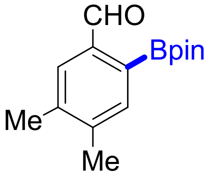
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 156.7, 156.4, 128.7, 118.3, 113.4, 84.1, 56.7, 56.2, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 32.1.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_5$ $[M+H]^+$ 293.1560, found 293.1551.

Ortho-borylation of 3,4-dimethylbenzaldehyde (2u):

The *ortho*-borylated 3,4-dimethylbenzaldehyde was prepared as described in the general procedure using 3,4-dimethylbenzaldehyde (**1u**) (134.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 145.6 mg of **2u** (56%) as solid.



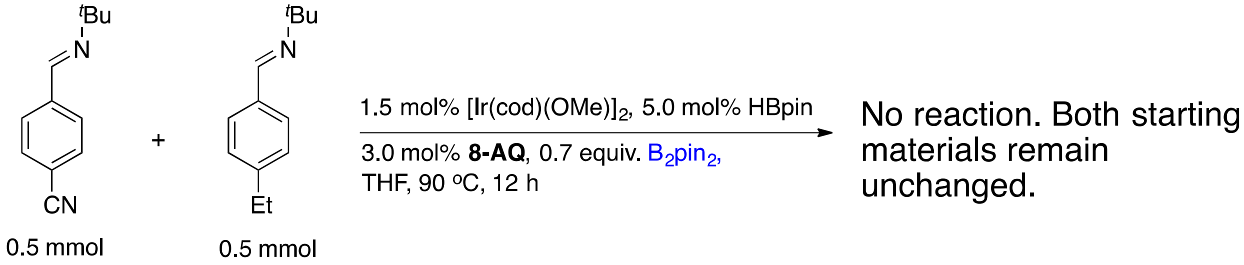
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 2.32 (s, 6H), 1.38 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 142.7, 140.0, 139.7, 137.2, 128.8, 84.4, 25.0, 20.0, 19.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.9.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_3$ $[M+Na]^+$ 283.1481, found 283.1472.

Controlled experiment for 4-cyanobenzaldehyde borylation:



In a glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol%), 8-AQ (4.32 mg, 3.0 mol%), HBpin (7.25 μL, 5.0 mol%), B_2pin_2 (177.8 mg, 0.7 equiv), dry THF (2.5 mL, 0.4M) and 1:1 mixture of 4-cyanobenzaldehyde-derived imine and 4-ethylbenzaldehyde-derived imine (93.0 mg, 0.5 mmol and 94.5 mg, 0.5 mmol). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 °C. The reaction mixture was stirred for 12 h. Monitoring by GC-MS, it was found that no reaction occurred.

Ligand screening for *meta*-borylation of benzaldehyde: General Procedure:

A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**) (106.0 mg, 1.0 mmol), $^tBuNH_2$ (420.3 μL, 4.0 mmol) and dry dichloromethane (3.0 mL) and stirred for 4 h at room temperature. The crude mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol%), appropriate amount of **L** (**L5**: 8.76 mg; **L6**: 4.68 mg, **L7**: 8.04 mg, **L8**: 7.08 mg 3.0 mol%), HBpin (7.25 μL, 5.0 mol%), B_2pin_2 (177.8 mg, 0.7 equiv) and dry THF (2.5 mL, 0.4M). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 ^{o}C. The reaction mixture was stirred for 12 h and the results are summarized in the **Table 2.3**.

Effect of imine substituent: Proof of hypothesis for *meta*-borylation: General Procedure:

A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**) (106.0 mg, 1.0 mmol), R–NH_2 (420.3 μL, 4.0 mmol, for R = ^{t}Bu; 490.3 μL, for R = ^{i}Pr; and 10.0 equiv. for R = Me) and dry dichloromethane (3.0 mL) and stirred for 4 h at room temperature. The crude mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol%), **L8 (TMP)** (7.08 mg 3.0 mol%), HBpin (7.25 μL, 5.0 mol%), B_2pin_2 (177.8 mg, 0.7 equiv) and dry THF (2.5 mL, 0.4M). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 ^{o}C. The reaction mixture was stirred for 12 h and the results are summarized in the **Table 2.4**.

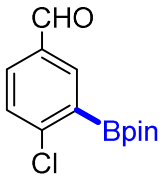
General procedure for *meta*-borylation of benzaldehydes*:*

A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**) (106.0 mg, 1.0 mmol), $^{t}BuNH_2$ (420.3 μL, 4.0 mmol) and dry dichloromethane (3.0 mL) and stirred for 4 h at room temperature. The crude mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol%), **L8 (TMP)** (7.08 mg 3.0 mol%), HBpin (7.25 μL, 5.0 mol%), B_2pin_2 (177.8 mg, 0.7 equiv) and dry THF (2.5 mL, 0.4M). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 90 ^{o}C. After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave *meta*-borylated product.

Meta-borylation of 4-chlorobenzaldehyde (**3b**):

The *meta*-borylated 4-chlorobenzaldehyde was prepared as described in the general procedure using 4-chlorobenzaldehyde (**1b**) (140.5 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 202.0 mg of **3b** (76%) as sticky liquid. Crude reaction mixture showed the *meta*/*ortho* ratio was 81/19 (GC ratio).

The same procedure was followed using methylamine (10.0 equiv.) instead of *tert*-butylamine and the outcomes are as follows: Selectivity: *meta*/*ortho* = 100/0; Isolated yield: 66%.



^{1}H NMR (400 MHz, CDCl$_3$): δ 9.98 (s, 1H), 8.19 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 1.38 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 191.1, 143.3, 137.6, 135.5, 134.0, 123.5, 84.8, 25.0.

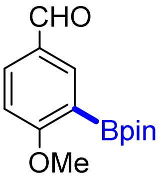
^{11}B NMR (128 MHz, CDCl$_3$): δ 32.2.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BClO_3$ $[M+H]^+$ 267.0959, found 267.0948.

Meta-borylation of 4-methoxybenzaldehyde (**3c**):

The *meta*-borylated 4-methoxybenzaldehyde was prepared as described in the general procedure using 4-methoxybenzaldehyde (**1h**) (136.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 194.0 mg of **3c** (74%) as solid.

The same procedure was followed using methylamine instead (10.0 equiv.) instead of *tert*-butylamine and the outcomes are as follows: Selectivity: *meta*/*ortho* = 100/0; Isolated yield: 70%.



^{1}H NMR (800 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.20 (s, 1H), 7.95 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 1.36 (s, 12H).

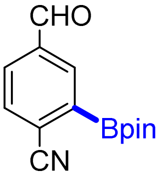
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 169.0, 140.1, 134.2, 129.4, 110.6, 84.1, 56.2, 24.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.1.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_4$ $[M+H]^+$ 263.1455, found 263.1445.

Meta-borylation of 4-cyanobenzaldehyde (**3d**):

The *meta*-borylated 4-cyanobenzaldehyde was prepared as described in the general procedure using 4-cyanobenzaldehyde (**1e**) (131.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 247.0 mg of **3d** (96%) as sticky liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.37 (s, 1H), 8.02 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 1.40 (s, 12H).

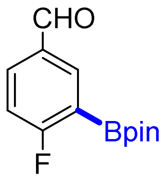
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 137.5, 134.1, 131.0, 122.4, 118.0, 85.4, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.8.

HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BNO_3$ $[M+HCOO]^-$ 302.1200, found 302.1194.

Meta-borylation of 4-fluorobenzaldehyde (3e):

The *meta*-borylated 4-fluorobenzaldehyde was prepared as described in the general procedure using 4-fluorobenzaldehyde (**1d**) (124.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 200.0 mg of **3e** (80%) as solid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 9.98 (s, 1H), 8.29 (d, J = 4.0 Hz, 1H), 7.97-8.01 (m, 1H), 7.17 (t, J = 8.8 Hz, 1H), 1.38 (s, 12H).

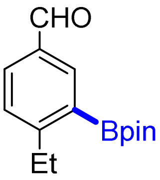
^{13}C NMR (100 MHz, CDCl$_3$): δ 190.8, 170.8 (d, $J_{C\text{-}F}$ = 260.1 Hz), 140.5 (d, $J_{C\text{-}F}$ = 10.1 Hz), 134.0 (d, $J_{C\text{-}F}$ = 10.7 Hz), 132.6 (d, $J_{C\text{-}F}$ = 2.6 Hz), 116.6 (d, $J_{C\text{-}F}$ = 25.1 Hz), 84.6, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.4.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BFO_3$ $[M+H]^+$ 251.1255, found 251.1254.

Meta-borylation of 4-ethylbenzaldehyde (3f):

The *meta*-borylated 4-ethylbenzaldehyde was prepared as described in the general procedure using 4-ethylbenzaldehyde (**1g**) (134.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 213.0 mg of **3f** (82%) as sticky liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.26 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 2.98 (q, J = 7.6 Hz, 2H), 1.37 (s, 12H), 1.22 (t, J = 7.6 Hz, 3H).

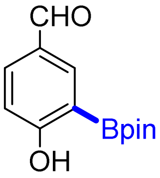
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 159.0, 138.9, 133.7, 131.4, 129.3, 84.3, 29.5, 25.3, 17.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.9.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_3$ $[M+H]^+$ 261.1584, found 261.1584.

Meta-borylation of 4-hydroxybenzaldehyde (**3g**):

The *meta*-borylated 4-hydroxybenzaldehyde was prepared as described in the general procedure using 4-hydroxybenzaldehyde (122.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (5% ethylacetate/hexane as eluent) gave 196.0 mg of **3g** (79%) as sticky liquid.



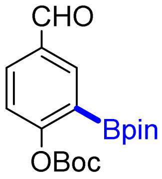
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.38 (s, 1H), 8.14 (d, J = 1.6 Hz, 1H), 7.93 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 1.39 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 168.9, 140.5, 134.4, 129.3, 116.8, 85.3, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 33.3.

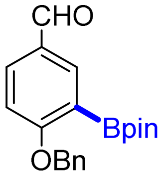
HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BO_4$ $[M+H]^+$ 249.1220, found 249.1227.

Meta-borylation of *tert*-butyl (4-formylphenyl)carbonate (3h):



The *meta*-borylated 4-boc protected benzaldehyde was prepared as described in the general procedure using *tert*-butyl (4-formylphenyl)carbonate (222.0 mg, 1.0 mmol). After completion (judged by GC, conversion: 99%), THF was removed under reduced pressure and chromatographic separation with silica gel (5% ethylacetate/hexane as eluent) gave 151.0 mg of **3h** (61%) as liquid. During silica-gel column chromatography, the Boc group knocked off to give the corresponding hydroxy compound.

Meta-borylation of 4-(benzyloxy)benzaldehyde (3i):



The *meta*-borylated 4-(benzyloxy)benzaldehyde was prepared as described in the general procedure using 4-(benzyloxy)benzaldehyde (212.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (12% ethylacetate/hexane as eluent) gave 300.1 mg of *meta*-borylated benzaldehyde **3i** (89%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 7.59 (d, J = 7.2 Hz, 2H), 7.31-7.40 (m, 3H), 7.04 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 1.38 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 168.0, 140.1, 136.7, 134.2, 129.7, 128.6, 127.8, 126.8, 112.0, 84.1, 70.1, 25.1.

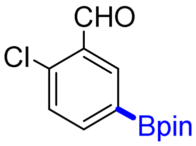
^{11}B NMR (128 MHz, $CDCl_3$): δ 33.6.

HRMS (ESI) *m/z* calcd for $C_{20}H_{23}BO_4$ $[M+H]^+$ 339.1689, found 339.1692.

Meta-borylation of 2-chlorobenzaldehyde (3j):

The *meta*-borylated 2-chlorobenzaldehyde was prepared as described in the general procedure using 2-chlorobenzaldehyde (140.5 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 173.0 mg of **3j** (65%) as colourless liquid.

The same procedure was followed using methylamine instead (10.0 equiv.) instead of *tert*-butylamine and the outcomes are as follows: Selectivity: *meta*/(*para*+*ortho*) = 100/0; Isolated yield: 73%.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 7.90 (one s & one d are overlapped, J = 7.6 Hz for d, 2H), 7.79 (d, J = 7.6 Hz, 1H), 1.38 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 137.7, 137.0, 134.4, 133.6, 128.8, 85.1, 25.3.

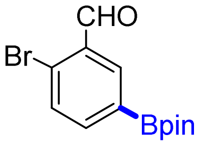
^{11}B NMR (128 MHz, $CDCl_3$): δ 33.0.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BClO_3$ $[M+H]^+$ 267.0959, found 267.0953.

Meta-borylation of 2-bromobenzaldehyde (3k):

The *meta*-borylated 2-bromobenzaldehyde was prepared as described in the general procedure using 2-bromobenzaldehyde (185.0 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 214.5 mg of **3k** (69%) as colourless liquid.

The same procedure was followed using methylamine instead (10.0 equiv.) instead of *tert*-butylamine and the outcomes are as follows: Selectivity: *meta*/(*para*+*ortho*) = 100/0; Isolated yield: 63%.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.39 (s, 1H), 8.07 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 1.36 (s, 12H).

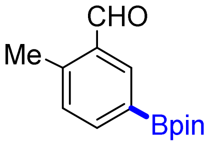
^{13}C NMR (100 MHz, CDCl$_3$): δ 192.4, 140.0, 135.2, 133.9, 129.1, 126.8, 84.1, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BBrO_3$ [M+HCOO]$^-$ 355.0352, found 355.0355.

Meta-borylation of 2-methylbenzaldehyde (**3l**):

The *meta*-borylated 2-methylbenzaldehyde was prepared as described in the general procedure using 2-methylbenzaldehyde (120.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (2% ethylacetate/hexane as eluent) gave 175.0 mg of **3l** (71%) as sticky liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.24 (s, 1H), 8.22 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 2.66 (s, 3H), 1.36 (s, 12H).

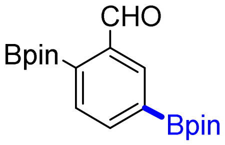
^{13}C NMR (100 MHz, CDCl$_3$): δ 193.7, 143.8, 140.2, 139.8, 133.8, 131.5, 84.3, 25.2, 20.5.

^{11}B NMR (128 MHz, CDCl$_3$): δ 33.3.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_3$ $[M+H]^+$ 247.1427, found 247.1426.

***Meta*-borylation of 2-borylatedbenzaldehyde (3m):**

The *meta*-borylated 2-borylatedbenzaldehyde was prepared as described in the general procedure using 2-borylatedbenzaldehyde (232.0 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (15% ethylacetate/hexane as eluent) gave 276.0 mg of *meta*-borylated benzaldehyde **3m** (77%) as gummy liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 8.33 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 1.39 (s, 12H), 1.34 (s, 12H).

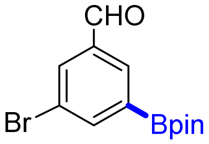
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 140.3, 139.2, 135.3, 134.3, 83.2, 24.9, 24.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ 34.0.

HRMS (ESI) *m/z* calcd for $C_{19}H_{28}B_2O_5$ $[M+H]^+$ 359.2129, found 359.2129.

***Meta*-borylation of 3-bromobenzaldehyde (3n):**

The *meta*-borylated 3-bromobenzaldehyde was prepared as described in the general procedure using 3-bromobenzaldehyde (185.0 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 305.0 mg of **3n** (98%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 8.09 (t, J = 1.6 Hz, 1H), 1.36 (s, 12H).

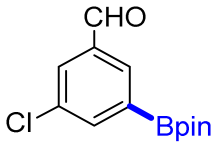
^{13}C NMR (100 MHz, CDCl$_3$): δ 191.1, 143.3, 137.6, 135.5, 134.0, 123.5, 84.8, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BBrO_3$ [M+HCOO]$^-$ 355.0352, found 355.0351.

Meta-borylation of 3-chlorobenzaldehyde (3o):

The *meta*-borylated 3-chlorobenzaldehyde was prepared as described in the general procedure using 3-chlorobenzaldehyde (140.5 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 248.0 mg of **3o** (93%) as sticky liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.00 (s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.93 (d, J = 1.6 Hz, 1H), 1.36 (s, 12H).

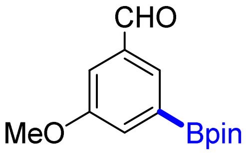
^{13}C NMR (100 MHz, CDCl$_3$): δ 191.2, 140.4, 137.4, 135.4, 135.1, 130.9, 84.8, 25.0.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BClO_3$ [M+H]$^+$ 267.0959, found 267.0951.

Meta-borylation of 3-methoxybenzaldehyde (3p):

The *meta*-borylated 3-methoxybenzaldehyde was prepared as described in the general procedure using 3-methoxybenzaldehyde (136.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 233.0 mg of **3p** (89%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 3.86 (s, 3H), 1.35 (s, 12H).

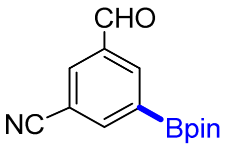
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 159.8, 137.5, 130.6, 127.1, 114.6, 84.4, 55.7, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.1.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_4$ $[M+Na]^+$ 285.1274, found 285.1264.

Meta-borylation of 3-cyanobenzaldehyde (3q):

The *meta*-borylated 3-cyanobenzaldehyde was prepared as described in the general procedure using 3-cyanobenzaldehyde (131.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 234.0 mg of **3q** (91%) as solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 8.48 (s, 1H), 8.29 (s, 1H), 8.21 (s, 1H), 1.36 (s, 12H).

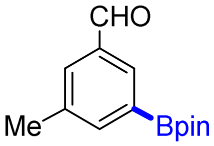
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 143.3, 140.0, 136.3, 134.6, 117.7, 113.5, 85.1, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.6.

HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BNO_3$ $[M+H]_+$ 258.1301, found 258.1300.

Meta-borylation of 3-methylbenzaldehyde (3r):

The *meta*-borylated 3-methylbenzaldehyde was prepared as described in the general procedure using 3-methylbenzaldehyde (120.1 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 194.0 mg of **3r** (79%) as colourless liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.01 (s, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 2.43 (s, 3H), 1.36 (s, 12H).

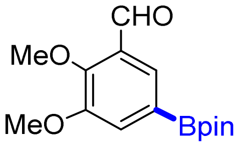
^{13}C NMR (100 MHz, CDCl$_3$): δ 192.9, 141.7, 138.4, 136.1, 134.9, 131.7, 84.4, 25.0, 21.2.

^{11}B NMR (128 MHz, CDCl$_3$): δ 32.4.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}BO_3$ [M+Na]$^+$ 269.1325, found 269.1314.

Meta-borylation of 2,3-dimethoxybenzaldehyde (3s):

The *meta*-borylated 2,3-dimethoxybenzaldehyde was prepared as described in the general procedure using 2,3-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol). After completion (judged by GC), THF was removed under reduced pressure and chromatographic separation with silica gel (chloroform as eluent) gave 268.7 mg of **3s** (92%) as colourless liquid.



^{1}H NMR (400 MHz, CDCl$_3$): δ 10.38 (s, 1H), 7.87 (s, 1H), 7.51 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 1.30 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 190.2, 154.8, 152.4, 129.2, 126.9, 123.5, 84.2, 62.2, 56.2, 24.9.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.0.

HRMS (ESI) *m/z* calcd for $C_{15}H_{21}BO_5$ [M+Na]$^+$ 315.1380, found 315.1375.

References:

1.(a) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

2. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

3. (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem.–Eur. J.* **2010**, *16*, 8155.

4. For a recent review of functional group directed borylation, see: Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229.

5. (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (c) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (d) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855. (e) Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (f) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (g) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134.

6. Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792.

7. Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

8. (a) Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Cho, J. Y.; Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **2000**, *122*, 12868. (c) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305. (d) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539.

9. For aromatic ketones borylation, see: Itoh, H.; Kikuchi, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2011**, *40*, 1007.

10. For secondary interaction directed *meta* -selective C–H borylation, see: Kuninobu, Y.; Ida, H.; Nishi, M., Kanai, M. *Nat. Chem.* **2015**, *7*, 712.

11. (a) Tomohiro, K.; Hideto, F.; Katsumi, K.; Shigeru, K. *PCT Int. Appl.* WO 2010110400, **2010**. (b) Takeshi, K.; Hiroshi, N.; Tomoko, I.; Mitsukane, Y.; Kensei, Y. *Jpn. Kokai Tokkyo Koho*, JP 2010173974, **2010**.

12. Matterson, D. S.; Talbot, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 1123.

13. For Ir-catalyzed nitrogen directed *ortho*-borylation, see: (a) Ros, A.; Estepa, B.; Lopáez-Rodríguez, R.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (b) Lopáez-Rodríguez, R.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 9915. (c) Ros, A.; Lopáez-Rodríguez, R.; Estepa, B.; Àlvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

14. For Rh-catalyzed nitrogen directed *ortho*-borylation, see: Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.

15. For aromatic imine-directed *ortho*-borylation, see: Sasaki, I.; Amou, T.; Ito, H.; Ishiyama, T. *Org. Biomol. Chem.* **2014**, *12*, 2041.

16. For imine-directed *ortho*-silylation, see: (a) Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149. (b) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *Dalton Trans.,* **2003**, 236.

17. The *o*-BpinC6H4CHO can easily be distinguished by the ~ 0.6 ppm downfield shift of its CHO resonance in 1H NMR spectra due to hydrogen bonding to a Bpin O.

18. The mechanism of the *ortho* C–H bond activation/borylation of aldehydes via in situ generated imines is related to the analogous ortho borylation of hydrazones as reported by Fernández-Lassaletta.13a

19. (a) Das, S.; Incarito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (b) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781. (c) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535.

20. For encapsulation of iridium species, which is facilitated via an electrostatic interaction, see: ref. 19b.

21. (a) For example of H-bonding of imine, see: Ligtenbarg, A. G.; Hage, R.; Meetsma, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 2*, **1999**, 807. (b) For H-bond directed ortho borylation, see: Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, Jr., R. E.; Smith, M. R., III *J. Am. Chem. Soc.* **2012**, *134*, 11350.

22. Isolation of the 3h was failed due to the elimination of the Boc group during silica gel column chromatography, it was isolated as 3g.

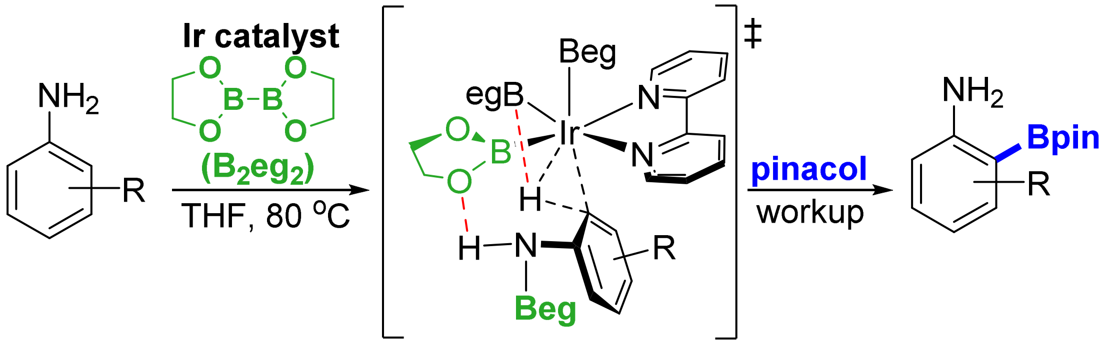
23. Lopáez-Rodríguez, R.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 9915.

24. Farahnaz, N.; Gholami, M. D. *Lett. Org. Chem.* **2012**, *9*, 720.

25. Miyaji, T.; Braun, T. J.; Guillaume, M.; Kim, Y.-K. *PCT Int. Appl. WO 2013-EP69300,* **2014**.

Chapter 3

Achieving high ortho-selectivity in aniline C–H borylations by modifying boron substituents



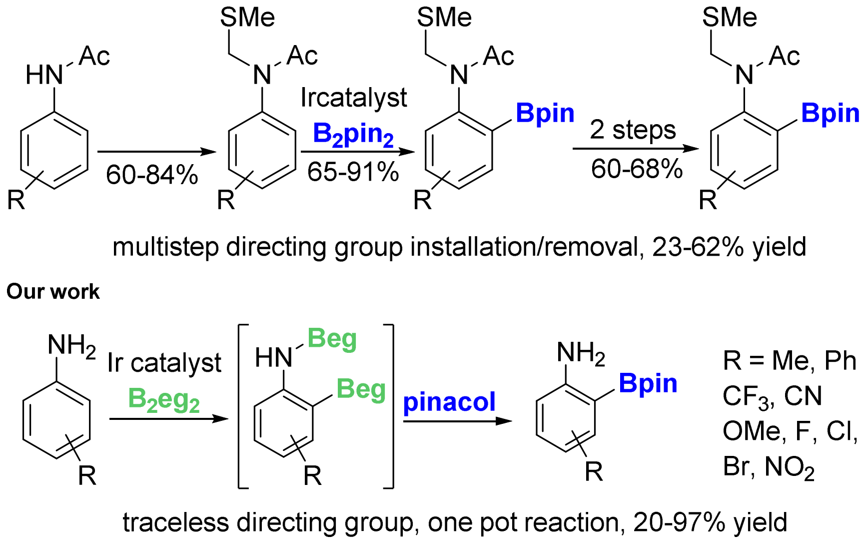
Objective: To probe the role played by H-bonding interaction to achieve the target of regioselective *ortho* C-H borylation of aniline and heterocycles.

Discussion:

Anilines are basic building block in dyes, pharmaceutical, agrochemical, and polymers.[1] Commercial preparation of aniline is by benzene nitration followed by hydrogenation. Derivatization of aniline through electrophilic aromatic substitution (EAS)[2] generates most commercially available substituted anilines. Even though the NH_2 group is a strong *ortho/para* director,[3] traditional nitration conditions gives major *para* isomer accompanied with 32–49% *meta*-nitroaniline. For EASs unsubstituted aniline gets functionalized at typically C4 position, for *ortho*-selective functionalization substitution at C4 position is necessary. Conventionally aniline *ortho* functionalization is best accomplished by masking it with carbamate functionality then carrying out directed *ortho* metalation (*DoM*) of carbamate[4] derivatives, this approach requires installation and removal of directing group. Undoubtedly directed *ortho* metalation is a powerful[5] approach yet catalytic methods that can render complementary selectivities and exhibits high functional group compatibility[6] are desirable. Several existing examples of catalytic *ortho* functionalizations of aniline requires protection and deprotection chemistry.

Transition metal catalyzed C-H borylation is a synthetic methodolgy that transforms sp^2, sp^3 and sp C-H bonds into versatile C-B bonds.[7,8,9] Site-selectivity in C-H borylation is governed by sterics, thus, to achieve regioselective *ortho*-borylation functional group directed approach for *ortho* C-H borylation has been developed which can be classified into three categories such as: i) chelate-directed[10] *ortho*-borylation, where a directed metallation group bearing substrate coordinate to the metal to create a 16 electron intermediate containing an empty coordination site that can assist the cleavage of an *ortho* C–H bond from 14 electron intermediate,; ii) a relay directed[11] *ortho*-borylation, where a reversible attachment of substrate to the metal takes place through sigma-bond metathesis; and iii) an outer-sphere-directed[12] *ortho*-borylation (Lewis acid-base,[13,14,15] hydrogen bonding[12,16,17] controlled and electrostatically[18] directed) where recognition of functionality of the substrate occurs by the ligand present on the catalyst and metal centre is not a directing element.[19,20] In an electrostatic mechanism for *ortho*-borylation, there is only a subtle variation from that of ion-pairing mechanism proposed by Phipps[21] and coworkers for *meta*-selective C-H borylations, whereas in other *meta*-selective borylation, outer sphere mechanism governs selectivity.[13,17,22] There also exists an example where both inner- and outer-sphere mechanisms are probable.[23]

The recently disclosed *ortho* C-H borylations of phenol and aniline derivatives by Kanai and Kuninobu[15] provides excellent *ortho* selectivities but the necessary requirement of thiomethyl methylene and acyl groups on N and ligand synthesis[24] prior to reaction makes it somewhat unappealing (**Scheme 3.1**).



Scheme 3.1. Comparison of Kanai-Kuninobu C-H borylation of N-Acylated Anilines to Our work

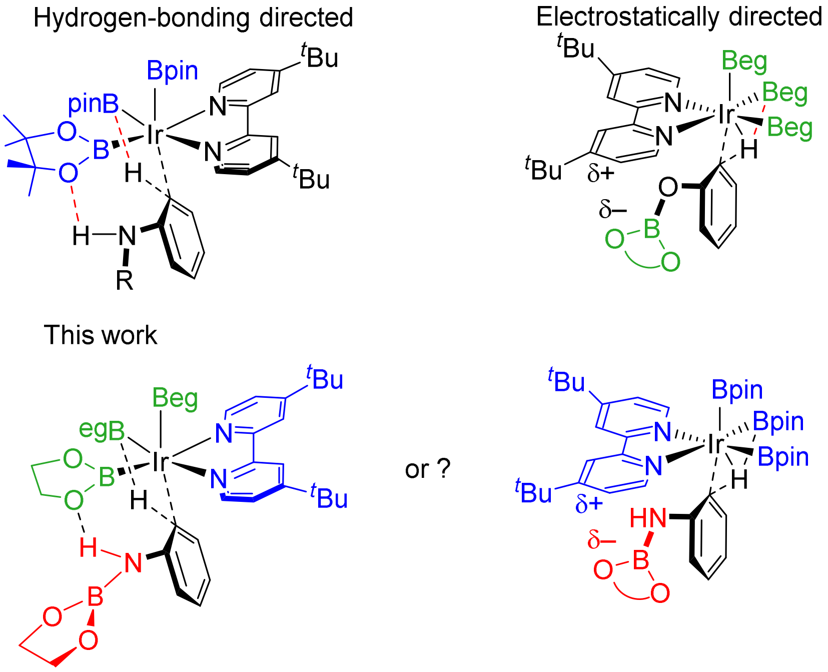
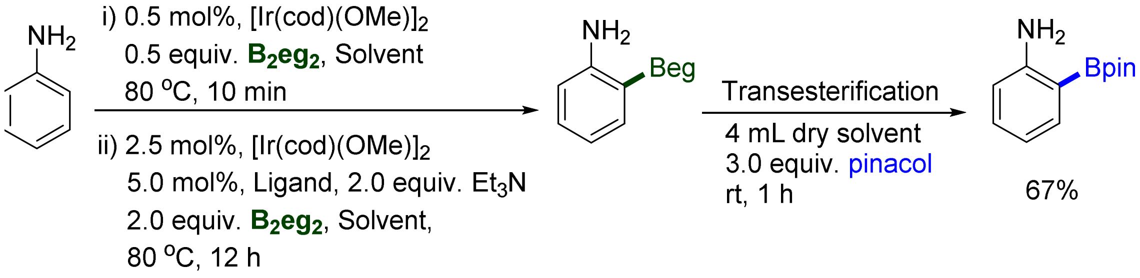


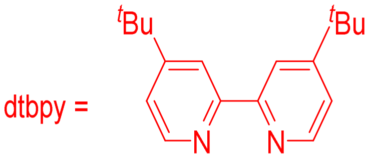
Fig 3.1. Proposed transition states for *ortho* borylations of anilines and phenols

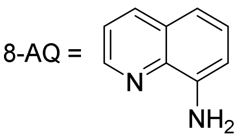
Recently regioselective *ortho*-borylation of phenols[18] was reported. Experimental and computational studies indicates an electrostatic interaction between bipyridine bound to Ir and OBpin of protected phenol. However, the requirement of 4-substituents larger than H limits its utility. While closer inspection of calculated transition states revealed significant distortion of transition state containing Bpin group, augmented *ortho*-selectivity was attained on replacing B_2pin_2 by sterically less demanding B_2eg_2. This poses questions whether selectivies for *ortho* borylation of aniline could also be improved using B_2eg_2 and will transition state stabilization in case of anilines also occur by electrostatic interactions or by H-bonding (**Fig 3.1**). Experimental and theoretical work done in this present work resolves these questions.

Table 3.1. Evaluation for the *ortho* C–H borylation conditions



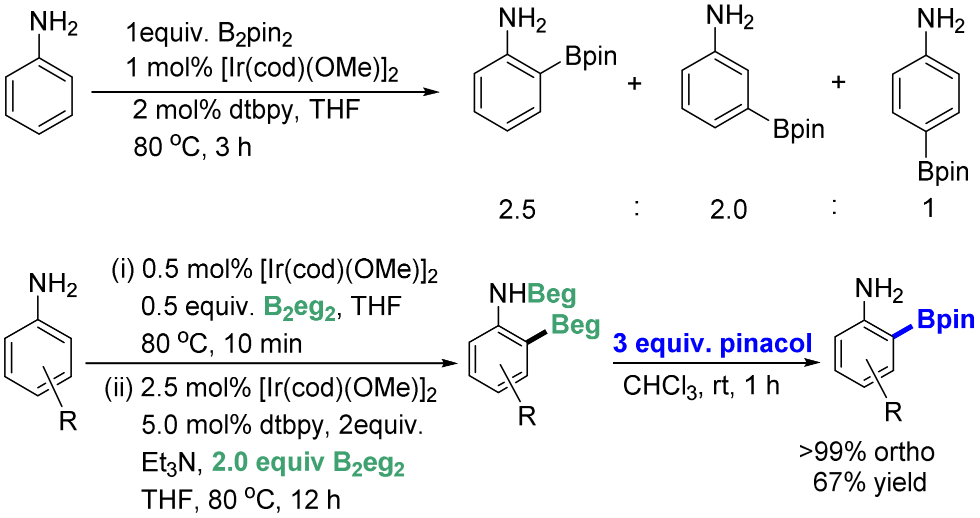
#	Solvent	Ligand	Transesterification Solvent	GC-MS conversion (%)
1	CyH	dtbpy	Toluene	No reaction
2	Toluene	dtbpy	Toluene	70
3	Toluene	8-AQ	$CHCl_3$	No reaction
4	CyH	8-AQ	$CHCl_3$	No reaction
5	THF	8-AQ	$CHCl_3$	No reaction
6	THF	dtbpy	Toluene	98
7	**THF**	**dtbpy**	**$CHCl_3$**	**100 (67%)**





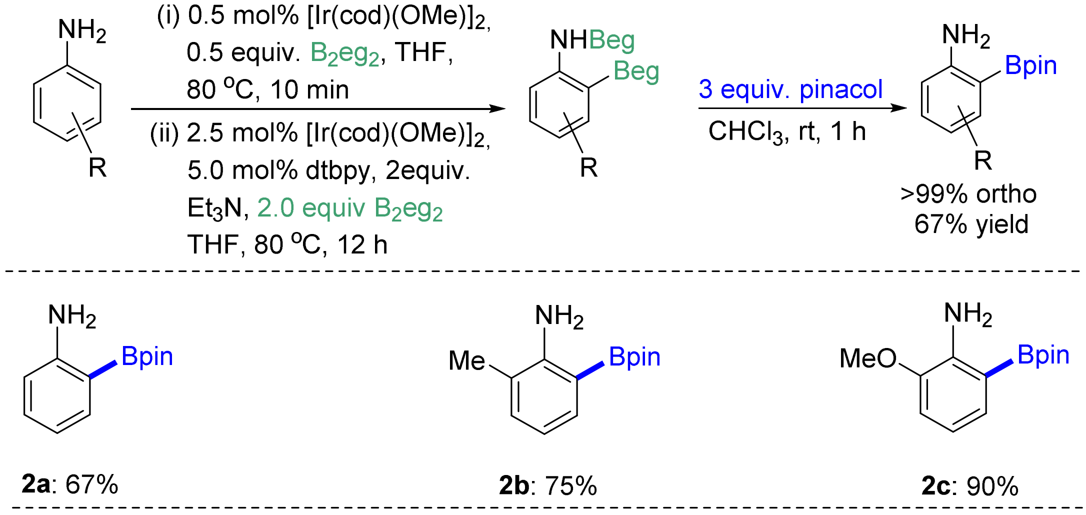
For optimization of Ir-catalyzed *ortho*-borylation of aniline, various conditions as mentioned in **Table 3.1** were screened. Finally, a THF solution of aniline, 0.5 mol% $[Ir(cod)(OMe)]_2$ and 0.5 equiv. B_2eg_2 was heated for 10 min. for complete protection of aniline NH to form PhN(H)Beg. Then 2.5 mol% $[Ir(cod)(OMe)]_2$, 5 mol% dtbpy, 2 equiv. each of B_2eg_2 and Et_3N, heated at 80 °C until borylation completed, this condition yielded best results. After completion of borylation, transesterification of Beg group, more stable Bpin product was obtained in 67% yield. Comparison of regioselectivites for aniline C-H borylation with B_2eg_2 and B_2pin_2 is done in **Scheme**

3.2. Remarkably with B_2eg_2 immaculate *ortho*-selectivity was observed, producing exclusively *ortho* isomer in contrast the ratio for Ir-catalyzed borylation of aniline with B_2pin_2 is 2.7:1.8:1 *ortho*:*meta*:*para*. Next substituted anilines were examined under optimized conditions, reactions were performed in 0.5 mmol scale. When the borylation was performed on 5 mmol scale using 0.25 and 0.75 mol% of catalyst in steps (i) and (ii) (in experimental part under large scale ortho-borylation of aniline), 75% isolated yield of *ortho*-borylated product was obtained.



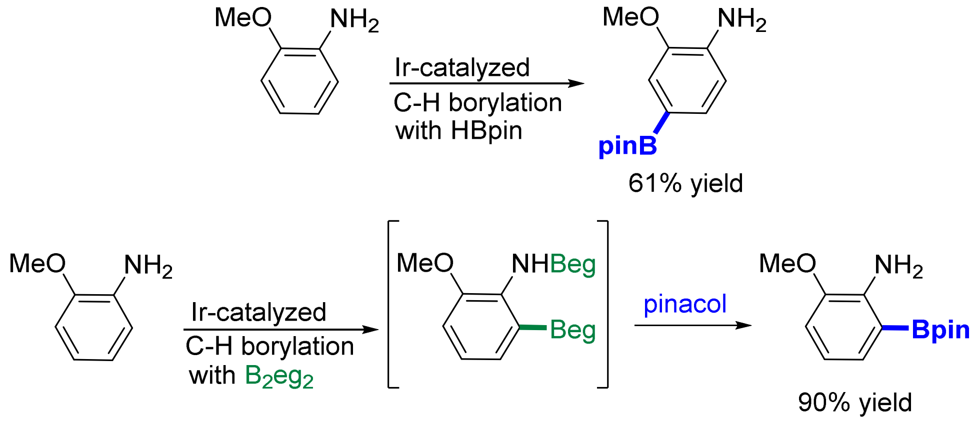
Scheme 3.2. Analogy of C-H borylation of aniline with B_2eg_2 and B_2pin_2

While examining substrate scope it was observed that the present work overcomes the limitation that was existing in previous approaches of aniline *ortho*-borylation that 2-substituted aniline without a blocking group at 4-position were not compatible. Gratifyingly *ortho*-selectivity did not get eroded with *ortho*-substituted anilines instead the *ortho*-borylated products are obtained with excellent regioselectivity and good yields (**Scheme 3.3**).



Scheme 3.3. ***Ortho*-borylation of substituted anilines with B_2eg_2**

Different selectivities are obtained in C-H borylation with Bpin and Beg ligands on Ir which is highlighted in **Scheme 3.4**. An elegant example which showcases the hallmark of this developed methodology for *ortho*-borylation of aniline is exhibited by 2-methoxyaniline which under Ir-catalyzed borylation with HBpin yields regioselectively 4-borylated isomer, in contrast it afforded exclusively *ortho*-borylated product using modified boron reagent B_2eg_2 as traceless directing group as well as boron source under Ir-catalyzed reaction.



Scheme 3.4. Comparison of regioselective outcome of C-H borylation of anilinewith Bpin and Beg reagents

In summary in Ir-catalyzed C-H borylations of anilines, the substituents on Ir-boryl ligands have significant impact on selectivity, consequently on switching boron reagent from B_2pin_2 which gave regioisomeric mixture with anilines without a blocking group at 4-position to less sterically encumbered B_2eg_2 yielded highly *ortho*-selective borylated product. Moreover high yields and selectivities are obtained for 2- and 3-substituted anilines as well. ^1H NMR experiments confirms ArylN(H)Beg species generation prior to C-H borylation and good yields are now possible for various anilines, including those with groups at the 2 and 3-positions. DFT computational analyses corroborate H-bonding interactions (N-H$\cdots$O) between ArylN(H)Beg and O atoms of sterically less demanding Beg ligands and enables the enhancement in *ortho* selectivity. ^1H NMR experiments show that N-borylation fully generates PhN(Me)Beg prior to CHB. The *ortho* TS where the Beg unit is oriented anti to the bipyridine ligand TS has the lowest Gibb's energy.

Experimental:

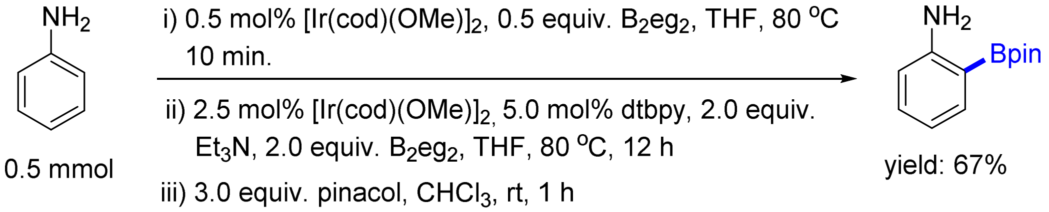
All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBPin) and bis(pinacolato)diboron (B_2Pin_2) were procured from Sigma-Aldrich and A. K. Scientific respectively and used directly. B_2eg_2 was produced as previously reported from $B_2(OH)_4$ and ethylene glycol.[16] 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). All borylations were conducted in an argon-filled glovebox, unless otherwise stated.

^{1}H, ^{13}C, and ^{11}B NMR spectra collected at the Centre of Biomedical Research (CBMR, Lucknow) were recorded on Bruker 400 MHz NMR spectrometers. ^{1}H, ^{13}C, and ^{11}B NMR spectra collected at Michigan State University were recorded on Varian 500 MHz NMR spectrometers. The boron bearing carbon atom was not observed due to quadrupolar relaxation. 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, ttt = triplet of triplet of triplet). 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+). GCMS (Agilent Technology) was obtained from Centre of Biomedical Research.

Evaluation for the *ortho* C–H borylation conditions:

In a glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (1.65 mg, 0.5 mol%), B_2eg_2 (35.5 mg, 0.5 equiv.), aniline (**1a**) (46.6 mg, 0.5 mmol) dry solvent (CyH, PhMe, THF: 0.5 mL) and stirred on pre-heated aluminum block at 80 °C for 10 min. The microreactor was again charged with $[Ir(cod)(OMe)]_2$ (8.28 mg, 2.5 mol%), ligand 5.0 mol% (dtbpy: 6.71 mg; 8-AQ: 3.6 mg), B_2eg_2 (142.0 mg, 2.0 equiv.), Et_3N (139.0 µL, 2.0 equiv.) and dry solvent (1.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h, THF was removed under reduced pressure using dry transesterification solvent as transferring solvent. After which transesterification was performed using dry transesterification solvent (PhMe, $CHCl_3$: 4.0 mL) and pinacol (177.0 mg, 3.0 equiv.) and stirred at room temperature for 1 h. Removal of solvent under reduced pressure and chromatographic separation with silica gel gave *ortho*-borylated aniline.

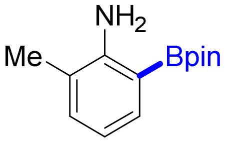
Ortho-borylation of aniline (2a):



In a glove box, a 5.0 mL wheaton microreactor was charged with $[Ir(cod)(OMe)]_2$ (1.65 mg, 0.5 mol%), B_2eg_2 (35.5 mg, 0.5 equiv.), aniline (**1a**) (46.6 mg, 0.5 mmol) dry THF (0.5 mL) and stirred on pre-heated aluminum block at 80 °C for 10 min. The microreactor was again charged with $[Ir(cod)(OMe)]_2$ (8.28 mg, 2.5 mol%), dtbpy (6.71 mg, 5.0 mol%), B_2eg_2 (142.0 mg, 2.0 equiv.), Et_3N (139.0 µL, 2.0 equiv.) and dry THF (1.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h, THF was removed under reduced pressure using dry $CHCl_3$ as transferring solvent. After which transesterification was performed using dry $CHCl_3$ (4.0 mL) and pinacol (177.0 mg, 3.0 equiv.) and stirred at room temperature for 1 h. Removal of solvent under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane as eluent) gave 73.4 mg of *ortho*-borylated aniline (67%) as a liquid. Spectral data are in accordance with the reported data.[25]

Ortho-borylation of 2-methylaniline (2b):

The *ortho*-borylated 2-methylaniline is prepared following the procedure used for the preparation of compound 2a using 2-methylaniline (**1b**) (53.58 mg, 0.5 mmol). Removal of solvent under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane as eluent) gave 87.4 mg of *ortho*-borylated 2-methylaniline (75%) as a white solid (mp = 44-45 °C).



^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.77 (bs, 2H), 2.14 (s, 3H), 1.35 (s, 12H).

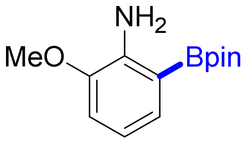
^{13}C NMR (100 MHz, CDCl$_3$): δ 151.8, 134.7, 133.7, 121.4, 116.8, 83.5, 24.9, 17.5.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.2.

HRMS (ESI) *m/z* calcd for $C_{13}H_{20}BNO_2$ $[M+H]^+$ 234.1665, found 234.1662.

Ortho-borylation of 2-methoxyaniline (2c):

The *ortho*-borylated 2-methoxyaniline is prepared following the procedure used for the preparation of compound 2a using 2-methoxyaniline (**1c**) (61.6 mg, 0.5 mmol). Removal of solvent under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane as eluent) gave 112.0 mg of *ortho*-borylated 2-methoxyaniline (90%) as a white solid (mp = 102-103 °C).



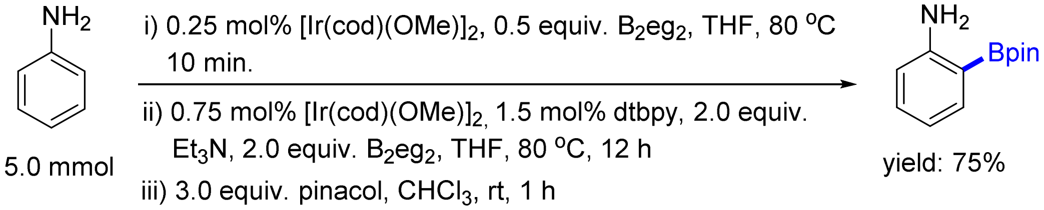
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.22 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 4.97 (bs, 2H), 3.84 (s, 3H), 1.34 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 146.4, 143.9, 128.0, 116.2, 112.8, 83.5, 55.5, 24.9.

^{11}B NMR (128 MHz, CDCl$_3$): δ 31.0.

HRMS (ESI) *m/z* calcd for $C_{13}H_{20}BNO_3$ $[M+H]^+$ 250.1614, found 250.1612.

Large scale *ortho*-borylation of aniline:



Lower Catalyst loading
Total Ir: 0.5+1.5 = 2.0 mol%

In a glove box, a 15 mL pressure tube was charged with $[Ir(cod)(OMe)]_2$ (8.3 mg, 0.25 mol %), B_2eg_2 (355 mg, 0.5 equiv.), aniline (465.6 mg, 5.0 mmol), dry THF (5.0 mL) and stirred on a preheated oil bath at 80 °C for 10 min. The pressure tube was charged again with $[Ir(cod)(OMe)]_2$ (24.86 mg, 0.75 mol %), dtbpy (20.13 mg, 1.5 mol %), B_2eg_2 (1.42 g, 2.0 equiv.), Et_3N (1.39 mL, 2.0 equiv.) and dry THF (6.0 mL). The pressure tube was capped with a teflon pressure cap and placed into a preheated oil bath at 80 °C. After 12 h, THF was removed under reduced pressure using dry $CHCl_3$ as transferring solvent and transesterification was performed using dry $CHCl_3$ (10.0 mL) and pinacol (1.77 g, 3.0 equiv.) at room temperature for 1 h. Removal of solvent under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane as eluent) gave 821 mg of *ortho*-borylated aniline (75%) as a solid. Spectral data are in accordance with the reported data.[25]

References:

1. Travis, A. S. In The Chemistry of Anilines; John Wiley & Sons, Ltd, 2007; pp 715–782.

2. Berliner, E. Electrophilic Aromatic Substitution Reactions. *Prog. Phys. Org. Chem.* **1964**, *2*, 253.

3. Clayden, J.; Greeves, N.; Warren, S. Organic Chemistry; Oxford University Press, 2012.

4. Takagishi, S.; Katsoulos, G.; Schlosser, M. *Synlett* **2002***, 1992*, 360.

5. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed Engl.* **2004**, *43*, 2206.

6. Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J.-C.; Batsanov, A. S.; Marder, T. B.; Snieckus,V. *Chem. Eur. J.* **2010**, *16*, 8155.

7. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890.

8. Hartwig, J. F. *Acc. Chem. Res*. **2012**, *45*, 864.

9. Lee, C.-I.; Zhou, J.; Ozerov, O. V. *J. Am. Chem. Soc*. **2013**, *135*, 3560.

10. For selected examples, see: (a) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, ***131***, 5058; (b) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159; (c) Ros, A.; Estepa, B.; Lopez-Rodriguez, R.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11724.

11. (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534; (b) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

12. For the concept of the outer-sphere direction, see: (a) Taube, H.; Posey, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 1463. For the first example of the outer-sphere directed *ortho*-borylation, see: (b) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2012**, *134*, 11350.

13. Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc*. **2016**, *138*, 84.

14. Li, H. L.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed Engl*. **2017**, *56*, 1495.

15. Li, H.-L.; Kanai, M.; Kuninobu, Y. *Org. Lett*. **2017**, *19*, 5944.

16. Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E., Jr.; Smith, M. R., III. *Angew. Chem. Int. Ed*. **2013**, *52*, 12915.

17. Davis, H. J.; Genov, G. R.; Phipps, R. J. *Angew. Chem. Int. Ed*. **2017**, *56*, 13351.

18. Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E., Jr; Singleton, D. A.; Smith, M. R., III. *J. Am. Chem. Soc*. **2017**, *139*, 7864.

19. Davis, H. J.; Phipps, R. J. *Chem. Sci*. **2017**, *8*, 864.

20. Haldar, C.; Hoque, E.; Bisht, R.; *Tetrahedron Lett*. **2018**, *59*, 1269.

21. Davis, H. J.; Mihai, M. T.; Phipps, R. J. *J. Am. Chem. Soc*. **2016**, *138*, 12759.

22. Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem*. **2015**, *7*, 712.

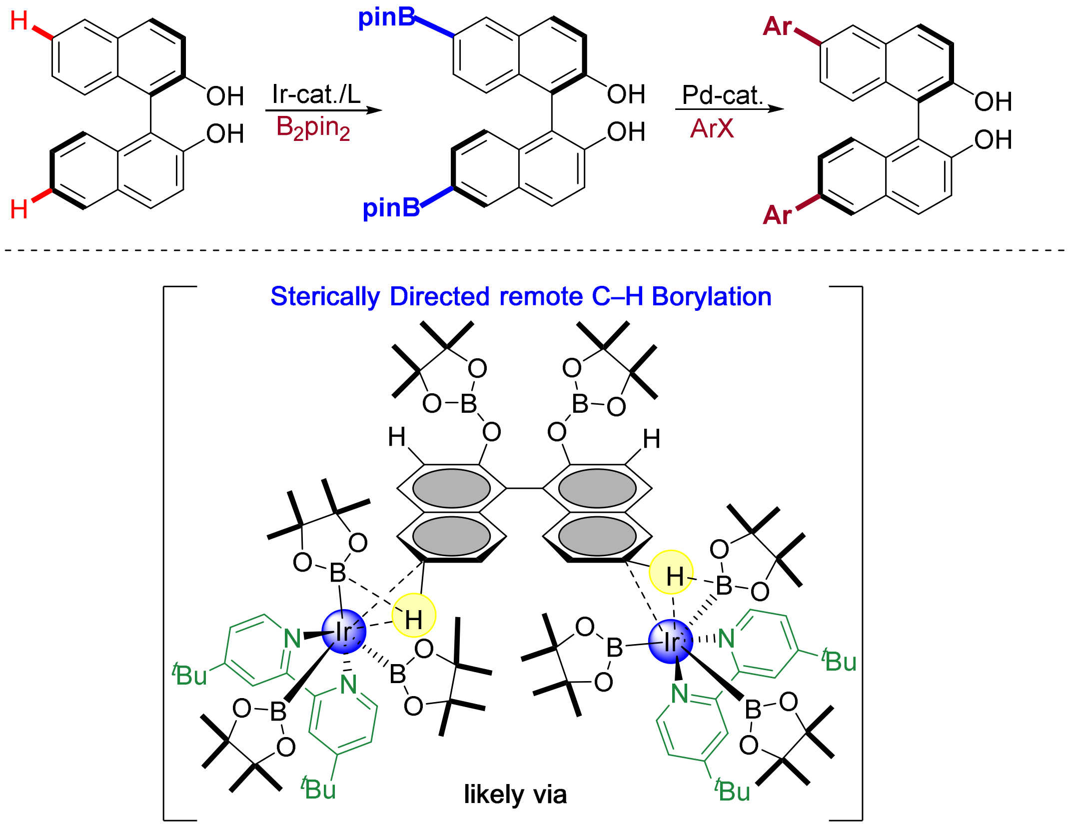
23. Yamamoto, T.; Ishibashi, A.; Suginome, M. *Org. Lett*. **2017**, *19*, 886.

24. The ligand for the Kanai-Kuninobu ortho CHB of aniline is prepared via a Suzuki cross-coupling of 5-bromo-2,2´-bipyridine ($14,000/mol) with 1-Bpin-4-(trifluoromethyl)benzene ($870/mol) in 73% yield. B2pin2 ($50/mol) is the borylating agent. Prices are the lowest per mole values of all commercial sources listed by SciFinder Scholar on 02/01/18.

25. Kong, C.; Driver, T. G. *Org. Lett*. **2015**, *17*, 802.

Chapter 4

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



likely via

TS-1

Objective: To achieve the target of remote diborylation and arylation of BINOL by manipulating catalyst-ligand-substrate interaction.

Discussion:

A double-fold remote C–H activation and borylation of BINOL is described, which proceeds via an sterically directed C–H activation mechanism. The developed strategy was successfully combined with Suzuki cross-coupling as one-pot way for the rapid synthesis of a variety of useful optically pure BINOL derivatives. It has been shown that (R)-BINOL retains its chirality during borylation and Suzuki cross coupling.

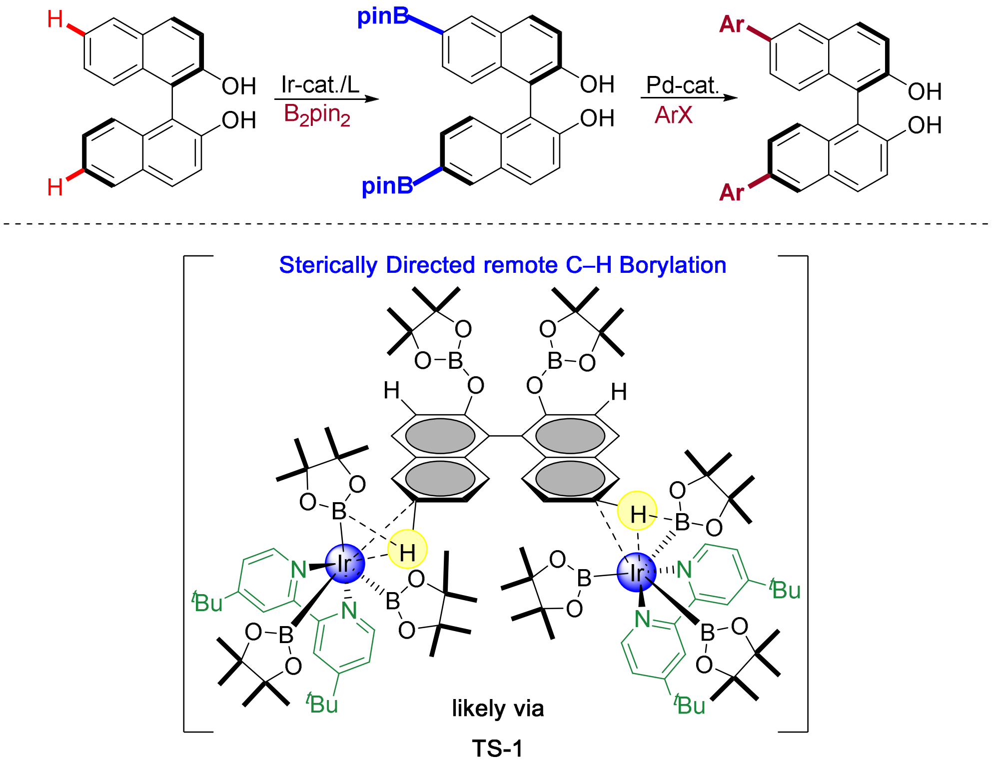
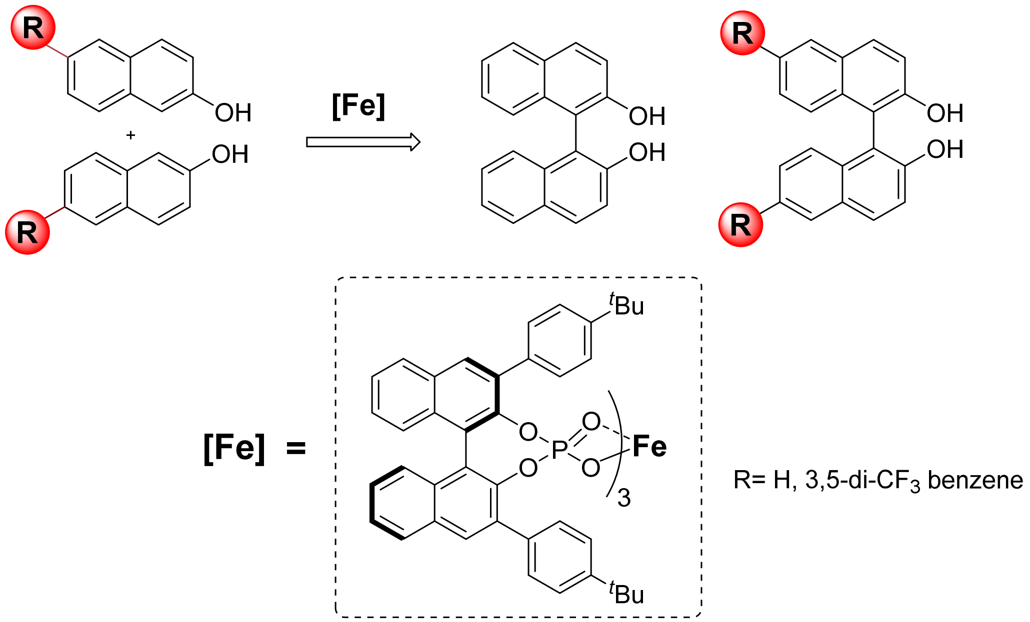


Fig 4.1. Probable transition state for remote diborylation

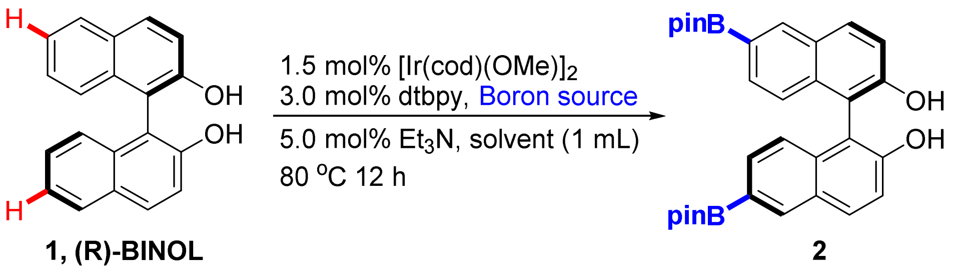
Literature precedences reveal that synthesis of enantioenriched 3,3′-disubstituted and 7,7′-disubstituted BINOLs have been achieved by chiral copper,[1] iron,[2] and dinuclear vanadium[3] catalysts. On the other hand synthesis of chiral 6,6′-disubstituted BINOL scaffold remained an unmet discovery. Pappo and their workers[4] have accomplished the synthesis of chiral 6,6′-disubstituted BINOL and unsubstituted BINOL employing chiral iron phosphate complex which follows an oxidative radical-anion coupling mechanism as shown in **Scheme 4.1**.



Scheme 4.1. Enantioselective oxidative coupling of 2-naphthols by chiral iron phosphate complex [Fe]

We envisaged that whether outcome of borylation of BINOL can be made regioselective upon employing the sterically demanding boron reagent B_2pin_2 (**Fig 4.1**). By varying amount of HBpin used for the generation of OBpin intermediate we got optimised condition. In the optimised condition a THF solution of (R)-BINOL, 3.0 equivalent of HBpin and 5.0 mol% of triethylamine was stirred at 60 ^{o}C for an hour to ensure the complete generation of the OBpin intermediate. To this, 1.5 mol% Ir-catalyst, 3.0 mol% dtbpy, 2.5 equiv of B_2pin_2 and THF was added and the resulting mixture was heated at 80 ^{o}C for 16 h. The screening results are summarized in **Table 4.1**.

Table 4.1. Evaluation for the remote C–H borylation conditions: General Procedure[a]



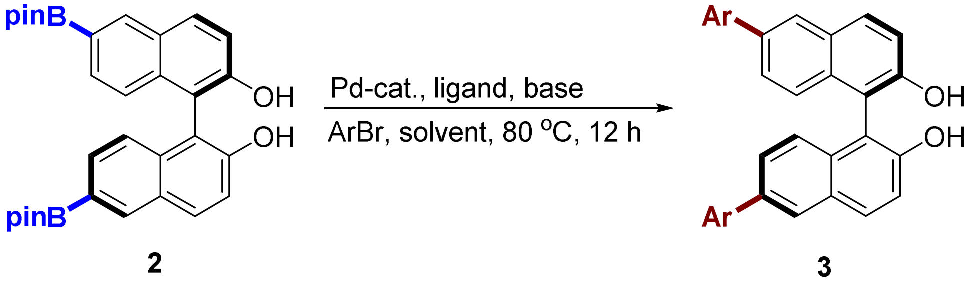
#	HBpin	B_2pin_2	Solvent	Conversion (%)
1	4.0 equiv.	-	THF	complex mixture
2	-	2.0 equiv.	THF	complex mixture
3[b]	2.5 equiv.	2.0 equiv.	PhMe	solvent borylation
4[b]	2.5 equiv.	2.0 equiv.	CyH	multiple borylation
5[b]	2.5 equiv.	2.0 equiv.	THF	44%
6[b]	3.0 equiv.	2.5 equiv.	THF	95% (87%)[c]

[a] Reactions were conducted with 0.1 mmol scale and conversion are based on crude NMR analysis. [b] In this case, sequence of addition is important [c] In parentheses, isolated yields are reported; 16 h.

To this end, we turned our attention towards the optimization of the Suzuki cross-coupling reaction and the results are shown in **Table 4.2**. We first examined the Suzuki coupling of 6,6'-diborylated BINOL with 3,5-bis(trifluoromethyl)-1-bromobenzene employing 5 mol% $Pd(PPh_3)_4$ catalyst, K_2CO_3 as a base in PhMe/H_2O mixed solvent at 80 °C (**Table 4.2**, entry 1).

However, no formation of the desired cross-coupling product was observed. Use of other bases and solvents were not effective (entries 2-3. On the other hand, employment of Clark's conditions[5] (entry 4) with *o*-tolylphosphine ligand, it gave a slightly better conversion (85%). But, when the reaction was performed in presence of $PdCl_2$•dppf•CH_2Cl_2 and aqueous Na_2CO_3 in dioxane/DME solvent, it afforded the desired product in 90% conversion based on the crude NMR analysis (entry 5)

Table 4.2. Optimization for the Suzuki cross coupling reaction: General Procedure[a]



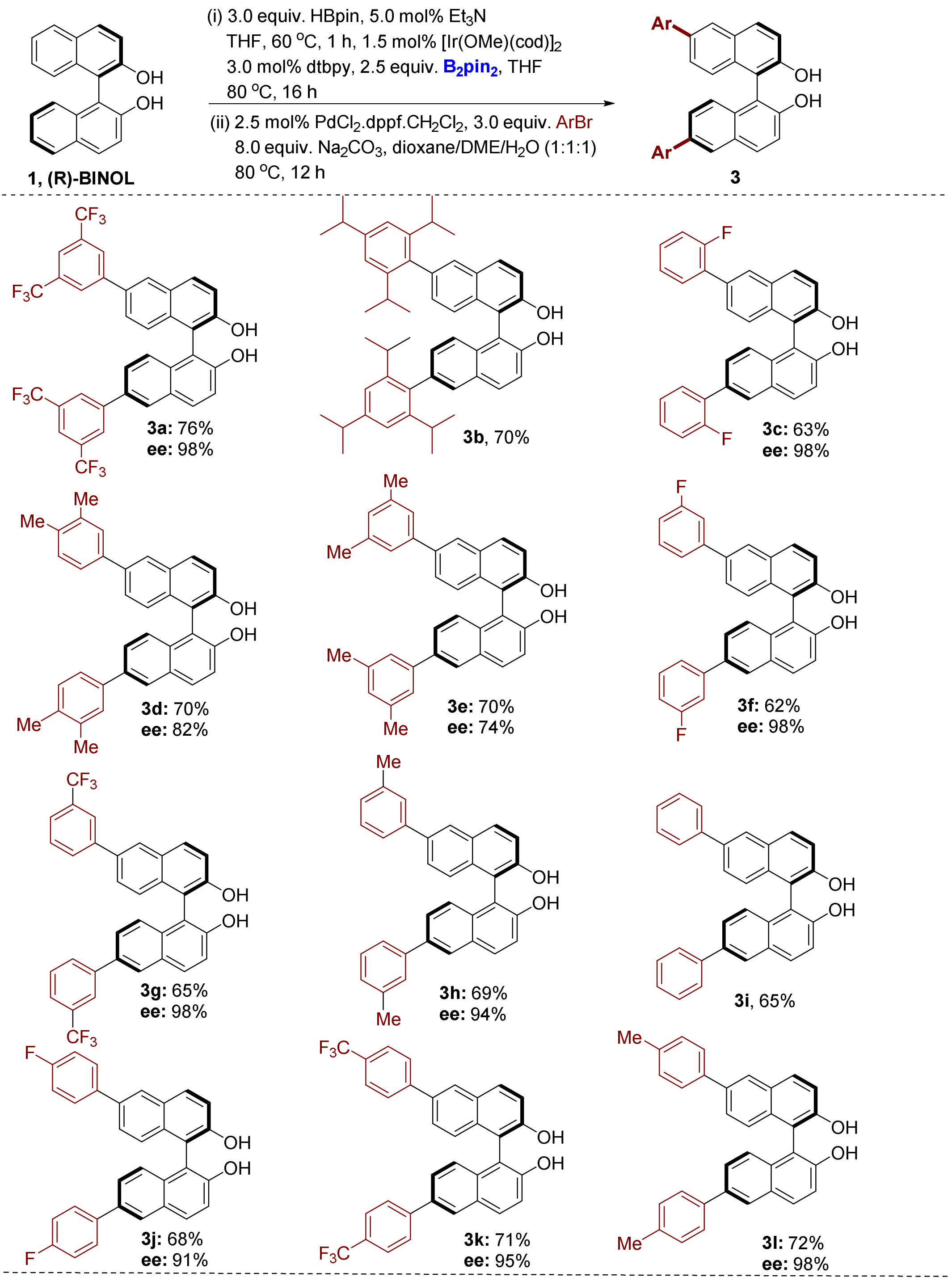
ArBr = 3,5-bis(trifluoromethyl)-1-bromobenzene

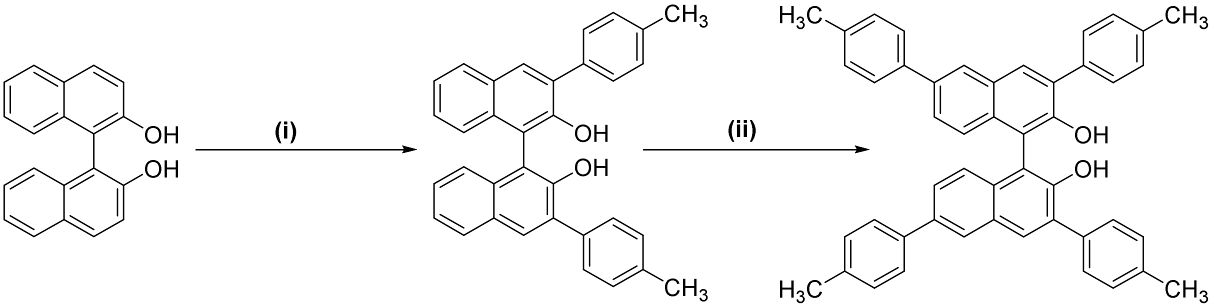
#	Catalyst (mol%)	Ligand (mol%)	Base (eq.)	Solvent	Conv. (%)[b]
1	5% $Pd(PPh_3)_4$	-	K_2CO_3 (2)	$PhMe/H_2O$ (6/1)	nr
2	5% $Pd(PPh_3)$	-	K_2CO_3 (2)	DME/H_2O (1/1)	nr
3	5% $Pd(PPh_3)_4$	-	CsF (3)	THF/H_2O (10/1)	nr
4	2% $Pd_2dba_3.CHCl_3$	4% P(o-tolyl)$_3$	K_2CO_3 (8)	THF/H_2O (10/1)	85
5	**2.5% $PdCl_2dppf.CH_2Cl_2$**	**-**	**Na_2CO_3 (8)**	**dioxane/DME/H_2O (1/1/1)**	**90 (79)[c]**

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

With these optimized conditions various electronically different coupling partners were screened which afforded remote difunctionalized product with good yield and moderate to high enantioselectivity. Gratifyingly, various coupling partners regardless of what substituent present in the aryl ring of the coupling partners, afforded decent amount of the isolated yields of the products under the combined one-pot borylation and Suzuki-coupling reaction. For example, electron-rich disubstituted arylbromides 3,5-dimethyl-1-bromobenzene (**3es**) and 3,4-dimethylbromobenzene (**3ds**) afforded 70% and 70% yields respectively. Electronically neutral simple bromobenzene (**3is**), electron-deficient and electron-rich *para*-substituted arylbromides such as, 4-bromofluorobenzene (**3js**), 4-trifluoromethylbromobenzene (**3ks**) also smoothly underwent the borylation/Suzuki reaction to give coupling product. *Meta*-substituted arylbromides containing both the electron donating group and electron-withdrawing groups (**3hs,3fs**) also compatible under the developed reaction conditions. Moreover 2-substituted arylbromides (**3cs**) were also found to be efficient as shown in **Table 4.3**.

Table 4.3. Substrate scope of remote C-H borylation/Suzuki reaction





Scheme 4.2. Sequential double-fold *ortho* and remote borylation and arylation of BINOL:

Conditions: (i) 2.0 mol% Ir, 4.0 mol% dtbpy, 4.0 eq. B_2eg_2, 4.0 eq. Et_3N, THF, 80 ^oC, 12 h; then, 2.5 mol% $PdCl_2$•dppf•CH_2Cl_2, 3.0 eq. 1-bromo-4-methyl benzene, 8.0 eq. Na_2CO_3, dioxane/DME/H_2O (1/1/1), 80 ^oC, 12 h.

Conditions: (ii) 3.0 equiv. HBpin, 5.0 mol% Et_3N, THF, 60 ^oC for 1 h, then, 1.5 mol% Ir, 3.0 mol% dtbpy, 2.5 equiv. B_2pin_2, THF, 80 ^oC, 16 h; then, 2.5 mol% $PdCl_2$•dppf•CH_2Cl_2, 3.0 eq. 1-bromo-4-methyl benzene, 8.0 eq. Na_2CO_3, dioxane/DME/H_2O (1/1/1), 80 ^oC, 12 h.

In conclusion, a double-fold C–H borylation of BINOL has been achieved at remote position. Regioselectivity of remote C-H actvation/ borylation is governed by sterics. Significant role is played by Bpin group which also acts as a traceless directing group. Suzuki cross-coupling subsequent to C-H borylation makes this protocol amenable for the development of chiral scaffold of various ligands and catalysts employed in asymmetric synthesis and organocatalysis.

Experimental:

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBPin), bis(pinacolato)diboron (B_2Pin_2), tetrahydroxydiboron were procured from A. K. Scientific. 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). 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 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, ttt = triplet of triplet of triplet). 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.

General procedure for optimization of remote C-H diborylation: In a glove box, a 5.0 mL wheaton microreactor was charged with (R)-BINOL (28.6 mg, 0.1 mmol), HBpin (36.2 μL, 2.5 equiv. for entries 3-5, 43.5 μL, 3.0 equiv. for entry 6, 58.0 μL, 4.0 equiv. for entry 1), dry solvent (THF; PhMe; CyH; 1.0 mL), $[Ir(cod)(OMe)]_2$ (1.0 mg, 1.5 mol%), dtbpy (0.8 mg, 3.0 mol%), B_2pin_2 (50.8 mg, 2.0 equiv. for entries 2-5, 63.5 mg, 2.5 equiv. for entry 6) and Et_3N (0.7 μL, 5 mol%). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C and the reaction mixture was stirred for 12 h. The results are summarized in the **Table 4.1**.

Isolation of bis-borylated compound 2: In a glove box, a 5.0 mL wheaton microreactor was charged with (R)-BINOL (28.6 mg, 0.1 mmol), HBpin (43.5 μL, 3.0

equiv.), Et_3N (0.7 μL, 5 mol%), dry THF (1.0 mL) and stirred at 60 °C for 1 h. $[Ir(cod)(OMe)]_2$ (1.0 mg, 1.5 mol%), dtbpy (0.80 mg, 3.0 mol%), B_2pin_2 (63.5 mg, 2.5 equiv.) and dry THF (1.0 mL) was then added. The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 16 h, solvent was evaporated and chromatographic separation with silica gel (*n*-hexane/ethylacetate = 2/1) gave 46.8 mg of 6,6'-bis (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-binaphthalene]-2,2'-diol **2** (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 2H), 8.03 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 1.2 Hz, J = 8.4 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 5.13 (s, 2H) 1.37 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 136.7, 135.2, 132.3, 132.2, 128.8, 123.3, 117.8, 110.7, 83.9, 24.9.

HRMS (ESI) *m/z* calcd for $C_{32}H_{36}B_2O_6$ $[M+H]^+$ 539.2776, found 539.2780.

General procedure for Suzuki cross coupling: The crude diborylated mixture was transferred in another 5.0 mL wheaton microreactor using appropriate volume of dry solvent (PhMe; DME; THF). In a glove box this microreactor was then charged with appropriate amount of catalyst ($Pd(PPh_3)_4$: 5.7 mg, 5 mol%; $PdCl_2$•dppf.CH_2Cl_2: 2.0 mg, 2.5 mol%; Pd_2dba_3•$CHCl_3$: 2.1 mg, 2 mol%), P(*o*-tolyl)$_3$ (1.2 mg, 4 mol%), appropriate amount of base (K_2CO_3: 27.6 mg, 2 equiv.; CsF: 45.5 mg, 3 equiv. ; Na_2CO_3: 84.8 mg, 8 equiv.; K_2CO_3: 110 mg, 8.0 equiv.) and 1-bromo-3,5-bis(trifluoromethyl)benzene (87.9 mg, 3.0 equiv.). Appropriate volume of degassed water was added outside the glove box. Then the microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h reaction mixture cooled to room temperature and extracted using ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. The results are summarized in the **Table 4.2**.

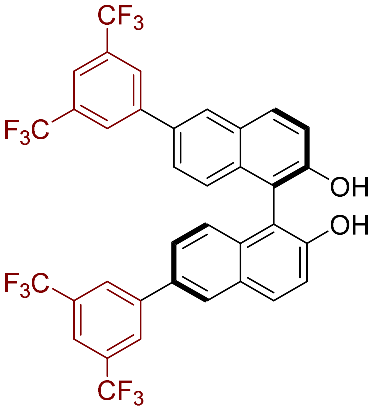
General procedure for one-pot diborylation/arylation:

In a glove box, a 5.0 mL wheaton microreactor was charged with (R)-BINOL (28.6 mg, 0.1 mmol), HBpin (43.5 μL, 3.0 equiv.), Et_3N (0.7 μL, 5 mol%), dry THF (1.0 mL) and stirred at 60 °C for 1 h. $[Ir(cod)(OMe)]_2$ (1.0 mg, 1.5 mol%), dtbpy (0.80

mg, 3.0 mol%), B_2pin_2 (63.5 mg, 2.5 equiv.) and dry THF (1.0 mL) was then added. The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 16 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 aryl bromide (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 pre-heated aluminum block at 80 °C. Then the microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h reaction mixture cooled to room temperature and extracted using ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. Solvent evaporated and chromatographic separation with silica gel gave diarylated product.

Remote C-H borylation/Suzuki reaction altering boron reagent:

*Synthesis of 6,6'-bis(3,5-bis(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol (**3a**)*:

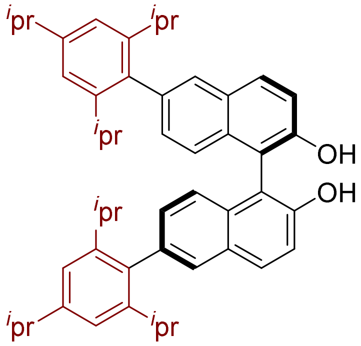


The diarylated product **3a** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3,5-bis(trifluoromethyl)benzene (87.9 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (15% ethyl acetate in hexane) gave 54.0 mg of 6,6'-bis(3,5-bis(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol **3a** (76%). Spectral data are in accordance with the reported data.[4]

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 18.67 min., t_R (minor) = 11.48 min., %ee = 98%.

Synthesis of 6,6'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (3b):

The diarylated product **3b** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-2,4,6-triisopropylbenzene (84.9 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (10% ethyl acetate in hexane) gave 48.3 mg of 6,6'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol **3b** (70%).



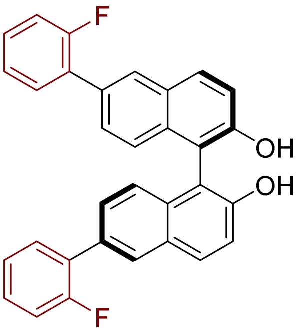
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.26-7.23 (m, 1H), 7.09 (d, J = 2.0 Hz, 2H) 5.19 (s, 1H), 2.97 (sep, J = 6.8 Hz, 1H), 1H), 2.70-2.61 (m, 2H), 1.33 (d, J = 6.8 Hz, 6H), 1.13 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 148.0, 146.82, 146.8, 136.6, 131.9, 131.4, 130.2, 129.3, 128.8, 123.7, 120.6, 117.9, 111.0, 34.3, 30.3, 24.4, 24.2, 24.1

HRMS (ESI) *m/z* calcd for $C_{50}H_{58}O_2$ $[M+NH_4]^+$708.4819, found 708.4794.

*Synthesis of 6,6'-bis(2-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol (**3c**)*:

The diarylated product **3c** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-2-fluorobenzene (52.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (12% ethyl acetate in hexane) gave 30.0 mg of 6,6'-bis(2-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol **3c** (63%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.56-7.50 (m, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.35-7.16 (m, 4H), 5.14 (br s, 1H).

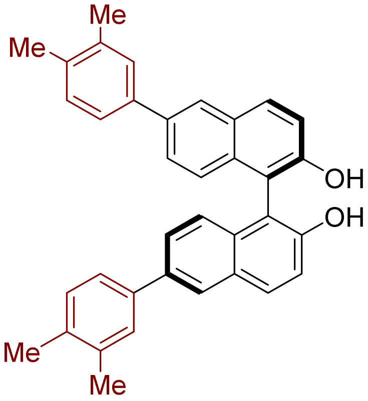
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 153.1, 132.7, 131.8, 131.6. 130.8 (d, J = 3.3 Hz), 129.4, 129.0 (d, J = 8.1 Hz), 128.8, 128.6 (d, J = 2.8 Hz), 124.5 (d, J = 3.5 Hz), 124.4, 118.2, 116.3, 116.1, 110.7.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 475.1510, found 475.1535.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 15.74 min., t_R (minor) = 40.71 min., %ee = 98%.

*Synthesis of 6,6'-bis(3,4-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol (**3d**)*:

The diarylated product **3d** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3,4-dimethylbenzene (55.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 34.6 mg of 6,6'-bis(3,4-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol **3d** (70%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.58 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.46-7.41 (m, 3H), 7.26-7.22 (m, 2H), 7.39-7.36 (m, 1H), 5.10 (br s, 1H).

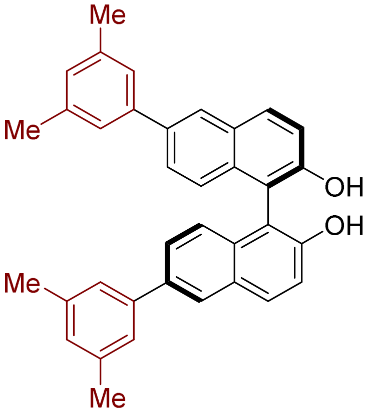
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 138.4, 137.0, 136.9, 135.7, 132.4, 131.6, 130.2, 129.8, 128.5, 127.1, 126.0, 124.7, 124.6, 118.1, 110.8, 19.9, 19.4.

HRMS (ESI) *m/z* calcd for $C_{36}H_{30}O_2$ $[M+H]^+$ 495.2324, found 495.2316.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 16.24 min., t_R (minor) = 44.17 min., %ee = 82%.

*Synthesis of 6,6'-bis(3,5-dimethylphenyl)-[-1,1'-binaphthalene]-2,2'-diol (**3e**)*:

The diarylated product **3e** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3,5-dimethylbenzene (55.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 34.6 mg of 6,6'-bis(3,5-dimethylphenyl)-[-1,1'-binaphthalene]-2,2'-diol **3e** (70%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.58 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.29 (s, 2H), 7.26 (d, J = 8.8 Hz, 1H), 7.02 (s, 1H), 5.10 (br s, 1H), 2.40 (s, 6H).

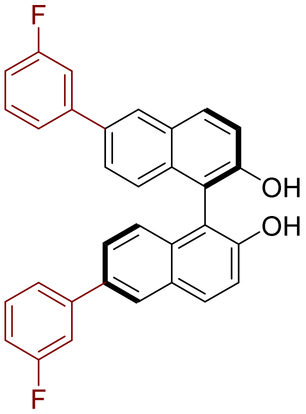
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 140.8, 138.4, 137.2, 132.5, 131.7, 129.7, 128.9, 127.3, 126.3, 125.2, 124.7, 118.1, 110.7, 21.4.

HRMS (ESI) *m/z* calcd for $C_{36}H_{30}O_2$ $[M+H]^+$ 495.2324, found 495.2326.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 10.87 min., t_R (minor) = 8.98 min., %ee = 74%.

*Synthesis of 6,6'-bis(3-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol (**3f**)*:

The diarylated product **3f** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3-fluorobenzene (52.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (12% ethyl acetate in hexane) gave 29.4 mg of 6,6'-bis(3-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol **3f** (62%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 1.6 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.55 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.47-7.36 (m, 4H), 7.26 (d, J = 8.8 Hz, 1H), 7.09-7.04 (m, 1H), 5.25 (br s, 1H).

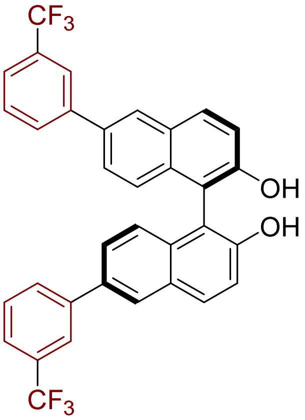
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 162.0, 153.1, 143.0 (d, J = 7.6 Hz), 135.6, 132.9, 131.8, 130.3 (d, J = 8.4 Hz), 129.6, 126.8, 126.5, 124.9, 122.8 (d, J = 2.7 Hz), 118.5, 114.0 (dd, J = 4.4 Hz, J = 21.4 Hz), 110.8.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 475.1510, found 475.1520.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 21.71 min., t_R (minor) = 56.54 min., %ee = 98%.

*Synthesis of 6,6'-bis(3-(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol (**3g**)*:

The diarylated product **3g** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3-(trifluoromethyl)benzene (67.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (10% ethyl acetate in hexane) gave 37.3 mg of 6,6'-bis(3-(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol **3g** (65%).



^{1}H NMR (400 MHz, CDCl$_3$): δ 8.13 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.62-7.56 (m, 3H), 7.46 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 5.19 (br s, 1H).

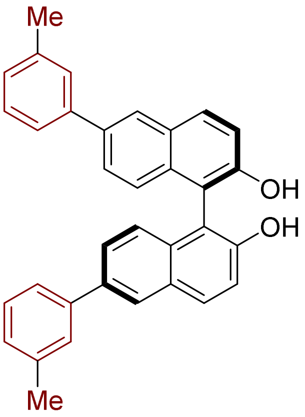
^{13}C NMR (100 MHz, CDCl$_3$): δ 153.2, 141.6, 135.5, 132.9, 131.9, 131.1, 130.5, 129.7, 129.4, 126.8 (d, J = 7.0 Hz), 125.5, 125.1, 124.0, 122.8, 118.6, 110.7.

HRMS (ESI) *m/z* calcd for $C_{34}H_{20}F_6O_2$ $[M+H]^+$ 575.1446, found 475.1449.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 15.25 min., t_R (minor) = 44.8 min., %ee = 98%.

*Synthesis of 6,6'-di-m-tolyl-[1,1'-binaphthalene]-2,2'-diol (**3h**)*:

The diarylated product **3h** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-3-methylbenzene (51.3 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 32.2 mg of 6,6'-di-m-tolyl-[1,1'-binaphthalene]-2,2'-diol **3h** (69%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 1.6 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 1.6 Hz, J = 8.8 Hz, 1H), 7.41-7.38 (m, 2H), 7.33 (d, J = 9.2 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 5.02 (br s, 1H), 2.36 (s, 3H).

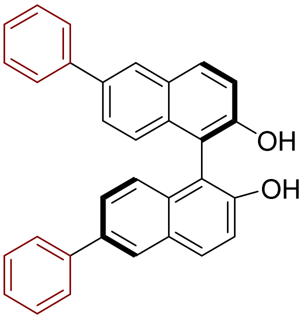
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 140.8, 138.4, 137.1, 132.5, 131.7, 129.7, 128.8, 128.0, 127.2, 126.3, 124.7, 124.3, 118.2, 110.8, 99.9, 21.6

HRMS (ESI) *m/z* calcd for $C_{34}H_{26}O_2$ $[M+H]^+$ 467.2011 found 467.2042.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 36.7 min., t_R (minor) = 17.05 min., %ee = 94%.

*Synthesis of 6,6'- diphenyl-[-1,1'-binaphthalene]-2,2'-diol (**3i**)*:

The diarylated product **3i** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner bromobenzene (47.1 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (10 % ethyl acetate in hexane) gave 28.5 mg of 6,6'- diphenyl-[-1,1'-binaphthalene]-2,2'-diol **3i** (65%).



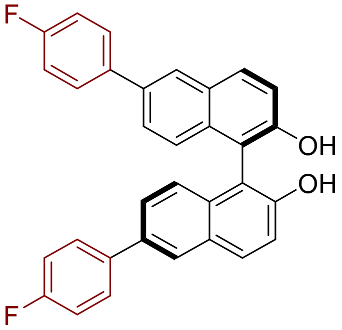
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 1.6 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.69-7.67 (m, 2H), 7.60 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.49-7.35 (m, 4H), 7.28 (d, J = 8.8 Hz, 1H), 5.11 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 140.8, 137.0, 132.6, 131.8, 129.8, 128.9, 127.3, 127.20, 126.4, 124.8, 118.2, 110.7.

HRMS (ESI) *m/z* calcd for $C_{32}H_{22}O_2$ $[M+H]^+$ 439.1698 found 439.1699.

*Synthesis of 6,6'-bis(4-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol (**3j**)*:

The diarylated product **3j** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-4-fluorobenzene (52.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 32.2 mg of 6,6'-bis(4-fluorophenyl)-[1,1'-binaphthalene]-2,2'-diol **3j** (68%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 8.04 (d, J = 9.6 Hz, 1H), 7.64-7.61 (m, 2H), 7.53 (dd, J = 1.8 Hz, J = 8.6 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.16 (t, J = 8.4 Hz, 2H), 5.14 (br s, 1H).

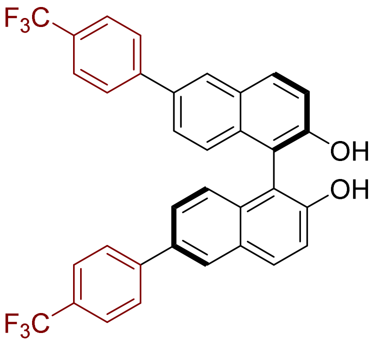
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 136.9, 136.0, 132.5, 131.7, 129.7, 128.7 (d, J = 8.0 Hz), 127.0, 126.2, 124.9, 118.4, 115.9, 115.7, 110.8.

HRMS (ESI) *m/z* calcd for $C_{32}H_{20}F_2O_2$ $[M+H]^+$ 475.1510 found 475.1512.

HPLC Conditions: Chiralcel® OD-H Column, 10% iPrOH/hexanes, 1.0 mL/min: t_R (major) = 50.87 min., t_R (minor) = 23.35 min., %ee = 91%.

*Synthesis of 6,6'-bis(4-(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol (**3k**)*:

The diarylated product **3k** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-4-(trifluoromethyl)benzene (67.5 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (10% ethyl acetate in hexane) gave 40.7 mg of 6,6'-bis(4-(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol **3k** (71%).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 1.6 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 1.8 Hz, J = 8.6 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.30 (br s, 1H).

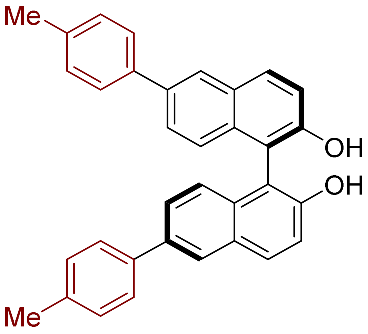
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 144.3, 135.4, 133.1, 131.8, 129.6, 129.3 (d, J = 32.2 Hz), 127.4, 126.8 (d, J = 10.8 Hz), 125.8, 124.3 (d, J = 270.4 Hz), 125.1, 118.7, 110.9.

HRMS (ESI) *m/z* calcd for $C_{34}H_{20}F_6O_2$ $[M+H]^+$ 575.1446, found 475.1455.

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 5.67 min., t_R (minor) = 8.06 min., %ee = 95%.

*Synthesis of 6,6'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol (**3l**)*:

The diarylated product **3l** is prepared following the general procedure for one-pot diborylation/arylation using bromopartner 1-bromo-4-methylbenzene (51.3 mg, 3.0 equiv.). Solvent evaporated and chromatographic separation with silica gel (7% ethyl acetate in hexane) gave 33.5 mg of 6,6'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol-[1,1'-binaphthalene]-2,2'-diol **3**l (72%).



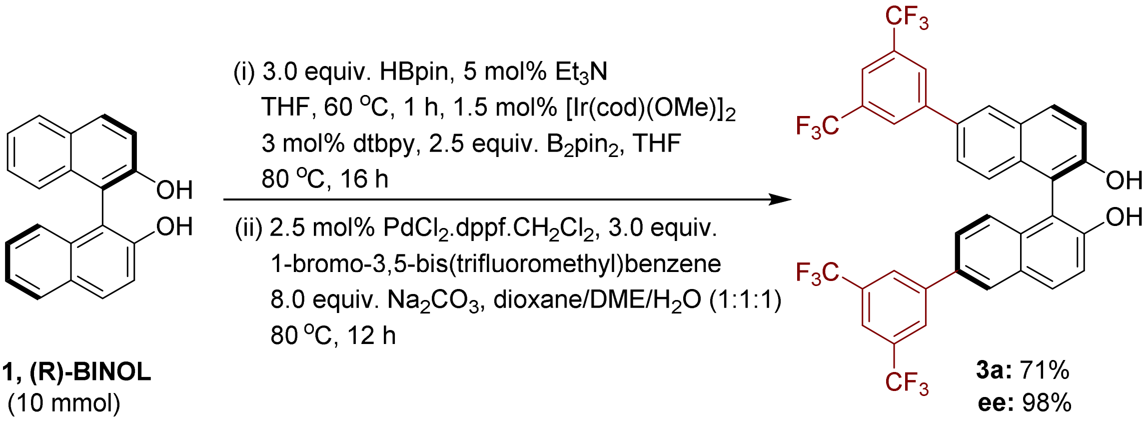
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.60-7.57 (m, 3H), 7.43 (d, J = 8.8 Hz, 1H), 7.29-7.25 (m, 3H), 5.10 (br s, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 137.9, 137.1, 136.9, 132.4, 131.7, 129.8, 129.6, 127.1, 127.0, 126.0, 124.7, 118.2, 110.8, 21.1.

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, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 43.61 min., t_R (minor) = 16.24 min., %ee = 98%.

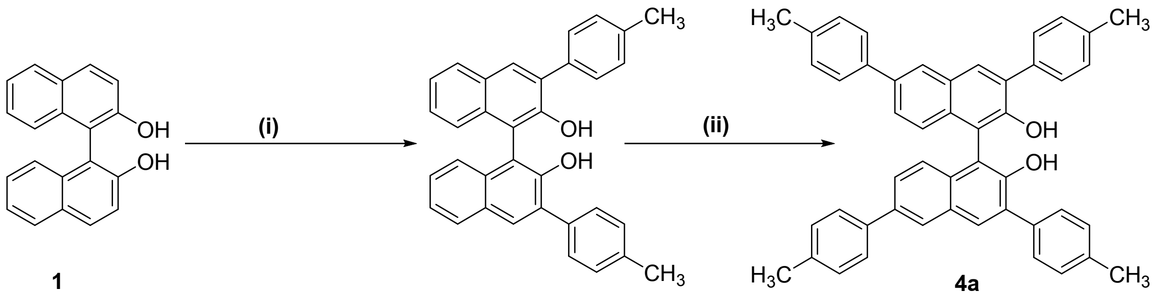
Gram Scale Synthesis of double-fold remote borylation/arylation:



In a glove box, a 15.0 mL pressure tube was charged with (R)-BINOL (2.9 g, 10.0 mmol), HBpin (4.4 mL, 3.0 equiv.), Et_3N (70 μL, 5 mol%), dry THF (10 mL) and stirred at 60 °C for 1 h. $[Ir(cod)(OMe)]_2$ (100.0 mg, 1.5 mol%), dtbpy (80.0 mg, 3.0 mol%), B_2pin_2 (6.35 gm, 2.5 equiv.) and dry THF (2 mL) was then added. The pressure tube was capped with a teflon pressure cap and placed into a pre-heated oil bath at 80 °C. After 16 h, solvent was evaporated and crude mixture was transferred in another 15.0 mL pressure tube using dry dioxane/DME (6.0 mL). In a glove box this pressure tube was then charged with $PdCl_2$.dppf.CH_2Cl_2 (204.1 mg, 2.5 mol%), Na_2CO_3 (8.5 gm, 8.0 equiv.) and 1-bromo-3,5-bis(trifluoromethyl)benzene (8.8 gm, 3.0 equiv.). 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 cooled to room temperature and extracted using 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 5.0 gm of (R)-(+)-6,6'-bis(3,5-bis(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol **3a** (71%). Spectral data are in accordance with the reported data.**Error! Bookmark not defined.**

HPLC Conditions: Chiralcel® OD-H Column, 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_R (major) = 18.67 min., t_R (minor) = 11.48 min., %ee = 98%.

Sequential double-fold ortho and remote borylation and arylation of BINOL:



In a glove box, a 5.0 mL wheaton microreactor was charged with (R)-BINOL (286 mg, 1.0 mmol), dry THF (4.0 mL), [Ir(cod)(OMe)]$_2$ (13.3 mg, 2.0 mol%), dtbpy (10.7 mg, 4.0 mol%), B_2eg_2 (567 mg, 4.0 equiv.) and Et_3N (557.5 μL, 4 equiv.). The microreactor was then capped and placed into a pre-heated oil bath at 80 °C. After 12 h, solvent was evaporated and crude mixture was transferred in another microreactor using dry dioxane/DME (4.0 mL). In a glove box this microreactor was then charged with $PdCl_2$.dppf.CH_2Cl_2 (20.4 mg, 2.5 mol%), Na_2CO_3 (848 mg, 8.0 equiv.) and 1-bromo-4-methylbenzene (513.1 mg, 3.0 equiv.). Degassed water (2.0 mL) was added outside the glove box. Then the microreactor was capped and placed into pre-heated oil bath at 80 °C. After 12 h reaction mixture cooled to room temperature and extracted using ethyl acetate (3 x 40 mL) and dried over Na_2SO_4. Solvent evaporated and chromatographic separation with silica gel (8% ethyl acetate in hexane) gave 343 mg of 3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol (77%). Then in a glove box, a 5.0 mL wheaton microreactor was charged with 3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol (233 mg, 0.5 mmol), HBpin (217.5 µL, 3 equiv.), Et_3N (3.5 µL, 5 mol%), dry THF (1.0 mL) and stirred at 60 °C for 1 h. $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol%), dtbpy (4.0 mg, 3.0 mol%), B_2pin_2 (317.5 mg, 2.5 equiv.) and dry THF (1.0 mL) was then added. The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 16 h, solvent was evaporated and crude mixture was transferred in another 5.0 mL wheaton microreactor using dry dioxane/DME (2 mL). In a glove box this microreactor was then charged with $PdCl_2$.dppf.CH_2Cl_2 (10.2 mg, 2.5 mol%), Na_2CO_3 (424 mg, 8.0 equiv.) and 1-bromo-4-methylbenzene (256.5 mg, 3.0 equiv.). Degassed water (1.0 mL) was added outside the glove box. Then the microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 80 °C. After 12 h reaction mixture cooled to room temperature and extracted using ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. Solvent evaporated and chromatographic separation with silica gel (12% ethyl acetate in hexane) gave 229.6 mg of **4a** 3,3',6,6'-tetra-p-tolyl-[1,1'-binaphthalene]-2,2'-diol (71%).

^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.05 (s, 1H), 7.66-7.57 (m, 4H), 7.33-7.29 (m, 6H), 5.40 (br s, 1H), 2.44 and 2.41 (Two singlets of methyl merged, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 138.0, 137.7, 137.0, 134.4, 131.9, 131.3, 131.0, 129.7, 129.6, 129.4, 129.3, 127.0, 126.8, 125.9, 124.8, 124.3, 112.5, 21.3, 21.1.

HRMS (ESI) *m/z* calcd for $C_{48}H_{38}O_2$ $[M+H]^+$ 647.2950, found 647.2993.

References

1. (a) Zhang, Q.; Cui, X.; Chen, L.; Liu, H.; Wu, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 7823. (b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (c) Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc*. **2008**, *130*, 12232. (d) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264. (e) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc*. **2006**, *128*, 16448. (f) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559. (g) Podlesny, E. E.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 1408. (h) O'Brien, E. M.; Morgan, B. J.; Mulrooney, C. A.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem*. **2010**, *75*, 57. (i) Temma, T.; Habaue, S. *Tetrahedron Lett*. **2005**, *46*, 5655. (j) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 5500. (k) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856. (l) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137.

2. Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082.

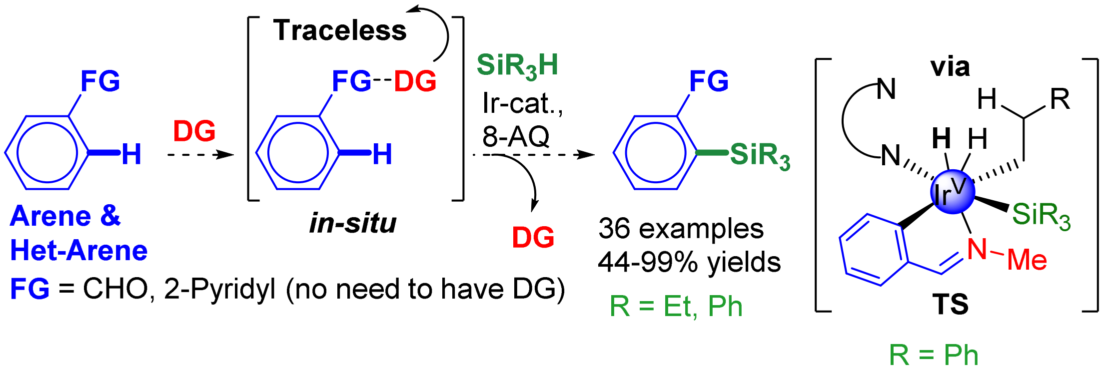
3. (a) Sako, M.; Takizawa, S.; Yoshida, Y.; Sasai, H. Tetrahedron: Asymmetry **2015**, *26*, 613. (b) Takizawa, S. Chem. Pharm. Bull. **2009**, *57*, 1179. (c) Takizawa, S.; Katayama, T.; Sasai, H. *Chem. Commun*. **2008**, 4113. (d) Takizawa, S.; Katayama, T.; Somei, H.; Asano, Y.; Yoshida, T.; Kameyama, C.; Rajesh, D.; Onitsuka, K.; Suzuki, T.; Mikami, M.; Yamataka, H.; Jayaprakash, D.; Sasai, H. *Tetrahedron* **2008**, *64*, 3361. (e) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.- B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc*. **2007**, *129*, 13927. (f) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4532.

4. Narute, S.; Parnes, R.; Toste, F. D.; Pappo, D. *J. Am. Chem. Soc* .**2016**, *138*, 16553.

5. Ahmed, I.; Clark, D. A. *Org. Lett.* **2014**, *16*, 4332.

Chapter 5

Ortho-selective $C(sp^2)$–H silylation of arenes and heteroarenes: Detailed mechanistic investigation of Ir(I)-Ir(III) and Ir(III)-Ir(V) catalytic cycle



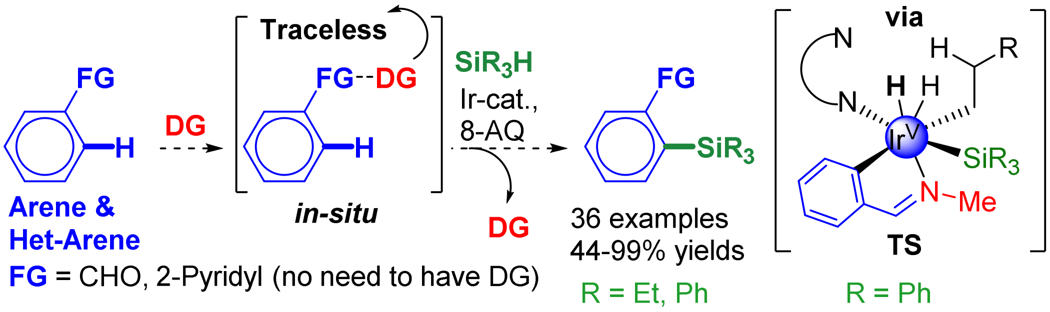
Objective: To accomplish the target of *ortho*-silylation of aromatic aldehyde and 2-phenylpyridines and perform detailed mechanistic investigation.

Discussion

The direct and selective catalytic functionalization of C-H bond constitutes most broadly applicable and powerful class of transformation in organic synthesis. In this perspective, transition metal-catalyzed C–H bond activation and silylation of arenes and heteroarenes is of great interest attributed to the importance of the organosilicon compounds.[1] Conventional methods to synthesize arylsilyl compounds includes, the reaction[2] of aryl lithium or magnesium reagents with silicon electrophiles. The main limitation of this method is the low functional group compatibility of organo-magnesium and lithium reagents. Furthermore, there occurs production of massive amount of undesirable metal salt as the byproducts in large-scale synthesis. Alternatively, by the cross coupling[3] between aryl halides and silanes through transition metal catalysis, silyl substituents could also be introduced. Although, this method overcomes the functional group incompatibility of organo-magnesium and lithium reagents, but the necessity of prefunctionalization of arenes by the halogenation step, makes it an insipid protocol.

In the last ten years several approaches employing a variety of directing groups such as, imine,[4] oxazoline,[5] pyridine,[6] pyrazole,[7] secondary amine,[8] amide[9] and alkoxy[10] have been developed for the arene silylation. Eventhough these methods have made significant progress towards the *ortho*-silylation of arenes and heteroarenes, but have several limitations, such as: (1) presence of undesired directing group in the final product; (2) formation of mixture of mono- and bis-silylated products; (3) elevated temperatures (> 120-200 ^{o}C); (4) impractical ratios[11] of substrates to the silicon reagent (10:1 to 60:1); (5) narrow scope and functional group compatibility. Thus, it necessitates the development of general catalytic method that avoids abovementioned limitations.

Remarkable work is done by Mashima and their coworkers in this context for *ortho*-silylation[12] of 2-pyridyl and iminyl substrates by Ir-catalyst using a hemilabile *N*-xylyl-*N'*-methylperimidine carbene ligand providing thoroughly elucidated *ortho*-silylation mechanism. The major issues with this method are: For example, (1) poor scope of substrates; (2) multi-step NHC ligand synthesis; (3) high Ir loading, which is not commercially available; and (4) excess use of silane.



(eq. 1)

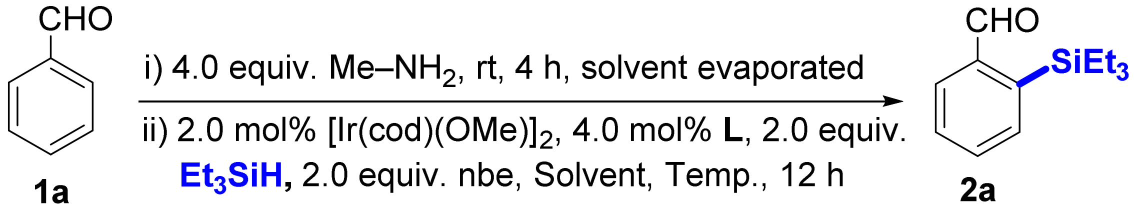
Accordingly, inspired by these challenges, we report herein a one-pot unified approach for the *ortho*-selective C–H activation/silylation of benzaldehydes and 2-phenylpyridines (**eq. 1**). Moreover our experimental findings indicate that this is the very first report involving Ir(III)→Ir(V) catalytic cycle with bidentate *N,N*-ligand system (8-AQ for the C–H bond silylations).

RESULTS AND DISCUSSION

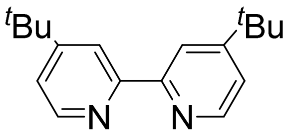
Initial studies for the *ortho*-silylation of benzaldehyde:

Encouraged by our recent discovery[13] of *ortho*- and *meta*-borylation of benzaldehydes via in situ generated imines, we proposed that imine might act as an easily traceless directing group for the *ortho*-silylation of aromatic aldehydes. Thus, first we employed dtbpy and TMP as ligands (**Table 5.1**, entries 1-2) and nbe as the standard hydrogen acceptor, the silylation didn't occur. Employment of hemi-labile **L1** and **L2** ligands were also unsuccessful (entries 3 & 4). Notably, use of bis-*N*-benzyl-8-aminoquinoline (**L3**) gave 32% GC conversion of the *ortho*-silylated benzaldehyde (entry 5). Improvement in conversion (54%) was observed (entry 6) on reducing the steric bulk of the employed ligand (**L3**) from bis-benzylamine to simple NH_2 (**8-AQ**). THF, 1,4-dioxane and CyH as solvents were not beneficial (entries 7-9). Moreover, silylation proceeded with equal efficiency, on lowering temperature to 100 °C (entry 10).

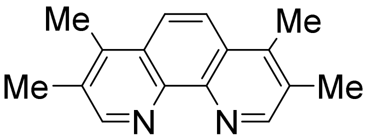
Table 5.1. Evaluation of Reaction Conditions[a]



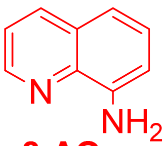
#	Ligand (L)	Alkene	Solvent	Temp °C	Conv (%)
1	dtbpy	nbe	PhMe	120	0
2	TMP	nbe	PhMe	120	0
3	L1	nbe	PhMe	120	0
4	L2	nbe	PhMe	120	0
5	L3	nbe	PhMe	120	32
6	8-AQ	nbe	PhMe	120	54
7	8-AQ	nbe	THF	120	39
8	8-AQ	nbe	1,4-dioxane	120	<5
9	8-AQ	nbe	CyH	120	<10
10	**8-AQ**	**nbe**	**PhMe**	**100**	**52 (49)[b]**



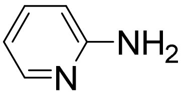
dtbpy



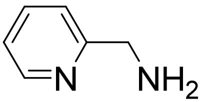
TMP



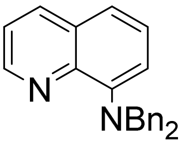
8-AQ



L1



L2



L3

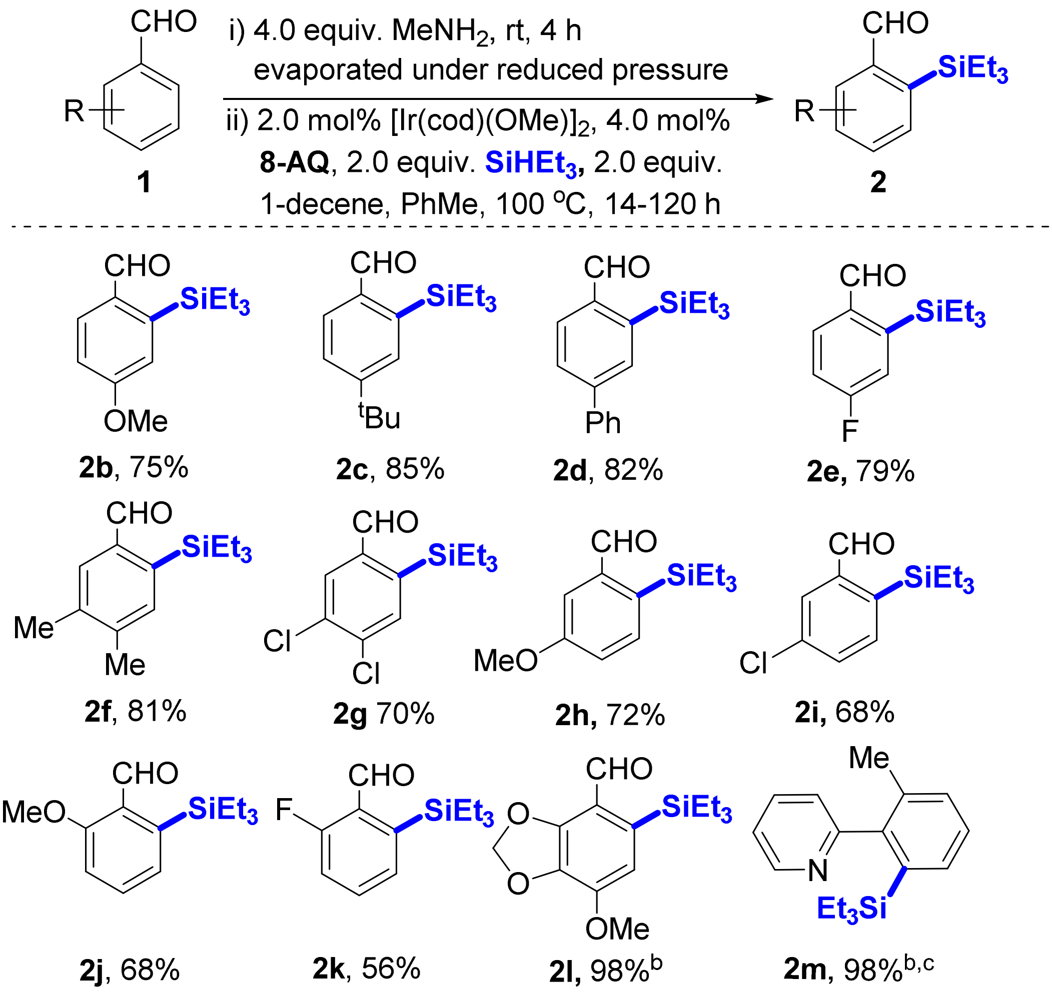
[a] Reactions were run with 0.2 mmol substrate, and conversions are calculated by GC-FID analysis from crude reaction mixture using dodecane as internal standard. [b] Isolated yield after column chromatography is given in parentheses.

Next while examining series of alkenes in the catalytic cycle of the *ortho*-silylation, we found that with 1-decene, 97% conversion and 93% isolated yield of desired product is obtained.

Scope of benzaldehydes for the *ortho*-silylation:

With these optimized conditions, the scope of the direct *ortho*-silylation of benzaldehydes **Table 5.2** was examined. The developed conditions are unbiased towards variety of substituents such as halogens (F, Cl,), alkyl groups (Et, ^{t}Bu), phenyl (Ph), methoxy (OMe), and amine (NMe_2).

Table 5.2. Scope of *ortho*-silylation for benzaldehydes[a]



[a]Reactions were conducted with 0.5 mmol substrate. Yields are for isolated ortho silylated products after column chromatography. [b]No MeNH2 used. [c]Reactions were set up under Mashima's silylation condition (condition A) and our condition (condition B): (details are in the experimental part)

Regardless of the nature of substituents (either electron rich or electron deficient), 4-substituted benzaldehydes afforded *ortho*-silylated product (entries **2b-2e**) without producing bis-silylation products. Silylation of 4-phenylbenzaldehyde is remarkable; the Ph C−H bonds are untouched under the employed conditions, giving exclusively *ortho*-silylation (entry **2d**). In case of 3-substituted benzaldehydes, *ortho*-silylation also underwent smoothly at the less hindered site of the substrate (entry **2h, 2i**). Similarly 2-substituted benzaldehydes, efficaciously yielded desired *ortho*-silylated products (entries **2j, 2k**). Moreover, for the synthesis of various drug molecules, agrochemicals, herbicides, insecticides, desiccants, surfactant agents and anti-inflammatory agents,[14] 2-phenylpyridines serves as significant intermediates. Thus, we subjected them also under developed silylation condition, to our delight, they afforded good to excellent yields of the product. It deserves mentioning here that substituted 2-phenylpyridines yielded either trace amount of product using Mashima's method or didn't react but they underwent reaction efficiently under our developed protocol.

Notably the catalyst loadings in **Table 5.2** is 2.0 mol% and the silylations were run at 0.5 mmol scale. Thus, to check the scalability of developed silylation at lower catalyst loadings (0.5 mol%), it was conducted using **1a** with 5.0 mmol scale and gratifyingly, it was successful without diminishing the yield (91%) of the product.

Mechanistic Investigation

While Mashima's Ir(NHC-carbene)-catalyzed direct dehydrogenative silylation and our Ir(*N*,*N*-bidentate)-catalyzed silylation chemistry both have fascinating features, the mechanisms responsible for *ortho*-silylation must be different. **Fig 5.1** and **Fig 5.2** shows the two plausible catalytic cycles (Pathway-I, Ir(I)–Ir(III) cycle and Pathway-II, Ir(III)–Ir(V) cycle) for the *ortho* silylation. Pathway-I is the traditional Ir(I)–Ir(III) catalytic cycle, which is very similar to the Hartwig's Rh(I)–Rh(III) catalytic cycle[15] for the arene silylation. Thus, according to the proposed Pathway-I, Ir^{I}–H intermediate (**A**), underwent oxidative addition with triethylsilane to generate penta-coordinated iridium(III) silyl dihydride species (**B**), which after insertion with decene forms another penta-coordinated iridium(III) silyl alkyl hydride (**C**) species. Alternatively, the same species (**C**) might be generated from the intermediate (**A**) by the insertion of decene followed by the oxidative addition with the triethylsilane. Subsequent hydrogen transfer from intermediate (**C**) to decene generates the iridium(I) silyl intermediate (**E**), which coordinates with the in situ generated imine to form species (**F**). Later on, the intermediate (**F**) reacts with the arene to afford the iridium (III) silyl aryl hydride complex (**G**). Complex (**G**) undergoes reductive elimination to form C–Si bond in the silylarene product and closing the catalytic cycle.

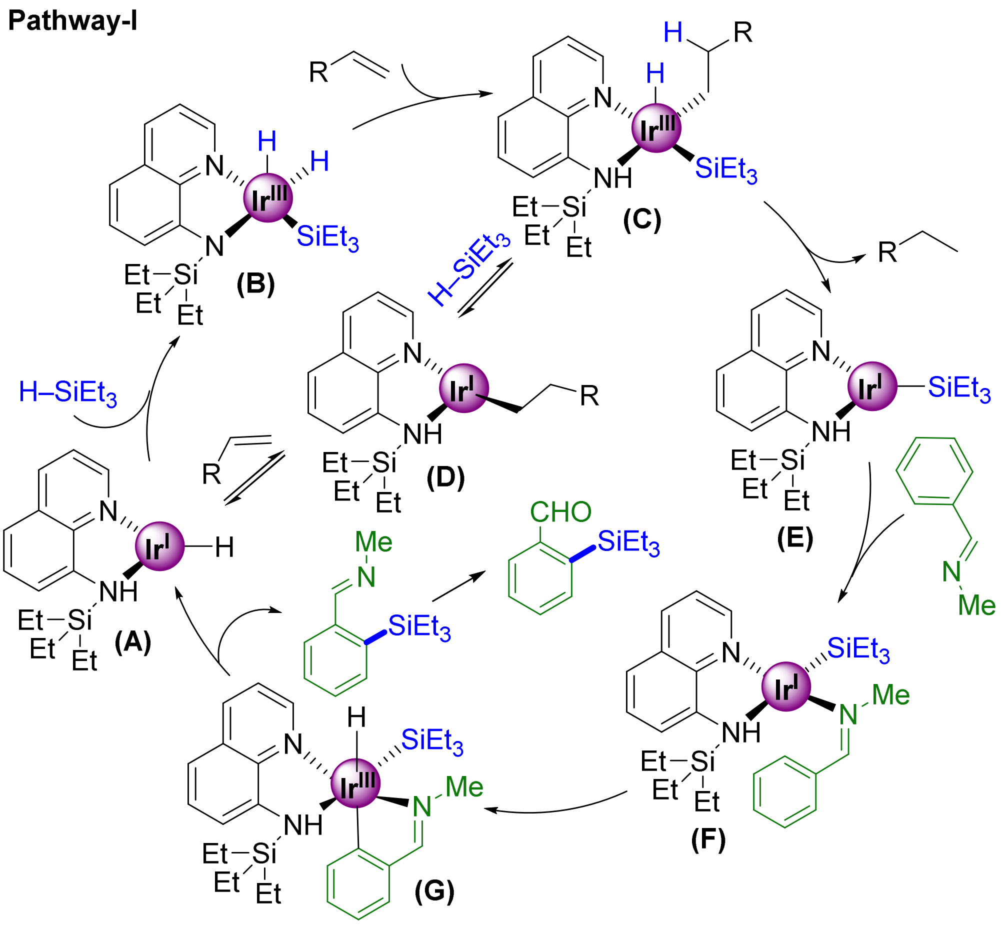


Fig 5.1. Plausible Mechanism for Ir(I)–Ir(III) Cycle

On the other hand, according to the Pathway-II, first, Ir^{I}–H intermediate (**A**), which is formed by the oxidative addition of a hydrosilane to the iridium center, reacts with triethylsilane to form Ir^{III}–$(H)_2(SiEt_3)$ species (**B**). The second step was the insertion of 1-decene into the Ir^{III}–H bond of intermediate (**B**) forming another five-coordinated Ir^{III}–H species (**C**), which coordinates with the in-situ generated imine to afford a coordinatively saturated 18-electron species (**H**).

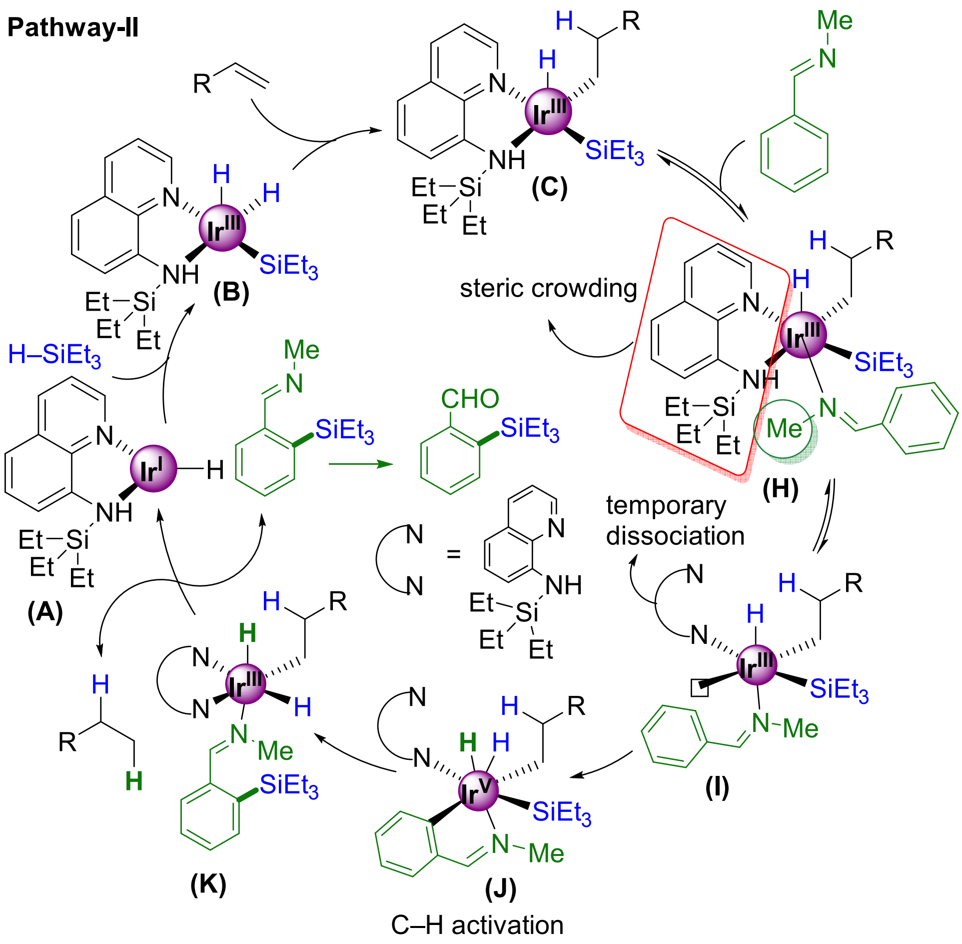


Fig 5.2. Plausible Mechanism for Ir(III)–Ir(V) Cycle

Plausible Mechanism for *Ortho*-silylation

In this context, we assume that due to the high sterics around the metal center between the imine substituent and the SiEt$_3$ group attached to the bidentate ligand (8-AQ), 18-electron complex (**H**) might suffer a temporary dissociation creating an open coordination site to give coordinatively unsaturated 16-electron complex (**I**), enabling the C–H activation step to generate Ir^{V}–(H)$_2$(SiEt$_3$) complex (**J**),[16,17] which after either reductive removal of decane or reductive elimination of C–Si bond produces the *ortho* silylated product and closing the catalytic cycle. In order to determine the exact mechanistic pathway, we set out for the details investigation. To simplify the mechanism so as to avoid the formation of side product (alkene silylation) formed with HSiEt$_3$,[18] we switched to bulkier and electronically different silane HSiPh$_3$

(triphenylsilane) in comparison to $HSiEt_3$. To our delight side product was not formed with $HSiPh_3$ and proposed mechanism is shown in Fig. 5.3. Using $HSiPh_3$, reactions were performed with two different ligand, dtbpy and 8-AQ.

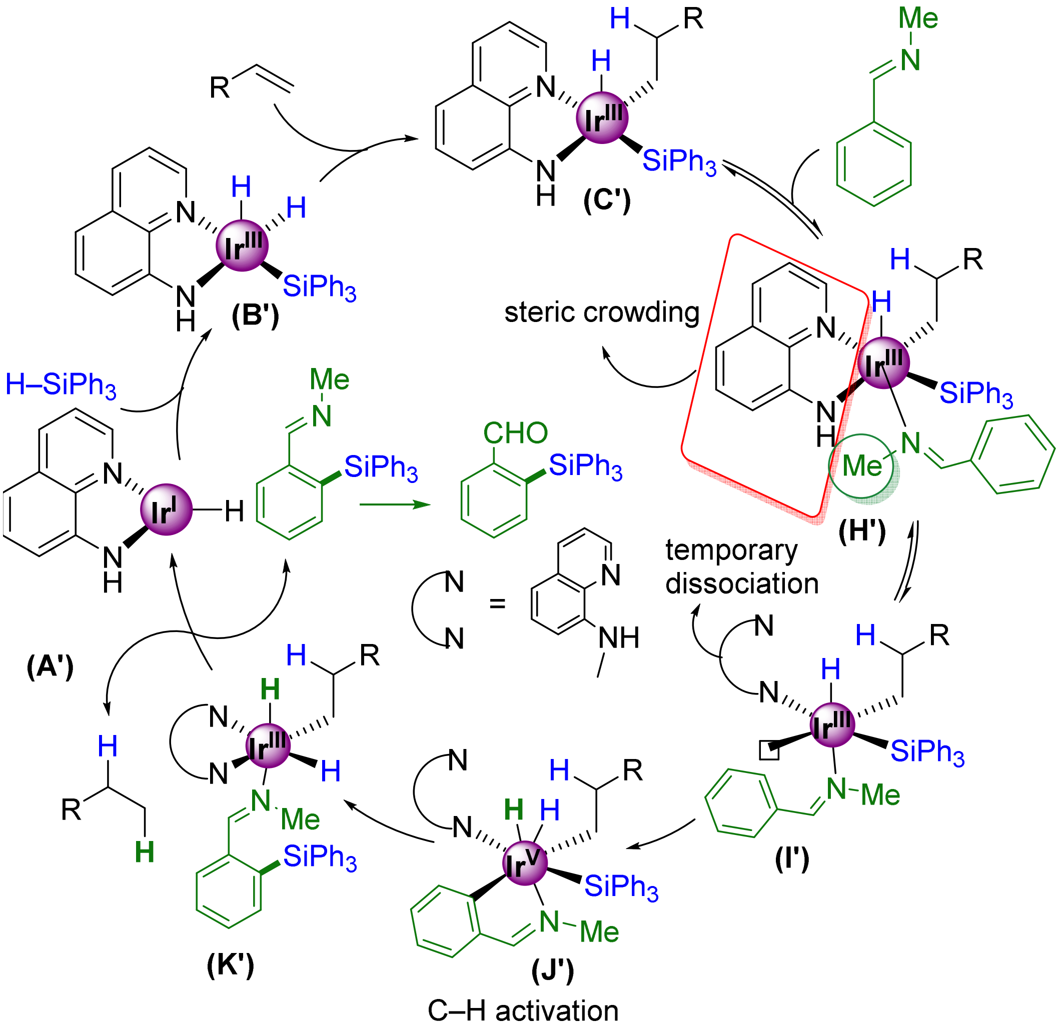


Fig 5.3 Proposed mechanism with triphenylsilane

If we compare this 8-AQ ligand with the standard dtbpy ligand system, it is evident that both the ligand have their different binding capacities. For example, while the dtbpy ligand is strongly coordinating in nature, 8-AQ ligand has two different coordinating nitrogen atoms (one is likely same with dtbpy, and another is hemi-labile in nature). Thus, due to the hemi-labile nature of the 8-AQ ligand, it should behave differently. We hypothesized that during the course of the reaction, the weakly coordinating site of the hemi-labile ligand (8-AQ) suffer a temporary dissociation and opens a vacant coordinating site. With dtbpy ligand and $HSiPh_3$ as silylating reagent no reaction occurred whereas 90% conversion to *ortho* silylated product occurred with 8-AQ ligand and triphenylsilane, indicating that, temporary dissociation to generate a vacant coordination site is necessary for *ortho* C-H activation and silylation.

Determination of the KIE:

To get better understanding of the proposed mechanism, in separate reaction vessels, KIE experiments were performed with **2a-*d*** and **2a** and the profile is shown in **Fig 5.4**. At the end of the 3 h when the reactions were stopped, the KIE value was found to be 0.52, suggesting an inverse secondary KIE. The reactions were repeated several times, and were reproducible. According to the literature report for the Hartwig's Rh(I)–Rh(III) catalytic cycle, the observed KIE value was 2.9 and is entirely different from our system. Thus, it is evident that our present catalytic system is entirely different from the Rh(I)–Rh(III) catalytic cycle.

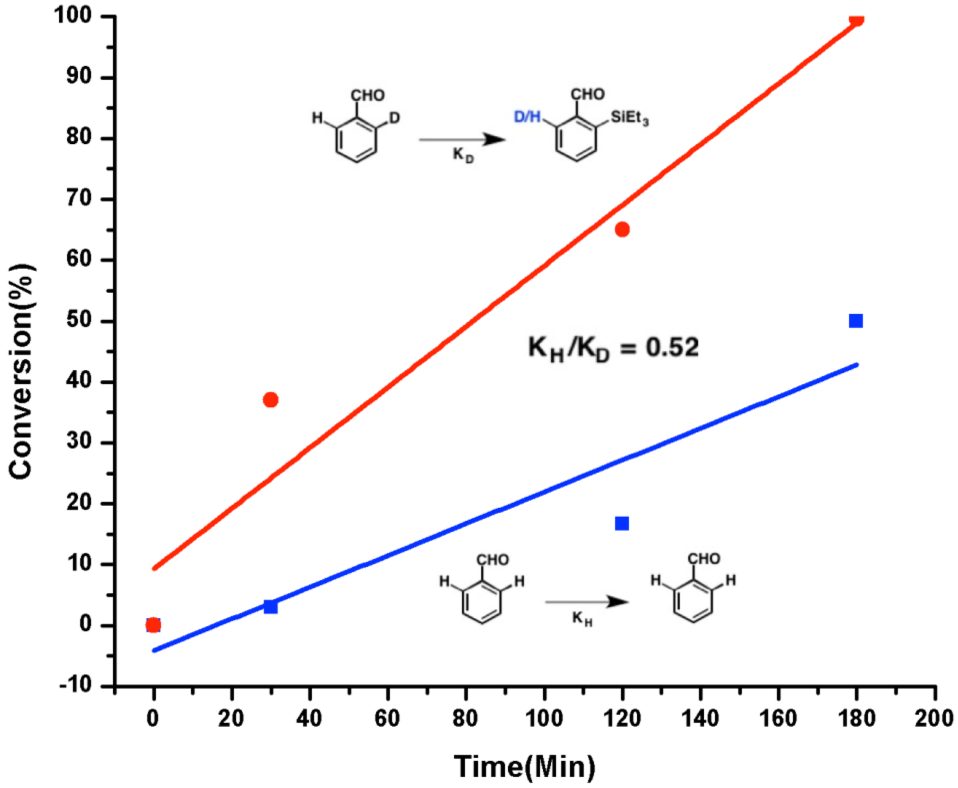


Fig 5.4 Studies of KIE with the *d*-labeling substrates

In summary, an Ir(III)→Ir(V) catalytic cycle for the direct *ortho*-silylation of arenes and heteroarenes has been developed. A wide range of substrates can be used for the *ortho*-selective silylation. A primary amine acted as a traceless directing group. Reductive removal of the sacrificial hydrogen acceptor occurred after the imine coordination and C–H bond activation of the substrate. At this moment, the role of the sacrificial hydrogen acceptor 1-decene compared to the nbe, is not clear entirely, perhaps stabilizing the Ir(III)-Ir(V) cycle, and computational calculations are required to gain further information. Such computational investigations will be the matter of future studies.

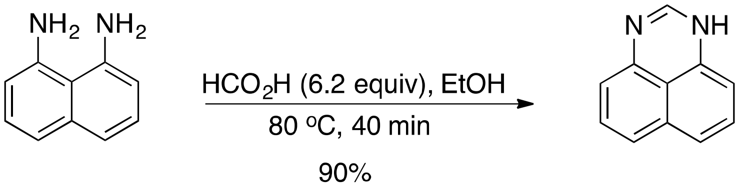
Experimental:

All commercially available chemicals were used as received unless otherwise indicated. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(cod)(OMe)]_2$ was procured from Sigma-Aldrich. Tetrahydrofuran (THF), toluene, cyclohexane and 1,4-dioxane were refluxed over sodium/benzophenone ketyl, distilled and degassed twice before silylation. 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). Methylamine was used as THF 2(M) solution.

^{1}H, and ^{13}C-NMR spectra were recorded on Bruker 400 MHz and 800 MHz NMR spectrometers. 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). 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+). Some of the aldehyde silylated compounds were appeared at HRMS as acetal because of the methanol solvent. 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.

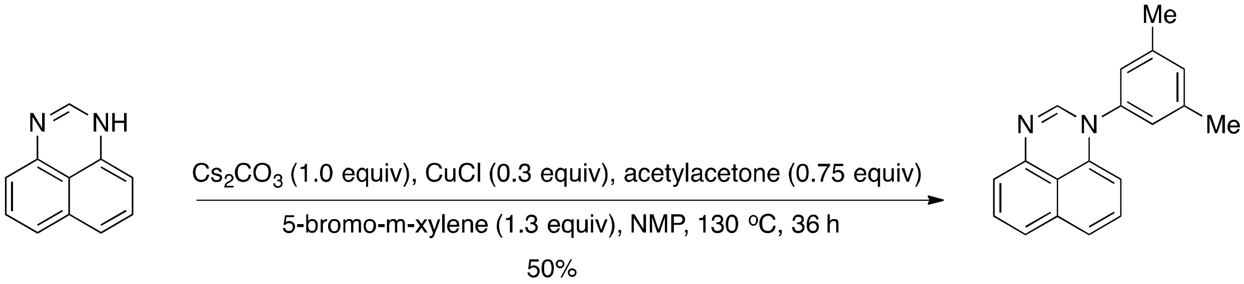
Preparation of Ir-NHC-catalyst reported by Mashima:[19]

Step 1: Synthesis of 1H perimidine:



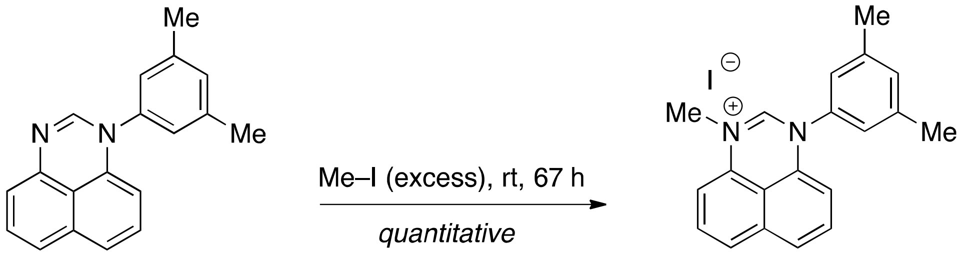
This was prepared according to the previously reported procedure.[20] In a 25 mL round bottom flask, 1,8-diaminonaphthalene (679.4 mg, 4.3 mmol), 3 mL of absolute ethanol and formic acid (1.0 mL, 26.5 mmol) was added and refluxed for 40 minutes. Upon completion, the reaction mixture was diluted with water (0.5 mL) and then basified with 2(N) NH_4OH. The resulting precipitate was filtered and washed with diethylether. The product yielded yellowish brown solid in 90% yield. Spectral data matched with reported data. Without further purification, it was used for the subsequent step.

Step 2: Synthesis of *N*-3,5-$(CH_3)_2C_6H_3$ perimidine:



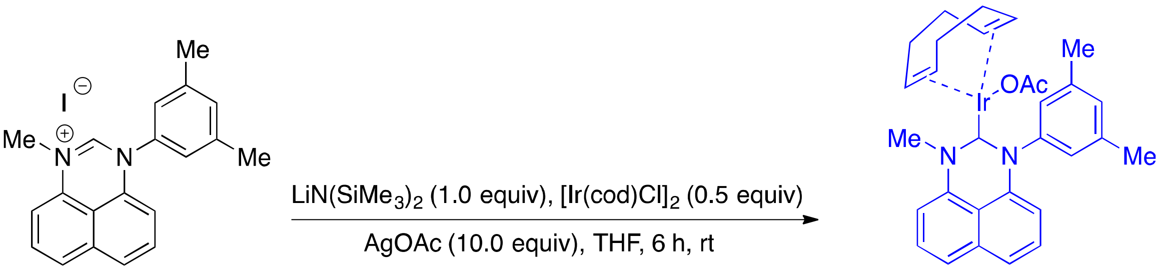
Perimidine (840.0 mg, 5 mmol), Cs_2CO_3 (1.63 g, 5 mmol), and CuCl (0.148 g, 1.5 mmol) were placed in two neck round bottom flask, and a mixture of acetylacetone (0.375 g, 3.775 mmol) and 5-bromo-m-xylene (1.21 g, 6.55 mmol) in NMP (10 mL) was added. The reaction mixture was degassed and heated at 130 °C for 36 h under an argon atmosphere. Saturated $NaHCO_3$ (200 mL) was added to the suspension after cooling to ambient temperature. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$ (200 mL). The organic layer was extracted with diethylether to give the desired compound in 50% yield and was used without further purification. Spectral data are in accordance with the reported data.

Step 3: Synthesis of *N*-Xylyl-*N*-methylperimidiumiodide:



A mixture of N-3,5-$(CH_3)_2C_6H_3$ perimidine and excess methyliodide was stirred covering with Al foil at room temperature for 67 h. After removal of excess methyl iodide, the resulting yellow powder was washed with diethylether to give the title compound.

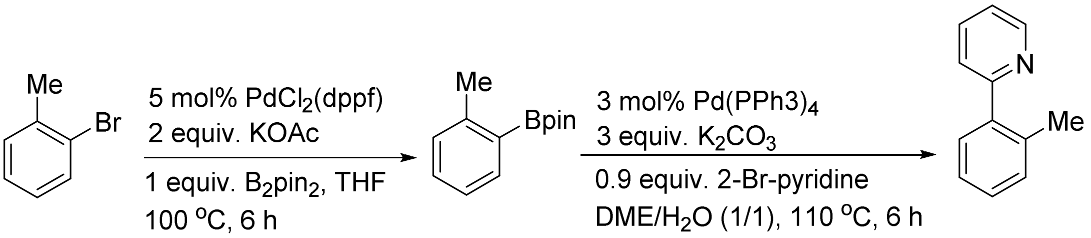
Step 4: Synthesis of the actual Ir-NHC catalyst reported by Mashima:



Ir-NHC-cat.

In two neck round bottom flask containing $LiN(SiMe_3)_2$ (167.0 mg, 1 equiv), $[Ir(cod)Cl]_2$ (336.0 mg, 0.5 equiv), N-Xylyl-N-methylperimidiumiodide (414.0 mg, 1 equiv), and AgOAc (1.67 g, 10 equiv), then THF (30 mL) was added. The resulting mixture was stirred at room temperature for 6 h. All volatiles were removed under reduced pressure and the resulting solid was extracted with dichloromethane to give the actual Ir-NHC-catalyst.

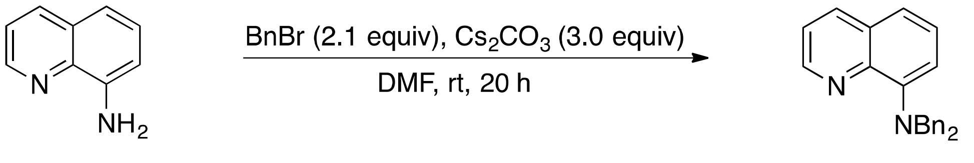
Preparation of 2-(*o*-tolyl)pyridine (1m):



1**m**, 82%

A 5.0 mL wheaton microreactor was charged with 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (36.5 mg, 5 mol%), KOAc (196 mg, 2 equiv), B_2Pin_2 (254 mg, 1 equiv), 2-bromotoluene (171 mg, 1 mmol) in THF (2.5 mL) in the glove box. The heterogeneous mixture was stirred at 100 ^oC temperature for 6 h (confirmed by GC/MS). The reaction mixture was filtered through a sintered (washed with ethylacetate) and dried under reduced pressure. To a 4,4,5,5-tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (218mg, 1.0 mmol), 2-bromopyridine (84.7 μL, 0.9 equiv), $Pd(PPh_3)_4$ (34.6 mg, 3 mol%) and K_2CO_3 (414 mg, 3 equiv) was added in a pressure tube in the glove box. Then 3 mL of dry dimethoxymethane (DME) and 3 mL of degassed water was added and the mixture was refluxed for 6 h at 110 ^oC. The reaction was then extracted with ethylacetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude mass was purified over column chromatography eluting with 1% ethylacetate in hexane to afford 138.5 mg (82%) of 2-(o-tolyl)pyridine (**1m**). Spectral data are in accordance with the reported data.[21]

Preparation of L3 Ligand:



L3, Yield: 46%

A 15 mL pressure tube was charged with 8-aminoquinoline (500 mg, 3.4 mmol), Cs_2CO_3 (3.3 g, 3.0 equiv) and benzylbromide (1.3 g, 2.1 equiv). Then 8 mL DMF was added under argon atmosphere. The reaction mixture was then stirred at room temperature for 20 h. (judged by GC-MS). To this reaction mixture, 100 mL water was added and then extracted with ethylacetate and wash with water (3 x 25 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude mass was purified over column chromatography eluting with 5% ethylacetate in hexane to afford 507 mg (46%) of *N,N*-dibenzylquinolin-8-amine.

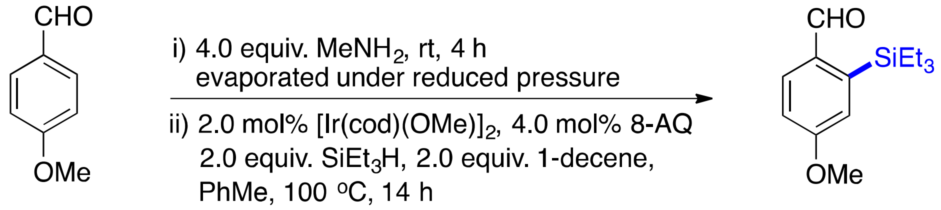
^1H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 4.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.27-7.42 (m, 13H), 7.01 (d, J = 7.2 Hz, 1H), 4.84 (s, 4H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 147.7, 147.0, 143.1, 138.8, 136.5, 129.8, 128.5, 128.1, 126.8, 126.4, 120.8, 120.6, 118.8, 56.7.

HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_2$ $[M+H]^+$ 325.1705, found 325.1703.

Evaluation of Reaction Conditions: A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**, 21.2 mg, 0.2 mmol), methylamine in THF solution (0.4 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (2.6 mg, 2.0 mol%), Ligand (**dtbpy**: 2.1 mg, **TMP**: 1.9 mg, **L1**: 0.75 mg, **L2**: 0.86 mg, **L3**: 2.6 mg, **8-AQ**: 1.2 mg, 4.0 mol%), nbe (37.7 mg, 2.0 equiv.), Et_3SiH (63.3 μL, 2.0 equiv.) and dry solvent as shown in the above-mentioned Table (0.4 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at the above-mentioned temperature. The reaction mixture was stirred for 12 h and monitored by GC/MS. The results are presented in the **Table 5.1**.

Ortho-silylation of 4-methoxybenzaldehyde: Method B:



1b, 0.5 mmol

2b, 75%

A 5.0 mL wheaton microreactor was charged with 4-methoxybenzaldehyde (**1b**, 68.0 mg, 0.5 mmol), methylamine in THF solution (1.0 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (6.6 mg, 2.0 mol%), 8-AQ (2.9 mg, 4.0 mol%), 1-decene (189.3 μL, 2.0 equiv.), Et_3SiH (159.2 μL, 2.0 equiv.) and dry PhMe (1.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 100 °C. The reaction mixture was stirred for 14 h. After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 94.0 mg of **2b** (75%) as colourless liquid.

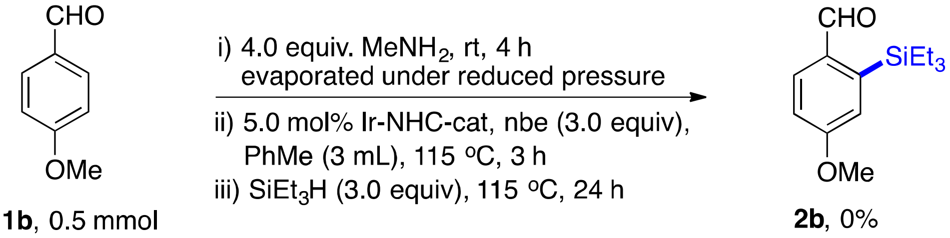
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.05 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 3.90 (s, 3H), 0.89-0.94 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$):

δ 191.8, 163.2, 143.2, 135.2, 134.2, 123.4, 113.2, 55.5, 7.8, 4.5.

HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Si$ $[M+Na]^+$ 273.1287, found 273.1277.

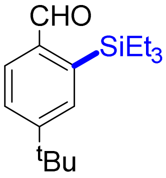
Ortho-silylation of 4-methoxybenzaldehyde: Method A:



A 5.0 mL wheaton microreactor was charged with 4-methoxybenzaldehyde (**1b**, 68.0 mg, 0.5 mmol), methylamine in THF solution (1.0 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with Ir-NHC-cat. (16.0 mg, 5 mol%), nbe (141.0 mg, 3 equiv), dry PhMe (3 mL). The microreactor was sealed and heated at 115 °C for 3 h. After which Et_3SiH (237.4 µL, 3 equiv) was added and stirred at 115°C for 24 h. Crude reaction mixture analysis by GC/MS and TLC showed no product formation, entire starting material remained unchanged.

Ortho-silylation of 4-tert-butylbenzaldehyde: Method B:

The *ortho*-silylated 4-tert-butylbenzaldehyde was prepared following method B using 4-tert-butylbenzaldehyde (**1c**, 81.1 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 117.6 mg of **2c** (85%) as solid.



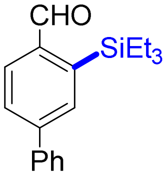
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 1.36 (s, 9H), 0.90-0.95 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 156.3, 140.0, 139.6, 133.7, 131.4, 126.3, 35.4, 31.2, 7.9, 4.7.

HRMS (ESI) *m/z* calcd for $C_{17}H_{28}OSi$ $[M+Na]^+$ 299.1807, found: 299.1786.

Ortho-silylation of 4-phenylbenzaldehyde: Method B:

The *ortho*-silylated 4-phenylbenzaldehyde was prepared following method B using 4-phenylbenzaldehyde (**1d**, 91.1 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 121.6 mg of **2d** (82%) as liquid.



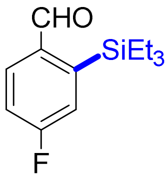
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.43-7.51 (m, 3H), 0.97 (bs, 15H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 193.1, 145.4, 141.2, 140.8, 140.3, 135.5, 131.2, 129.1, 128.4, 128.0, 127.6, 7.9, 4.6.

HRMS (ESI) *m/z* calcd for $C_{19}H_{24}OSi$ $[M+Na]^+$ 319.1494, found: 319.1472.

Ortho-silylation of 4-fluorobenzaldehyde: Method B:

The *ortho*-silylated 4-fluorobenzaldehyde was prepared following method B using 4-fluorobenzaldehyde (**1e**, 62.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 94.0 mg of **2e** (79%) as liquid.



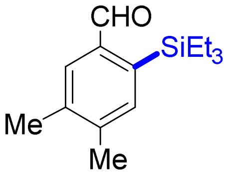
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.95-7.99 (m, 1H), 7.33 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 7.18 (dt, J = 9.2 Hz, J = 2.4 Hz, 1H), 0.90-0.93 (m,15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 165.6 (d, $J_{C\text{-}F}$ = 257 Hz), 144.9 (d, $J_{C\text{-}F}$ = 22.8 Hz), 138.2 (d, $J_{C\text{-}F}$ = 9.6 Hz), 134.1 (d, $J_{C\text{-}F}$ = 35.6 Hz), 123.5 (d, $J_{C\text{-}F}$ = 79.6 Hz), 116.3 (d, $J_{C\text{-}F}$ = 87.2 Hz), 7.7, 4.4.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}FOSi$ $[M+Na]^+$ 261.1087, found: 261.1075.

Ortho-silylation of 3,4-dimethylbenzaldehyde: Method B:

The *ortho*-silylated 3,4-dimethylbenzaldehyde was prepared following method B using 3,4-dimethylbenzaldehyde (**1f**, 67.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 100.5 mg of **2f** (81%) as liquid.



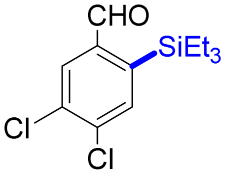
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.72 (s, 1H), 7.40 (s, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 0.89-0.93 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 142.6, 140.1, 138.1, 138.0, 137.5, 132.4, 20.3, 19.6, 7.8, 4.6.

HRMS (ESI) *m/z* calcd for $C_{15}H_{24}OSi$ $[M+Na]^+$ 271.1494, found: 271.1483.

Ortho-silylation of 3,4-dichlorobenzaldehyde: Method B:

The *ortho*-silylated 3,4-dichlorobenzaldehyde was prepared following method B using 3,4-dichlorobenzaldehyde (**1g**, 87.5 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 101.0 mg of **2g** (70%) as liquid.



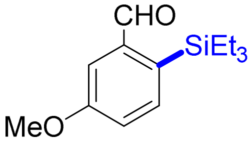
^{1}H NMR (800 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.99 (s, 1H), 7.68 (s, 1H), 0.91-0.93 (m, 15H).

^{13}C NMR ($CDCl_3$, 200 MHz): δ 191.1, 141.2, 140.7, 138.4, 138.2, 134.4, 132.7, 7.7, 4.4.

HRMS (ESI) *m/z* calcd for $C_{14}H_{22}Cl_2O_2Si$ $[M+Na]^+$ 343.0664, found: 343.0663.

Ortho-silylation of 3-methoxybenzaldehyde: Method B:

The *ortho*-silylated 3-methoxybenzaldehyde was prepared following method B using 3-methoxybenzaldehyde (**1h**, 68.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 90.0 mg of **2i** (72%) as colourless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 2.8 Hz, 1H), 7.12 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 3.87 (s, 3H), 0.87-0.93 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 160.7, 143.6, 138.0,131.9, 119.8, 114.2, 55.5, 7.8, 4.9.

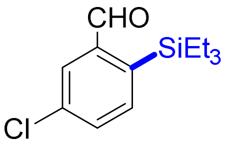
HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Si$ $[M+Na]^+$ 273.1287, found: 273.1285.

Ortho-silylation of 3-methoxybenzaldehyde: Method A:

The 3-methoxybenzaldehyde (**1h**, 68.0 mg, 0.5 mmol), was subjected to conditions following method A. Crude reaction mixture analysis by GC/MS showed 10% conversion and obtained 5% isolated product. Spectral data was in accordance with the reported data.

Ortho-silylation of 3-chlorobenzaldehyde: Method B:

The *ortho*-silylated 3-chlorobenzaldehyde was prepared following method B using 3-chlorobenzaldehyde (**1i**, 70 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 86.5 mg of **2i** (68%) as liquid.



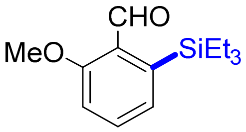
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.53 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 0.89-0.93 (m,15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1, 143.4, 138.8, 138.0, 136.2, 133.0, 130.5, 7.7, 4.5.

HRMS (ESI) *m/z* calcd for $C_{14}H_{23}ClO_2Si$ $[M+Na]^+$ 309.1054, found: 309.1054.

Ortho-silylation of 2-methoxybenzaldehyde: Method B:

The *ortho*-silylated 2-methoxybenzaldehyde was prepared following method B using 2-methoxybenzaldehyde (**1j**, 68.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 85.0 mg of **2j** (68%) as colourless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 7.49-7.52 (m, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 0.87-0.89 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 163.1, 141.2, 134.4, 130.0, 129.0, 112.5, 55.7, 8.1, 4.1.

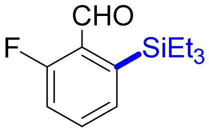
HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Si$ $[M+Na]^+$ 273.1287, found: 273.1299.

Ortho-silylation of 2-methoxybenzaldehyde: Method A:

The 2-methoxybenzaldehyde (**1j**, 68.0 mg, 0.5 mmol), was subjected to conditions following method A. Crude reaction mixture analysis by GC/MS and TLC showed no product formation, entire starting material remained unchanged.

Ortho-silylation of 2-fluorobenzaldehyde: Method B:

The *ortho*-silylated 2-fluorobenzaldehyde was prepared following method B using 2-fluorobenzaldehyde (**1k**, 62.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 66.7 mg of **2k** (56%) as liquid.



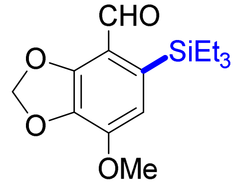
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.53-7.58 (m, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.14-7.19 (m, 1H), 0.89 (bs, 15H).

^{13}C NMR ($CDCl_3$, 200 MHz): δ 189.2 (d, $J_{C\text{-}F}$ = 18.4 Hz), 166.4, 142.2 (d, $J_{C\text{-}F}$ = 10.4 Hz), 134.9 (d, $J_{C\text{-}F}$ = 34.4 Hz), 132.6 (d, $J_{C\text{-}F}$ = 14.4 Hz), 129.0 (d, $J_{C\text{-}F}$ = 11.2 Hz), 117.2 (d, $J_{C\text{-}F}$ = 84.8 Hz), 7.9, 3.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}FOSi$ $[M+Na]^+$ 261.1087, found: 261.1088.

Ortho-silylation of 7-methoxybenzodioxole-4-carboxaldehyde: Method B:

The *ortho*-silylated 7-methoxybenzodioxole-4-carboxaldehyde was prepared following method B using substrate **1l** (90.0 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 109.0 mg of **2l** (74%) as liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.32 (s, 1H), 6.03 (s, 2H), 3.95 (s, 3H), 0.91-0.95 (m, 15H).

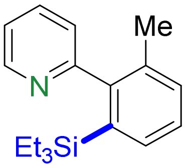
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 155.4, 144.5, 139.0, 137.1, 113.3, 110.6, 101.6, 56.5, 7.8, 5.7.

HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_4Si$ $[M+Na]^+$ 317.1185, found: 317.1166.

Ortho-silylation of 7-methoxybenzodioxole-4-carboxaldehyde: Method A:

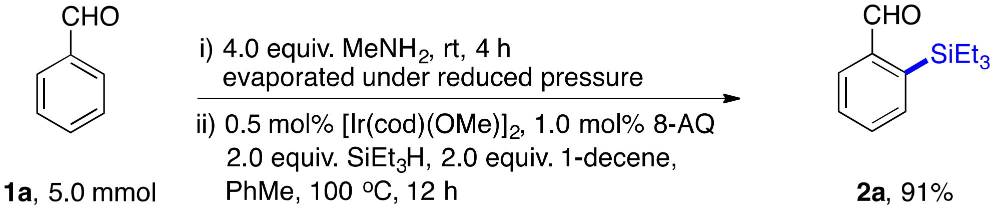
In a glove box, a 5.0 mL wheaton microreactor was charged with substrate **1l** (90 mg, 0.5 mmol), Ir-NHC-cat. (16.0 mg, 5 mol%), nbe (141.0 mg, 3 equiv.), dry PhMe (3 mL). The microreactor was sealed and heated at 115 °C for 3 h. After which Et_3SiH (237.4 μL, 3 equiv.) was added and stirred at 115°C for 24 h. Crude reaction mixture analysis by GC/MS showed no product formation, entire starting material remained unreacted.

Ortho-silylation of 2-methyl substituted 2-phenylpyridine: Method B:



The *ortho*-silylated 2-methyl substituted 2-phenylpyridine was prepared following method B, no $MeNH_2$ was used, using substrate **1m** (84.6 mg, 0.5 mmol). After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (10% EtOAc in hexane) gave 138 mg of **2m** (98%) as liquid. Spectral data are in accordance with the reported data.**Error! Bookmark not defined.**

Gram Scale Synthesis of *ortho*-silylated benzaldehyde using low catalyst loading: Method B:

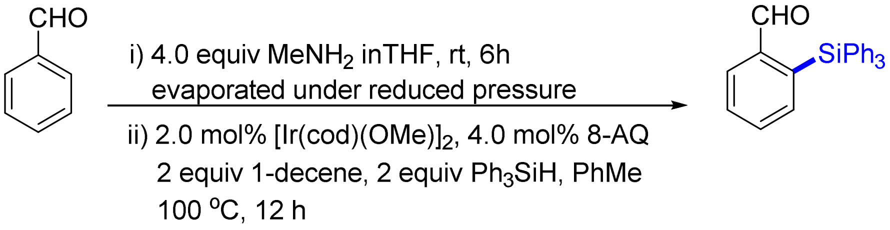


A 25 mL pressure tube was charged with benzaldehyde (**1a**, 530.6 mg, 5.0 mmol), methylamine in THF solution (10 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (16.6 mg, 0.5 mol%), 8-AQ (7.2 mg, 1.0 mol%), 1-decene (1893.0 μL, 2.0 equiv.), Et_3SiH (1592.0 μL, 2.0 equiv.) and dry PhMe (10.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 100 °C. The reaction mixture was stirred for 12 h. After completion (judged by GC/MS), PhMe was removed under reduced pressure and chromatographic separation with silica gel (1% EtOAc in hexane) gave 1.0 g of *ortho*-silylated benzaldehyde (**2a**, 91%) as liquid.

Synthesis of *ortho*-silylated benzaldehyde using Ph_3SiH and dtbpy ligand

A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**, 53.0 mg, 0.5 mmol), methylamine in THF solution (1.0 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (6.6 mg, 2.0 mol%), dtbpy (5.4 mg, 4.0 mol%), 1-decene (189.3 µL, 2.0 equiv.), Ph_3SiH (260.4 mg, 2.0 equiv.) and dry PhMe (1.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 100 ^{o}C. The reaction mixture was stirred for 14 h. After completion (judged by GC/MS), no reaction occurred.

Synthesis of *ortho*-silylated benzaldehyde using Ph_3SiH and 8-AQ ligand



A 5.0 mL wheaton microreactor was charged with benzaldehyde (**1a**, 53.0 mg, 0.5 mmol), methylamine in THF solution (1.0 mL, 4.0 equiv.) and stirred for 4 h at room temperature. The crude reaction mixture was dried under reduced pressure. In a glove box, this crude imine was charged with $[Ir(cod)(OMe)]_2$ (6.6 mg, 2.0 mol%), 8-AQ (2.9 mg, 4.0 mol%), 1-decene (189.3 µL, 2.0 equiv.), Ph_3SiH (260.4 mg, 2.0 equiv.) and dry PhMe (1.0 mL). The microreactor was capped with a teflon pressure cap and placed into pre-heated aluminum block at 100 ^{o}C. The reaction mixture was stirred for 14 h. After completion (judged by GC/MS), 90% conversion to *ortho* silylated product occurred.

References:

1. (a) Colvin, E. W. Silicon Reagents in Organic Synthesis, Academic Press, London, **1988**. (b) Chemistry of Organosilicon Compounds, Vol. 3 (Eds.: Rappoport, Z.; Apeloig, Y.), Wiley-VCH, New York, **2001**. (c) Mortensen, M.; Husmann, R.; Veri, E.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 1002. (d) Zhang, F.; Wu, D.; Xu, Y.; Feng, X. J. *Mater. Chem.* **2011**, *21*, 17590. (e) Showell, G. A.; Mills, J. S. *Drug. Discov. Today* **2003**, *8*, 551. (f) Franz, A. K.; Wilson, S. O. *Med. Chem.* **2013**, *56*, 388. (g) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012**, *337*, 1644. (h) Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954. (i) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

2. (a) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147. (b) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (c) Hirabayashi, K.; Ando, J.-i.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409. (d) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (e) Nguyen, T.-H.; Castanet, A.-S.; Mortier, J. *Org.Lett.* **2006**, *8*, 765. (f) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

3. (a) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843. (b) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449. (c) Denmark, S. E.; Smith, R. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104. (d) Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15958.

4.For Pt-catalyzed imine directed silylation, see: (a) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *J. Chem. Soc. Chem. Commun.* **1995**, 1129. For Ru-catalyzed imine-directed silylation, see: (b) Kakiuchi, F.; Matsumoto, M.; Tsuchiya, K.; Igi, K.; Hayamizu, T.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **2003**, *686*, 134.

5. For Ru-catalyzed oxazoline-directed silylation, see: (a) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 422. (b) Sakurai, T.; Matsuoka, Y.; Hanataka, T.; Fukuyama, N.; Namikoshi, T.; Watanabe, S.; Murata, M. *Chem. Lett.* **2012**, *41*, 374.

6. For Ru-catalyzed pyridine-directed silylation, see: (a) Kakiuchi, K.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S.; *Chem. Lett.* **2002**, 396. For Rh-catalyzed pyridine-directed silylation, see: (b) Tobisu, M.; Ano, Y.; Chatani, N. *Chem. Asian J.* **2008**, *3*, 1585. For Pd-catalyzed pyridine-directed silylation, see: (c) Xiao, Q.; Meng, X.; Kanai, M.; Kuninobu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 3168.

7. For Ru-catalyzed pyrazole-directed silylation, see: Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502.

8. For Ir-catalyzed secondary amine and pyridine-directed silylation, see: (a) Li, Q.; Driess, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 8471. (b) Wakai, T.; Kanai, M.; Kuninobu, Y. *Org. Lett.* **2015**, *17*, 1758.

9. For Sc-catalyzed alkoxy-directed silylation, see: Oyamada, J.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 10720.

10. For Pd-catalyzed amide-directed silylation, see: Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968.

11. (a) Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068. (b) Ishiyama, T.; Sato, K.; Nishio, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346.

12. Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149.

13. (a) Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2016**, 138, 84. (b) Bisht, R.; Chattopadhyay, B. *Synlett* **2016**, *27*, 2043.

14. (a) Shimizu, S.; Abe, N.; Goto, N.; Niwa, T.; Iguchi, A. Jpn. Pat. JP 01261367A, **1998**. (b) Peter, S.; Gerhard, H.; Elisabeth, H.; Ralf, K.; Hartmann, K.; Albrecht, H.; Norbert, G.; Helmut, W.; Karl-Otto, W.; Ulf, M. US Pat. US 5 733850, **1998**.

15. For Rh-catalyzed arene silylation involving Rh(I)–Rh(III) cycle, see: Chen, C.; Hartwig, J. F. J. Am. Chem. Soc. **2014**, 136, 12064.

16. An early report for the mechanism of Si-H and C-H bond activation by Ir(III)-Ir(V) catalytic cycle, see: (a) Klei, S.R.; Tilley, T. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 1816. (b) Sangtrirutnugul, P.; Tilley, T. D. *Organometallics* **2007**, *26*, 5557.

17. For the support of the Ir(III)-Ir(V) catalytic cycle by DFT calculations, see: Strout, D. L.; Zaric, S.; Niu, S.; Hall, M. B. *J. Am. Chem. Soc.* **1996**, *118*, 6068.

18. With HSiEt3, alkene-silylation was observed.

19. Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149.

20. (a) Sachs, F. *Liebigs Ann. Chim.* **1909,** 365, 53. (b) Herbert, J. M.; Woodgate, P. D.; Denny, W. A. *J. Med. Chem.* **1987**, 30, 2081.

21. Xi, L.-Y.; Zhang, R.-Y.; Liang, S.; Chen, S.-Y.; Yu, X.-Q. *Org. Lett.* **2014**, *16*, 5269.

Chapter 6

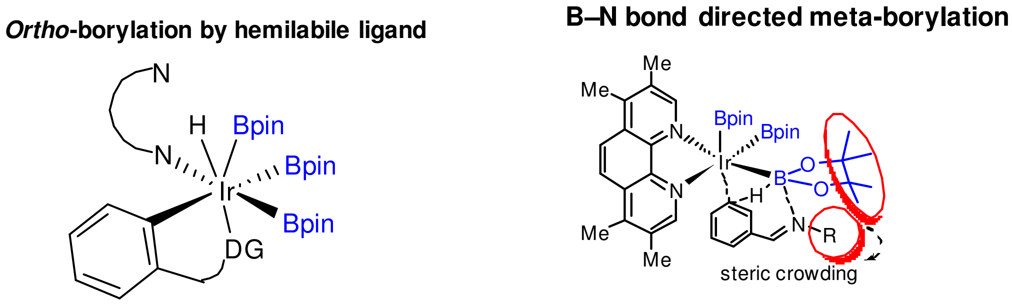
Summary of Research Work

Summary:

Transition metal-catalyzed C-H activation borylation/silylation has created a ripple effect in the field of direct C-H functionalization. The two competent approaches not only surmounted the limitations of traditional approaches instead have opened up new avenues in the field of C-H functionalization. The work compiled in this thesis elucidates the advancement that took place in C-H borylation since its inception. Sterics no longer remained the sole governing factor for regioselectivity, rather traceless directing group, non-covalent interaction and sterics of catalyst-ligand-substrate plays guiding role for site-selectivity.

The contemporary approach C-H silylation is also explored to unravel the unconventional catalytic manifold Ir(III)-(V) for accomplishing *ortho* C-H silylation of benzaldehydes and heteroarenes.

- Chapter 1 presents an overview of significant events that took place in C-H borylation and C-H silylation since their debut in the area of direct C-H functionalization.
- Chapter 2 explicitly demonstrates the decisive role played by nature of ligand for site-selectivity. Usage of hemilabile ligand furnished *ortho*-borylated products whereas congruous sterics and electronics of ligand after encapsulation into the cavity of trisboryl complex facilitated noncovalent B-N interaction and electrostatic interaction affording *meta*-selective products.



***Ortho*-borylation by hemilabile ligand**

B–N bond directed meta-borylation

Fig. 6.1. Transition states for *ortho*-borylation and *meta*-borylation of benzaldehydes

- Chapter 3 describes *ortho*-borylation of aniline and heteroaromatics by the aid of non-covalent interaction (H-bonding between N-H bond of substrate and O of Beg ligand present on the catalyst) is achieved.

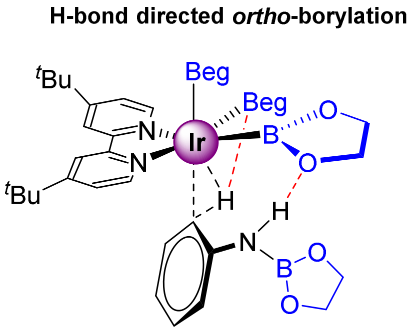


Fig. 6.2. Transition state for H-bond directed *ortho*-borylation of anilines and heteroaromatics

- Chapter 4 represents how by manipulating with the sterics of substrate-ligand-catalyst combination remote borylation of chiral BINOL is accomplished. Subsequent Suzuki cross-coupling yielded 6,6' diarylated product, the reported synthesis of which was multistep and tedious.

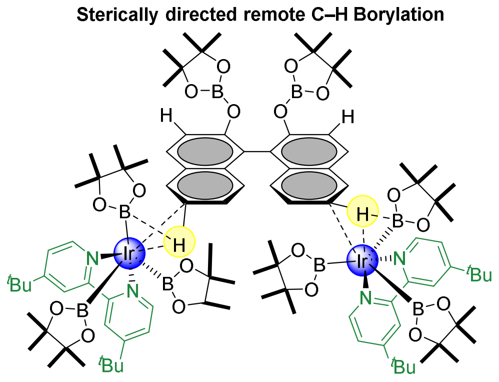
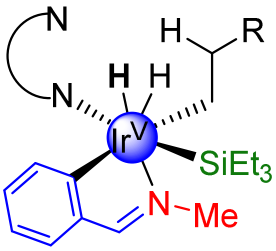


Fig. 6.3. Transition state for sterically controlled remote diborylation of BINOL

Chapter 5 displays a robust methodology for *ortho* C-H silylation of benzaldehydes and heteroarenes. Unconventional Ir(III)-(V) catalytic cycle is plausible which is supported by mechanistic experiments.`



***Ortho*-silylation by hemilabile ligand**

Fig. 6.4. Transition state for *ortho*-silylation by hemilabile ligand

1. Formal Ir-Catalyzed Ligand-Enabled *Ortho*- and *Meta*-Borylation of Aromatic Aldehydes via in Situ Generated Imines. Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc*. **2016**, *138*, 84.
2. Achieving High *Ortho*-Selectivity in Aniline C-H Borylations by Modifying Boron Substituents. Smith, M. R.; Bisht, R.; Haldar, C.; Pandey, G.; Dannatt, J. E.; Ghaffari, B.; Maleczka, R. E.; Chattopadhyay, B. *ACS Catal*. **2018**, *8*, 6216.
3. Double-Fold Remote C-H Bond Activation/Borylation of BINOL: A Unified Strategy for Direct Arylation of BINOL. Ranjana Bisht, Jagriti Chaturvedi, Gajanan Pandey and Buddhadeb Chattopadhyay. (Manuscript submitted).
4. *Ortho*-selective C(sp2)–H silylation of arenes and heteroarenes: Detailed mechanistic investigation of Ir(I)-Ir(III) and Ir(III)-Ir(V) catalytic cycle. Ranjana Bisht, Satyajit Roy, Gajanan Pandey and Buddhadeb Chattopadhyay. (Manuscript under preparation).

Seminars attended

1. *Meta*-Selective Borylation of Aromatic Aldehydes, JNOST, CDRI, 2017. (Oral presentation).
2. Formal Ir-Catalyzed Ligand-Enabled *Ortho*- and *Meta*-Borylation of Aromatic Aldehydes via in Situ Generated Imines, National seminar on “Role Of Analytical Techniques In Advanced Scientific Research” National P.G College Lucknow. (Awarded Best Oral presentation)

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Formal Ir-Catalyzed Ligand-Enabled Ortho and Meta Borylation of Aromatic Aldehydes via in Situ-Generated Imines

Ranjana Bisht[†] and Buddhadeb Chattopadhyay[*,†]

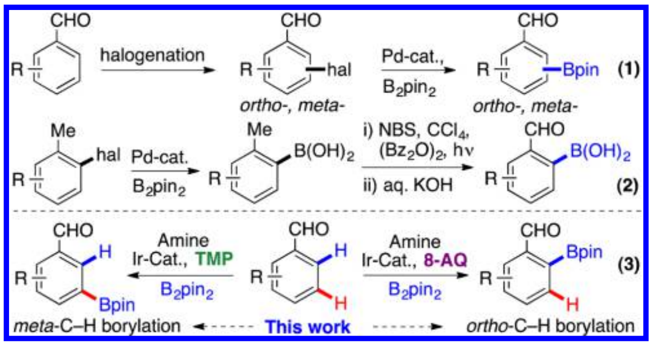
[†]Center of Bio-Medical Research, Division of Molecular Synthesis & Drug Discovery, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli Road, Lucknow, Uttar Pradesh 226014, India

Ⓢ *Supporting Information*

ABSTRACT: The ligand-enabled development of ortho and meta C−H borylation of aromatic aldehydes is reported. It was envisaged that while ortho borylation could be achieved using *tert*-butylamine as the traceless protecting/directing group, meta borylation proceeds via an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. These ligand−substrate electrostatic interactions and secondary B−N interactions provide an unprecedented controlling factor for meta-selective C−H activation/borylation.

Over the past decade, C−H bond functionalizations have attracted extensive attention as competent and ideal reactions.[1] From this perspective, C−H bond borylation has shown potential because of the synthetic versatility for which B−C bonds are well-known. A major challenge in C−H borylations is how to control the selectivity. Generally, steric effects often govern the regioselectivity of aromatics,[2] making C−H borylations complementary to widely used directed ortho metalations (DoMs).[3] However, the inherent functional group restriction and practical limitations of DoMs (e.g., groups like esters are incompatible with DoM and require low temperature) have strengthened efforts to develop efficient method for ortho C−H borylations. In this context, few methods for the functional-group-directed[4] ortho borylations[5] have been developed.

On the other hand, meta-selective C−H bond borylation of arenes remains a great challenge. The development of strategy for meta-selective C−H bond borylation is very difficult. Literature reports revealed that only one type of meta C−H borylation is available, that by Smith and Maleczka[6] and Hartwig[7] from 1,3-disubstituted arenes. The regiochemistry of this meta borylation results mainly from sterics.[8] Despite the broad utility of this sterically controlled meta borylation, the chemistry is limited mostly to 1,3-disubstituted arenes. Moreover, arenes bearing reactive functional groups such as aldehydes, ketones, etc. are not well tolerated.[9] Notably, when this Communication was in preparation, a paper describing a novel concept of a meta-selective C−H borylation by a secondary interaction between the ligand and the substrate appeared.[10] Unarguably, this method is one of the most efficient approaches toward meta borylation. However, there are many unsolved problems for the meta borylation. Thus, a critical challenge in developing these catalytic processes is the selective ortho and meta borylation of benzaldehydes. Traditionally, ortho- and meta-borylated benzaldehydes were prepared via halogenation of benzaldehydes followed by a Miyaura cross-coupling reaction with bis(pinacolato)diborane (eqs 1 and 2).[11,12] Herein we report the discovery of a one-pot unified strategy for ortho- and meta-selective C−H borylations of benzaldehydes using ligand-enabled iridium-catalyzed C−H activation (eq 3).



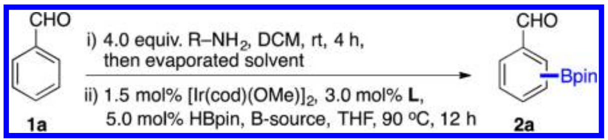
Recently, Fernández-Lassaletta,[13] Sawamura,[14] and Ishiyama[15] disclosed an elegant nitrogen-directed ortho borylation of 2-phenylpyridines and hydrazones. Inspired by these results, we hypothesized that imines may serve as an easily removable directing group[16] for ortho borylation of benzaldehydes. To test this hypothesis, benzaldehyde-derived imines were treated with B_2pin_2 under the standard borylation conditions using hydrazone-derived ligand **L1** developed by Fernández and Lassaletta[13a] (Table 1, entry 1). While no borylation was observed for the methyl and isopropyl imines, the *tert*-butyl imine gave good ortho selectivity (86%; entry 4).[17] Notably, when the crude reaction mixtures were monitored by GC/MS, the products appeared as aldehyde-borylated products.[18] Gratifyingly, the combination of *tert*-butylamine, 8-AQ, and B_2pin_2 was found to be the best borylation conditions, giving 100% ortho selectivity and an excellent isolated yield (87%) (entry 6). Notably, methylamine provided only 7% yield using 8-AQ as the ligand system (entry 7), presumably because the methyl imine is incapable of opening a vacant coordination site in order to undergo the ortho borylation because of the lower steric bulk compared with the *tert*-butyl imine.[19] Other ligand systems such as **L2**, **L3**, and **L4** were less effective than the 8-AQ ligand system (entries 8−10).

With these promising results in hand, borylations for a range of aldehydes were executed, and the results are shown in Table 2.

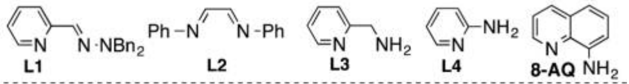
Received: November 7, 2015
Published: December 21, 2015

DOI: 10.1021/jacs.5b11683
J. Am. Chem. Soc. 2016, 138, 84−87

Table 1. Evaluation and Optimization of the Reaction Conditions[a]



#	R	Ligand (L)	B-source	Ratio (o/m/p)[b]	Yield (%)
1	Me	L1	B_2pin_2 (0.7 eq.)	–	0
2	^iPr	L1	B_2pin_2 (0.7 eq.)	–	0
3	^tBu	L1	HBpin (1.5 eq.)	33/37/30	53
4	^tBu	L1	B_2pin_2 (0.7 eq.)	86/8/6	57[c]
5	^tBu	8-AQ	HBpin (1.5 eq.)	–	0
6	^tBu	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	87[d]
7	Me	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	7
8	^tBu	L2	B_2pin_2 (0.7 eq.)	100/0/0	66[e]
9	^tBu	L3	B_2pin_2 (0.7 eq.)	95/3/2	72[f]
10	^tBu	L4	B_2pin_2 (0.7 eq.)	97/2/1	62[g]

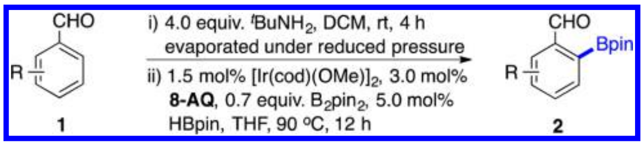


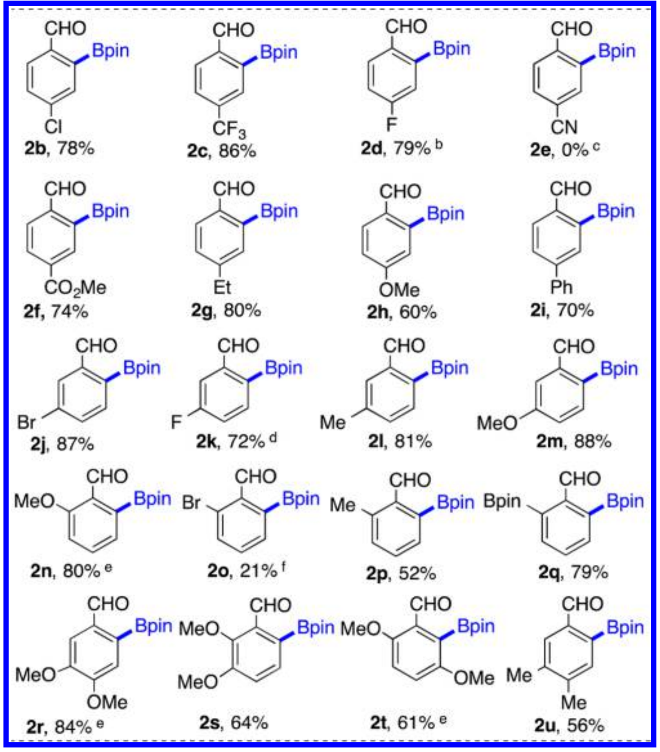
[a] Reactions were run with 1.0 mmol of substrate, and yields are for isolated ortho isomers after column chromatography. [b] Ratios were calculated by GC-FID analysis of the crude reaction mixtures. In GC/MS no imine-borylated products were found; only aldehyde-borylated products were observed. [c] Mono/*o,o*-di = 90/10. [d] Mono/*o,o*-di = 89/11. [e] Mono/*o,o*-di = 80/20. [f] Mono/*o,o*-di = 87/13. [g] Mono/*o,o*-di = 85/15.

The reactions were conducted under identical conditions, and the reaction times were not optimized. It was found that diverse substituents such as halogens (Cl, F, Br), alkyl groups (Me, Et, CF_3), phenyl, and methoxy were tolerated well under these borylation conditions. Irrespective of the substituent present in the aryl ring, 4-substituted benzaldehydes smoothly underwent C−H borylations to afford the ortho-directed products in good to excellent yields without any diborylations (entries **2b**−**d** and **2f**−**i**), except for entry **2d**, which resulted in 7% meta isomer. However, 4-cyanobenzaldehyde failed to undergo C−H borylation (entry **2e**). Employment of other ligand systems such as **L1**, **L2**, **L3**, and **L4** was also unsuccessful (see the Supporting Information (SI) for details). Remarkably, for borylation of 4-phenylbenzaldehyde, the Ph C−H bonds are unperturbed under the borylation conditions, producing exclusively the ortho-directed product (entry **2i**). Notably, meta-substituted benzaldehydes (entries **2j**−**m**) reacted regioselectively at the sterically less impeded C−H site. In the case of 3-fluorobenzaldehyde, though the expected borylation position is the most acidic proton, flanked by CHO and F, it did not undergo borylation exclusively (25% borylation) under these reaction conditions (entry **2k**). Instead, borylation occurred at the other ortho proton, which is less acidic. Next, we studied the scope of 2-substituted substrates. It was found that both electron-rich and electron-poor substituents are very efficient in these C−H borylations, giving exclusively ortho products (entries **2n**, **2p**, and **2q**). However, 2-bromobenzaldehyde borylation was not good (21% conversion; entry **2o**). Furthermore, we have shown that these borylations can be successfully employed to a range of highly electron-rich and differently substituted benzaldehydes (entries **2r**−**u**).

Next, we focused on the ligand screening for the meta-selective C−H activation/borylation. We chose benzaldehyde as our model system, and borylation was performed with bipyridines **L5**−**L7**. As shown in Table 3, there is a clear indication of increasing meta selectivity as the bipyridine ligand is made more electron-rich (entries 1−3). Encouraged by these initial results,

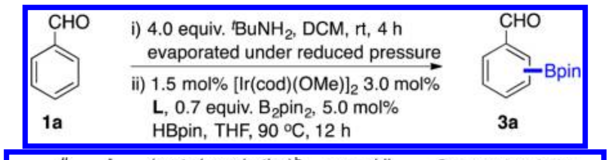
Table 2. Ortho Borylation of Substituted Benzaldehydes[a]



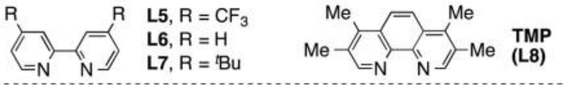


[a] Reactions were run with 1.0 mmol of substrate, and yields are for isolated aldehyde-borylated products after column chromatography. [b] Ortho/meta = 93/07. [c] No reaction occurred even with ligand **L1**. [d] ortho/ortho = 75/25. [e] Reactions were conducted using ligand **L1**. [f] 21% conversion; the product could not be isolated because of rapid protodeborylation.

Table 3. Ligand Screening for Meta Borylation[a]



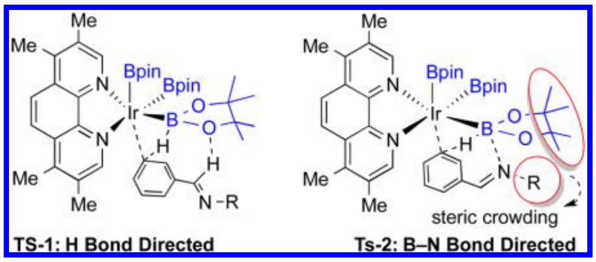
#	L	(meta/para/ortho)[b]	mono/di	Conversion (%)[c]
1	**L5**	11/61/28	89/11	63
2	**L6**	33/46/21	82/18	83
3	**L7**	47/37/16	88/12	88
4	**L8**	66/23/11	97/03	93 (67)[d]



[a] Reactions were run with 1.0 mmol of substrate. [b] GC ratios. [c] GC conversion was measured using dodecane as an internal standard. [d] The isolated yield of the meta-borylated aldehyde product is given in parentheses.

we next attempted borylation using TMP (**L8**) as the ligand. To our delight, improved meta selectivity (66% meta-borylated aldehyde product) was observed with excellent conversion (entry 4). To find out the origin of the increased selectivity, we hypothesized that two important factors might play significant roles: (i) an electrostatic interaction[20] arising from the encapsulation[21] by the tris(boryl)iridium complex attached with the electron-rich ligand and imine substrate and (ii) a secondary interaction of the substrate via either H-bonding[22] between the imine hydrogen atom and the boryl oxygen atom of the catalyst (Chart 1, **TS-1**) or an interaction between the imine N atom and the boryl B atom of the catalyst (**TS-2**).

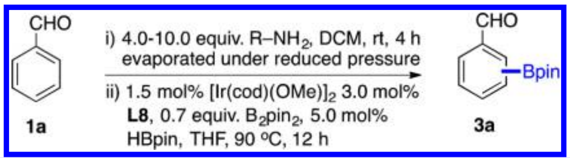
Chart 1. Hypothesis for the Origin of Meta Selectivity



As the electrostatic interaction that enhances the meta selectivity is present in both cases (**TS-1** and **TS-2**), the question of which transition state (**TS-1** or **TS-2**) actually controls the meta selectivity still remains. In the case of the H-bond-directed approach (**TS-1**), the imine substituent (R) is far away from the reaction center, and thus, the outcome of the meta borylation should not be dependent on the size of the R group. On the other hand, in the case of **TS-2**, the outcome should be affected by the size of the R group because of the close proximity of the R group and the boryl group of the catalyst. Thus, we hypothesized that steric alteration of the imine substituent R from ^{t}Bu to ^{i}Pr to Me should enhance the meta selectivity further.

To test this hypothesis, borylations were performed with the isopropyl imine and methyl imine of benzaldehyde. Remarkably, a clear trend for the enhancement of the meta selectivity was observed as the imine substituent R was made smaller (Table 4). We reasoned that the enhanced meta selectivity (100% for R = Me) results from the reduced steric crowding, which facilitates the secondary interaction through the imine N atom and boryl B atom of the catalyst (**TS-2**). However, the question of mechanism is open to debate, and the detailed mechanism of each step remains to be ascertained.

Table 4. Effect of the Imine Substituent: Proof of the Hypothesis for Meta Borylation[a]

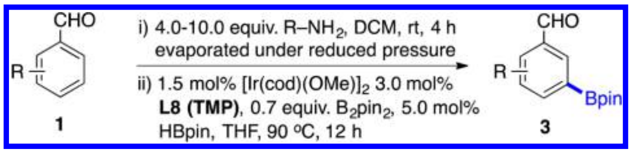


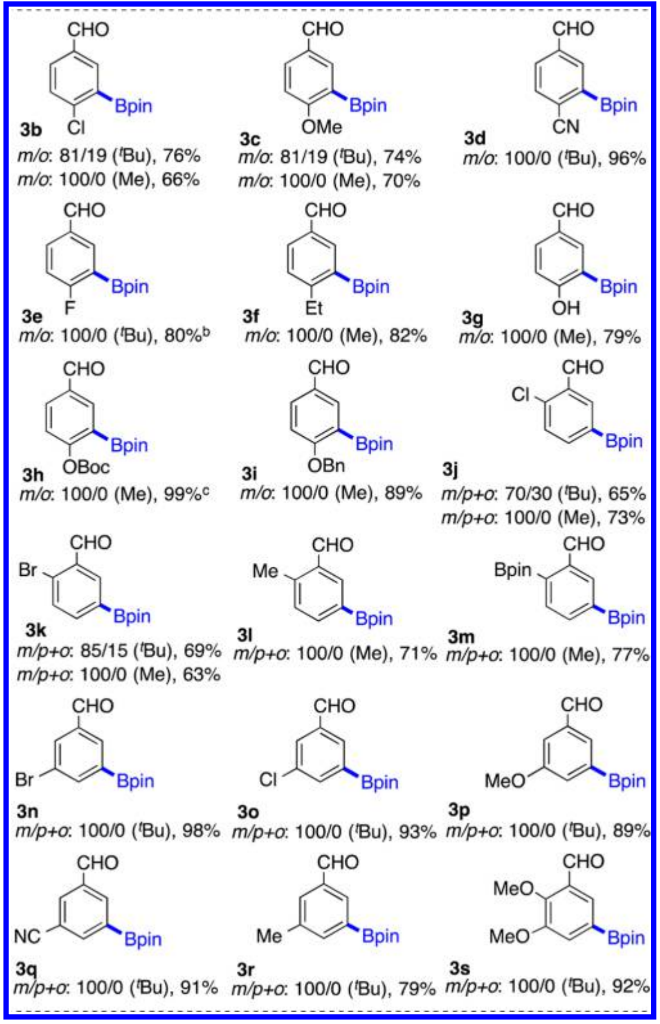
#	R	meta/(para+ortho)[b]	mono/di	Conversion (%)[c]
1	^{t}Bu	66/34	93/07	78 (57)
2	^{i}Pr	84/16	90/10	73
3	Me	97/03	97/03	80 (73)[d]

[a] Reactions were run with 1.0 mmol of substrate; see the SI for details. [b] GC ratios. [c] GC conversions, In GC/MS, no imine-borylated products were found; only aldehyde-borylated products were observed. [d] The isolated yield of the aldehyde-borylated product is given in parentheses.

Next, we explored the substrate scope for the meta borylation, and the results are summarized in Table 5. A wide range of substituents were well-tolerated under the borylation conditions, affording excellent meta selectivity and excellent isolated yields. For example, while 4-chlorobenzaldehyde gave 81/19 meta/ortho selectivity using *tert*-butylamine, it afforded 100% meta selectivity with methylamine as the protecting/directing group (entry **3b**). 4-Methoxybenzaldehyde gave 81/19 and 100/0 meta/ortho selectivity with *tert*-butylamine and methylamine, respectively (entry **3c**). Likewise, 4-cyano-, 4-fluoro-, 4-ethyl-, and 4-hydroxybenzaldehyde resulted the meta isomer as the sole product (entries **3d**–**g**). It deserves mention that even the use of a very bulky substituent such as an OBoc[23] or OBn group at the 4-position of the benzaldehyde afforded complete meta

Table 5. Meta Borylation of Substituted Benzaldehydes[a]





3b *m/o*: 81/19 (^{t}Bu), 76%
m/o: 100/0 (Me), 66%

3c *m/o*: 81/19 (^{t}Bu), 74%
m/o: 100/0 (Me), 70%

3d *m/o*: 100/0 (^{t}Bu), 96%

3e *m/o*: 100/0 (^{t}Bu), 80%[b]

3f *m/o*: 100/0 (Me), 82%

3g *m/o*: 100/0 (Me), 79%

3h *m/o*: 100/0 (Me), 99%[c]

3i *m/o*: 100/0 (Me), 89%

3j *m/p+o*: 70/30 (^{t}Bu), 65%
m/p+o: 100/0 (Me), 73%

3k *m/p+o*: 85/15 (^{t}Bu), 69%
m/p+o: 100/0 (Me), 63%

3l *m/p+o*: 100/0 (Me), 71%

3m *m/p+o*: 100/0 (Me), 77%

3n *m/p+o*: 100/0 (^{t}Bu), 98%

3o *m/p+o*: 100/0 (^{t}Bu), 93%

3p *m/p+o*: 100/0 (^{t}Bu), 89%

3q *m/p+o*: 100/0 (^{t}Bu), 91%

3r *m/p+o*: 100/0 (^{t}Bu), 79%

3s *m/p+o*: 100/0 (^{t}Bu), 92%

[a] Reactions were run with 1.0 mmol of substrate; for details, see the SI. Yields are for isolated meta-borylated aldehyde products after column chromatography. [b] 2.0 mmol of substrate was used. [c] 99% conversion.

selectivity (entries **3h** and **3i**). Thus, these observations are consistent with the notion that an electrostatic interaction and a secondary interaction between the imine N atom and the boryl B atom of the catalyst control the meta selectivity.

On the other hand, 2-substituted substrates proved to be challenging because of several open reactive sites for C−H activation/borylation. For example, 2-Bpin-, 2-bromo-, 2-chloro-, and 2-methylbenzaldehyde could give mixtures of isomers. To our delight, they resulted complete meta selectivity (entries **3j**−**m**). For meta-substituted benzaldehydes, as expected, borylations occurred at the meta position, and no other borylations were observed (entries **3n**−**r**). Moreover, highly electron-rich 2,3-dimethoxybenzaldehyde proved to be an excellent meta-borylation substrate, giving an excellent yield (entry **3s**).

In summary, we have developed two complementary methods for the ortho- and meta-selective C−H bond activation/borylation of aromatic aldehydes that cannot be obtained with DoM or any other methodology. While the ortho borylation proceeds through directed C−H activation/borylation using *tert*-butylamine as the traceless protecting/directing group, the meta borylation undergoes through an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. Both methods show very broad substrate scope and functional group tolerance. However, at this stage, we are not entirely certain about the working hypothesis for the meta-selective C−H activation/borylation, and further studies are underway, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11683.

Full characterization, copies of all spectral data, and experimental procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*buddhadeb.c@cbmr.res.in, buddhachem12@gmail.com

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Professor Milton R. Smith III (Michigan State University) is thanked for helpful suggestions. B.C. and R.B. thank DST, New Delhi for a Ramanujan Faculty Award and a JRF (SB/S2/RJN-45/2013), respectively. We thank Dr. Bikash Baishya and Mr. Ajay Verma for helpful discussions on NMR analysis, Mr. Durga Prasad and Mr. Prasant for HRMS, the reviewers for helpful suggestions, and the Director, CBMR for research facilities.

■ REFERENCES

(1) (a) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(3) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem. - Eur. J.* **2010**, *16*, 8155.

(4) For a recent review of functional-group-directed borylation, see: Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229.

(5) (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (c) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (d) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855. (e) Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (f) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (g) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134.

(6) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792.

(7) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(8) (a) Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Cho, J. Y.; Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **2000**, *122*, 12868. (c) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305. (d) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539.

(9) For borylation of aromatic ketones, see: Itoh, H.; Kikuchi, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2011**, *40*, 1007.

(10) For secondary-interaction-directed meta-selective C−H borylation, see: Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712.

(11) (a) Tomohiro, K.; Hideto, F.; Katsumi, K.; Shigeru, K. PCT Int. Appl. WO 2010110400, 2010. (b) Takeshi, K.; Hiroshi, N.; Tomoko, I.; Mitsukane, Y.; Kensei, Y. Jpn. Kokai Tokkyo Koho JP 2010173974, 2010.

(12) Matteson, D. S.; Talbot, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 1123.

(13) For Ir-catalyzed nitrogen-directed ortho borylation, see: (a) Ros, A.; Estepa, B.; López-Rodríguez, R.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (b) López-Rodríguez, R.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 9915. (c) Ros, A.; López-Rodríguez, R.; Estepa, B.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

(14) For Rh-catalyzed nitrogen-directed ortho borylation, see: Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.

(15) For aromatic imine-directed ortho borylation, see: Sasaki, I.; Amou, T.; Ito, H.; Ishiyama, T. *Org. Biomol. Chem.* **2014**, *12*, 2041.

(16) For imine-directed ortho silylation, see: (a) Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149. (b) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *Dalton Trans.* **2003**, 236.

(17) *o*-BpinC_6H_4CHO can easily be distinguished by the ~0.6 ppm downfield shift of its CHO resonance in ^{1}H NMR spectra due to hydrogen bonding to a Bpin O.

(18) The imine-borylated products can be seen in the crude ^{1}H NMR spectra (see the SI for details). We assumed that in the GC/MS, the imine-borylated products are hydrolyzed. Likewise, the products are hydrolyzed during silica gel column chromatography.

(19) The mechanism of the ortho C−H bond activation/borylation of aldehydes via in situ-generated imines is related to the analogous ortho borylation of hydrazones reported by Fernández-Lassaletta.[13a]

(20) (a) Das, S.; Incarito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (b) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781. (c) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535.

(21) For encapsulation of iridium species facilitated via an electrostatic interaction, see ref 20b.

(22) For an example of H-bonding of imines, see: (a) Ligtenbarg, A. G.; Hage, R.; Meetsma, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 2* **1999**, 807. For H-bond-directed ortho borylation, see: (b) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2012**, *134*, 11350.

(23) Isolation of **3h** failed because of elimination of the Boc group during silica gel column chromatography. **3g** was isolated instead.

Subscriber access provided by UNIVERSITY OF THE SUNSHINE COAST

Article

Achieving High Ortho Selectivity in Aniline C-H Borylations by Modifying Boron Substituents

Milton R. Smith, Ranjana Bisht, Chabush Haldar, Gajanan Pandey, Jonathan E Dannatt, Behnaz Ghaffari, Robert E. Maleczka, and Buddhadeb Chattopadhyay

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b00641 • Publication Date (Web): 09 May 2018

Downloaded from http://pubs.acs.org on May 9, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W.,
Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society.
However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Achieving High Ortho Selectivity in Aniline C–H Borylations by Modifying Boron Substituents

Milton R. Smith, III,[§,]* *Ranjana Bisht,*[†,‡] *Chabush Haldar,*[†] *Gajanan Pandey,*[‡] *Jonathan E. Dannatt,*[§] *Behnaz Ghaffari,*[§] *Robert E. Maleczka, Jr.,*[§,]* *and Buddhadeb Chattopadhyay,*[†,]*

[§]Department of Chemistry, Michigan State University, 578 South Shaw Lane, East Lansing, Michigan 48824-1322 USA

[†]Division of Molecular Synthesis & Drug Discovery, Centre of Bio-Medical Research (CBMR), SGPGIMS Campus, Raebareli Road, Lucknow 226014, U.P., India

[‡]Department of Applied Chemistry, Babasaheb Bhimrao Ambedkar University, Lucknow 226025, U.P., India

KEYWORDS. C–H activation • hydrogen bonding • computational chemistry • aniline • ortho functionalization

ABSTRACT. High ortho selectivity for Ir-catalyzed C–H borylations (CHBs) of anilines results when B_2eg_2 (eg = ethylene glycolate) is used as the borylating reagent in lieu of B_2pin_2, which is known to give isomeric mixtures with anilines lacking a blocking group at the 4-position. With this modification, high selectivities and good yields are now possible for various anilines, including those with groups at the 2 and 3-positions. Experiments indicate that ArylN(H)Beg species are generated prior to CHB and support the improved ortho selectivity relative to B_2pin_2 reactions arising from smaller Beg ligands on the Ir catalyst. The lowest energy transition states from DFT computational analyses have N–H···O hydrogen bonding interactions between PhN(H)Beg and O atoms in Beg ligands. Ir-catalyzed CHB of PhN(H)Me with B_2eg_2 is also highly ortho selective. ^{1}H NMR experiments show that N-borylation fully generates PhN(Me)Beg prior to CHB. The TS with the lowest Gibbs' was the ortho TS where the Beg unit is oriented anti to the bipyridine ligand.

INTRODUCTION. Anilines are chemicals with important dye, pharmaceutical, agrochemical, and polymer applications.[1] Aniline is commercially prepared by benzene nitration followed by hydrogenation of the nitrobenzene intermediate. Most commercially available substituted anilines are prepared by derivatizing aniline, often through electrophilic aromatic substitution (EAS).[2] The NH_2 group is classified as a strong ortho/para director,[3] even though traditional nitration conditions give 32–49% *meta*-nitroaniline along with the major para isomer.[4] The best selectivities for EASs are typically C4 functionalizations, and most ortho-selective examples are for anilines substituted at C4. For anilines that are unsubstituted at C4, EASs generate significant quantities of para isomers even in some of the most ortho-selective methods.[5] The best traditional synthetic method for aniline ortho functionalization is directed ortho metalation (DoM) of carbamate derivatives, followed by subsequent addition of an electrophile to the ortho carbanion.[6] This approach requires conversion of the aniline to the carbamate, which is removed after the reaction, if aniline products are desired.

Even though directed ortho metalation reactions are remarkably powerful,[7] catalytic methods can exhibit complementary selectivities and functional group tolerance.[8] There are several examples of catalytic ortho functionalizations of aniline. Most require the installation of a directing group prior to C–H functionalization. Removal of the directing group is required to restore the nitrogen functionality to that in the aniline starting material.[9–11] While the NH_2 group would be untouched in ideal catalytic ortho functionalization of primary anilines, the next most desirable process is one where there is no trace in the product of any in situ modification of the amino group during catalysis.

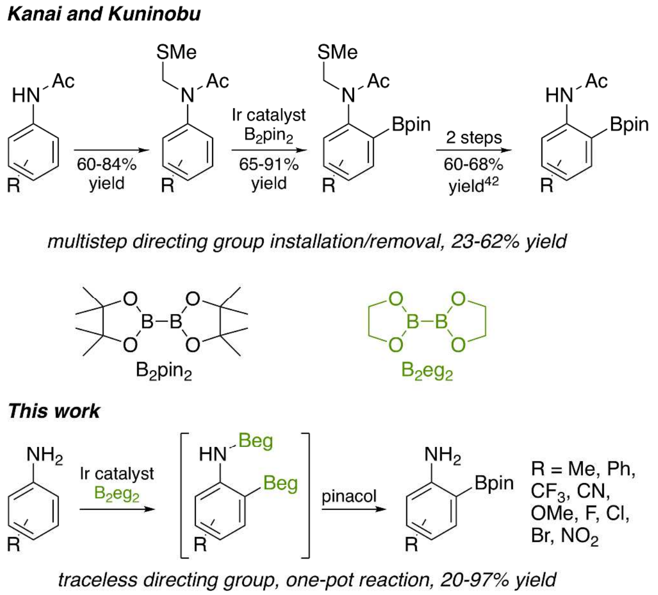
The traceless Ir-catalyzed C–H borylation (CHB) of primary anilines has been described in the literature.[12] C–H borylation is a synthetic method where sp^2, sp^3, and sp C–H bonds are converted to C–B bonds.[13–15] With few exceptions,[16,17] most examples require a catalyst, and metal-catalyzed CHBs have been reported for a number of transition metals.[13,18–20] Some of the earliest reports of metal-catalyzed CHBs of arene $C(sp^2)$–H bonds indicated that the least hindered C–H bonds were generally more reactive.[21–23] This feature became a hallmark of Ir-catalyzed CHBs because regioselectivities generally complement those found in EAS and DoM, as well as the regioselectivities in early examples of catalytic intra- and intermolecular C–H functionalizations that are ortho-selective.[24,25]

The first report of catalytic ortho CHBs relied on classic chelate-directed mechanisms where a substrate functional group binds to a vacant metal site.[26–28] Directing effects of this type have been branded as "inner-sphere".[29] Other inner–sphere approaches, like relay-directed ortho CHBs of silylated phenols and anilines, where reversible Si–H oxidative addition to Ir was proposed to direct borylation, were also developed.[30]

Mechanisms for ortho-directed CHBs have been proposed where the metal center is *not* a directing element.[31,32] In line with Taube's definition, these are defined as "outer-sphere" mechanisms.[29,33] Examples of outer–sphere direction in ortho CHBs include Lewis acid-base,[34–36] hydrogen bonding,[12,33,37] electrostatic interactions,[38] and an example where both inner- and outer-sphere mechanisms are plausible.[39] The electrostatic mechanism is a more subtle variant of the ion-pairing mechanisms proposed by Phipps and co-workers in recently designed meta-selective CHBs,[40] which complements other meta-selective CHBs where outer sphere mechanisms are proposed to account for selectivity.[34,37,41]

Kanai and Kuninobu recently disclosed ortho CHBs of aniline and phenol derivatives (Scheme 1).[36] The bipyridine with the best selectivity is not commercially available. It has an electron-withdrawing aryl group at the bipyridine 5-position and was synthesized from commercially available precursors.[42] To achieve ortho CHB of primary anilines thiomethyl methylene (CH_2SMe) and acyl groups must be attached to N. While this approach provides excellent ortho selectivities, ligand synthesis and the additional synthetic steps to add and subsequently remove functional groups at N are unappealing if ortho-borylated primary anilines are the desired product.

Scheme 1. Comparison of the Kanai-Kuninobu CHB of *N*-Acylated Anilines to This Work.[36,43,44]



The previously reported traceless CHBs of primary anilines built on an initial report of ortho CHBs of *N*-Boc anilines.[12,33] For these aryl carbamates, experiment and theory were consistent with an outer-sphere mechanism involving N–H···O hydrogen bonding between the aniline substrate and an Ir–Bpin ligand giving rise to the ortho selectivity.[33] As shown in Figure 1, previous CHBs required C4 substituents larger than H to achieve high ortho selectivity.[12,33] Additionally, substitution at C2 was deleterious to ortho selectivity. Given that C–B bonds can be readily converted to a host of functional groups, and the aforementioned limited scope of previous ortho-directed CHBs of anilines, a method overcoming these shortcomings would be highly desirable.

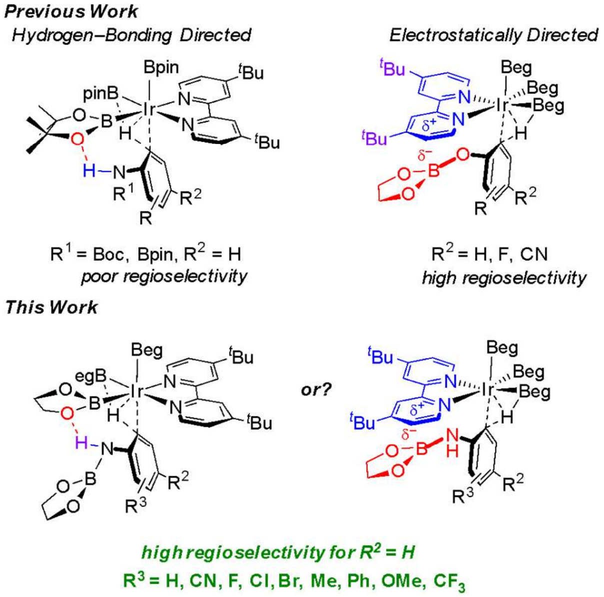


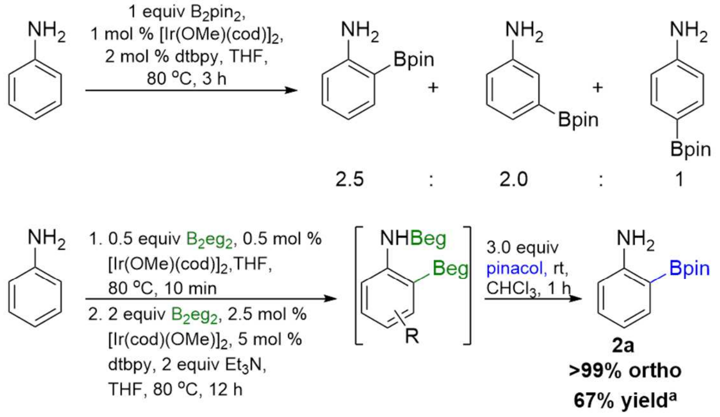
Figure 1. Proposed transition states for ortho borylations of anilines and phenols.

Traceless, ortho-directed CHB of phenols was also recently described.[38] The initial CHB substrates were phenol O-boronate esters ArOBpin (pin = pinacolate). Experimental and computational studies pointed to transition state stabilization arising from electrostatic interactions between the bipyridine bound to Ir and OBpin of the phenol boronate ester. Like previous aniline borylations, 4-substituents larger than H were necessary to achieve synthetically useful ortho selectivity.

An in silico redesign of the catalyst predicted that the ortho CHB transition state could be significantly stabilized if the Bpin groups on Ir and the phenolboronate ester were replaced with Beg (eg = ethylene glycolate). Indeed, this led to exquisite ortho selectivities for Ir-catalyzed CHBs of phenols when the diboron reagent B_2eg_2 was used in lieu of HBpin. This raised the question as to whether ortho selectivities for aniline CHBs could be similarly improved using B_2eg_2. If ortho selectivities indeed improve, is transition state stabilization due to electrostatic interactions or enhanced hydrogen bonding? This paper addresses these questions using experiment and theory synergistically.

RESULTS AND DISCUSSION. Ir-catalyzed CHB of aniline with B_2eg_2 was used to optimize reaction conditions. First, a THF solution of aniline, 0.5 equiv of B_2eg_2, and 0.5 mol % $[Ir(OMe)(cod)]_2$ was briefly heated to generate PhN(H)Beg, which was verified by $^{11}B/^{1}H$ NMR spectroscopy. Then NEt_3, dtbpy (dtbpy = 4,4′-di-^{t}Bu-2,2′-bipyridine), additional B_2eg_2 and $[Ir(OMe)(cod)]_2$ were added, and the resulting solution was heated at 80 °C until borylation ceased. The best results were obtained with a 2.5 mol % loading of $[Ir(OMe)(cod)]_2$, 5 mol % dtbpy, 2.0 equiv B_2eg_2, and 2.0 equiv of NEt_3. When CHB was complete, the eg group was transesterified by treating the reaction mixture with 3.0 equiv of pinacol, and the more stable Bpin product was purified and isolated in 67% yield. Conversion to products suffered at lower catalyst loadings; however, high regioselectivity was achieved. The regioselectivities for aniline CHBs with B_2pin_2 and B_2eg_2 are compared in Scheme 2. To avoid significant diborylation, the control reaction used less B_2pin_2 and a shorter reaction time. Notably, the 2.7:1.8:1 ortho:meta:para isomer ratio for CHB with B_2pin_2 is similar to the ratio previously reported for Ir-catalyzed aniline CHB with HBpin (ortho:meta:para = 2.3:1.5:1).[12] While the major regioisomer is the ortho product, which suggests some favorable interactions for ortho CHB with B_2pin_2, substantial quantities of meta and para CHB products dampen the synthetic utility. In contrast, B_2eg_2, which is easily prepared from commercially available $(OH)_2B–B(OH)_2$ and ethylene glycol, provides exquisite ortho selectivity.

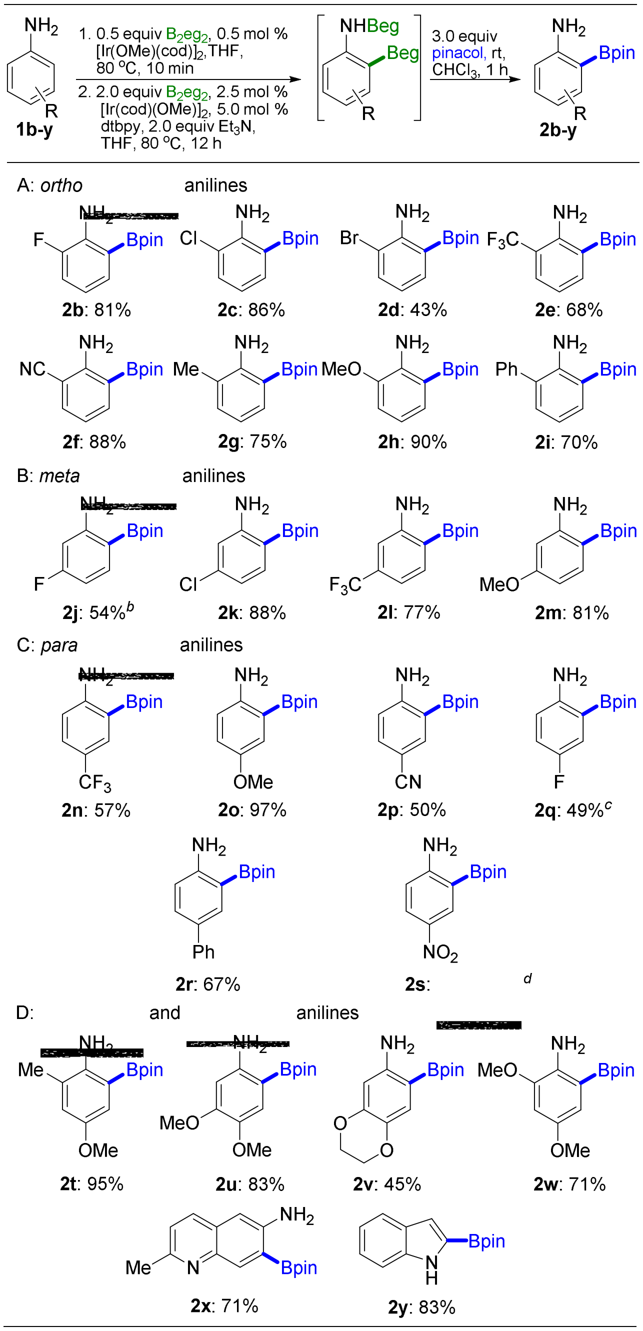
Scheme 2. Aniline CHBs with B_2pin_2 and B_2eg_2.



[a] At 0.5 mmol scale 67% yield was obtained. At 5 mmol scale with 1 mol % loading of $[Ir(OMe)(cod)]_2$, 0.25 mol % in step 1 and 0.75 mol % in step 2, the yield increased to 75%.

We next assessed the substrate scope for ortho selectivity. Table 1 lists the results for twenty-four substrates. The catalyst loadings in Table 1 are (6 mol % Ir) higher than we usually use for borylations because the reactions were run with 0.5 mmol of aniline substrates, using weighed amounts of the $[Ir(OMe)(cod)]_2$. When CHB of aniline was performed on a 5 mmol scale with 0.25 and 0.75 mol % of the precatalyst (2 mol % Ir) in steps 1 and 2 in Scheme 2, ortho-borylated product **2a** was isolated in 75% yield. The average isolated yield is 71(±4)% for substrates in Table 1. For substrate **1q**, 20% diborylation contributed to the low yield of monoborylated product. The only diborylated isomers detected were 2,6-regioisomers. Substrate **1s** had the lowest yield, but it is the first metal-catalyzed CHB of a nitro-containing substrate that gives more than trace quantities. In crude reaction mixtures, CHB was only detected at sites ortho to NH_2.

Table 1. Ortho Borylation of Substituted Anilines with B_2eg_2.[a]

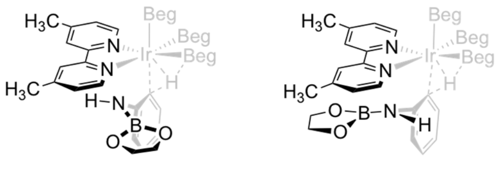


[a]All reactions were carried out on a 0.5 mmol scale, and yields are reported for isolated materials after column chromatographic separation. [b]The other *o*-borylated isomer was observed, but underwent rapid proto-deboronation. [c]20% *o*,*o*-diborylation was observed. [d]Isolated Yield: 20%; GC conversion: 50%.

Gratifyingly, CHBs of meta-substituted anilines **1j-1m** did not generate 5-borylated products, as had been found for Ir-catalyzed CHBs of anilines 1k-1m with HBpin.[12] The yields of ortho-borylated products from CHBs anilines **1k, 1l**, and **1m** increased over those previously reported from CHBs with HBpin by 46%, 24%, and 55%, respectively. Furthermore, this methodology outperforms previously reported CHB of *N*-Boc anilines. No CHBs of 2-substituted *N*-Boc anilines have been reported, and ortho selectivity eroded for substrates that lacked blocking groups at the 4-position. For example, CHB of 3-chloro-*N*-Boc-aniline provided 92% yield but exhibited an ortho:meta selectivity of only 2:1.[33] In addition, this yield does not include removal of the Boc group; however, substrate **1k** provided only the ortho borylated product, **2k**, and was isolated in 88% yield. Substrates **1b- i** underwent CHB with B_2eg_2 at C6 exclusively, yielding ortho-borylated products **2b-2i**. This stands in sharp contrast to previously reported CHBs of 2-substituted anilines with HBpin, where ortho borylation was not observed.[12] Borylation of quinoline **1x** proceeded smoothly providing the 7-borylated product **2x** in 71% isolated yield. Indole CHB with either B_2eg_2 or B_2pin_2 gives the 2-borylated products in comparable yields.[45] Compounds **2c-i**, **2r**, and **2u-v** are new. Of these, **2g** is the only structure whose boronic acid has been reported in the primary literature.[46] Significantly, the transformations in Table 1 do not require installing and removing a directing group and use dtbpy, the most commonly used ligand in Ir-catalyzed CHBs.

The improved selectivity raises the interesting question as to whether their molecular origins arise from ligand/substrate electrostatic interactions or hydrogen bonding (Scheme 2). To tackle this question, we turned to theory. DFT calculations used the M06 functional with a 6-31G* basis set for light atoms and an SDD basis set and core potential for Ir. The polarizable continuum model was the self-consistent reaction field method applied for the THF solvent. Compared to other systems that we have studied, transition state location was challenging. Low energy imaginary frequencies associated with Me group rotations in dtbpy ligands plagued calculations on the full system. Replacing bipyridine ^{t}Bu with Me groups made the problem more manageable, but Me rotations still generated multiple imaginary rotational frequencies when software default values for step sizes and integration grids were used. Ultimately, TSs with a single imaginary frequency corresponding to C–H scission were located. The maximum atom displacement in all calculated TSs exceeded software convergence thresholds. In addition, the RMS displacement exceeded the software convergence defaults in approximately half of the calculated TSs. For two of these TSs, the maximum displacement was ten times greater than the convergence default. We mention them only in passing (vide infra). Atomic Cartesian coordinates and energies for these TSs are included in the SI.

Four transition states (**TS1-4**) were located for ortho borylation. Starting points for TS location included syn and anti orientations of PhN(H)Beg moiety with respect to the bipyridine ligand (Figure 2) and two additional geometries with close contacts between the aniline N–H and O atoms of a Beg that is ligated to Ir. Figure 3 depicts the TSs and their relative Gibbs' energies. **TS1** is analogous to the lowest energy transition state for phenol ortho borylation. In the other three TSs the PhN(H)Beg H is hydrogen bonded to a Beg O. The H···O distances in TS2, TS3, and TS4 are 2.07, 2.28, and 2.49 Å, respectively.



anti → **TS1** *syn* → **TS4**

Figure 2. Proposed transition states for ortho borylations of anilines and phenols.

The $\Delta\Delta G^{\ddagger}$ values for **TS2-4** relative to **TS1** are given as G_{rel} in Figure 3. The hydrogen-bonded TSs **TS2**, **TS3**, and **TS4** are stabilized by 1.9, 2.6, and 1.7 kcal·mol^{-1}, respectively, relative to **TS1**. Notably, the starting geometry for **TS4** was similar to that for **TS1** except that the Beg moiety was syn to the 4,4′-dimethylpyridine ligand (Figure 2). The syn PhOBeg TS has short (~3.0 Å) contacts between the Beg group and the bipyridine ligand that are reminiscent of π-stacking.[38] The analogous TS was not found for PhN(H)Beg. Instead, the N(H)Beg group rotated about the N–C$_{\mathrm{ipso}}$ bond to engage in hydrogen bonding between the aniline proton and and an Ir–Beg oxygen. A TS analogous to the syn geometry for PhOBeg was located for CHB of PhN(Me)Beg (**TS8**, vide infra).

The highest energy hydrogen-bonded TS (**TS4**) has the longest H···O distance, but it is only 0.2 kcal·mol^{-1} less stable than **TS2**, where the H···O distance is 0.42 Å shorter. The number of heavy atoms in **TS1-4** is too large to apply the level of theory that is typically used to quantify stabilization from hydrogen bonding.[47] The $\nu_{\mathrm{N\text{-}H}}$ values for N–H vibrations of the N(H)Beg group in **TS2** (3533 cm^{-1}), **TS4** (3541 cm^{-1}), and **TS3** (3557 cm^{-1}) do not correlate with distance, which is not surprising since Beg O lone pair interactions with the aniline H differ with Beg ligand orientation. The $\nu_{\mathrm{N\text{-}H}}$ values in **TS2-4** are 62-38 cm^{-1} lower than that calculated for PhN(H)Beg ($\nu_{\mathrm{N\text{-}H}}$ = 3595 cm^{-1}) at the same level of theory. Based on the infrared shift, H···O distance, and N-H lengthening (see SI), the hydrogen bonding interaction is classified as a weak hydrogen bond which are mostly electrostatic in nature.[48]

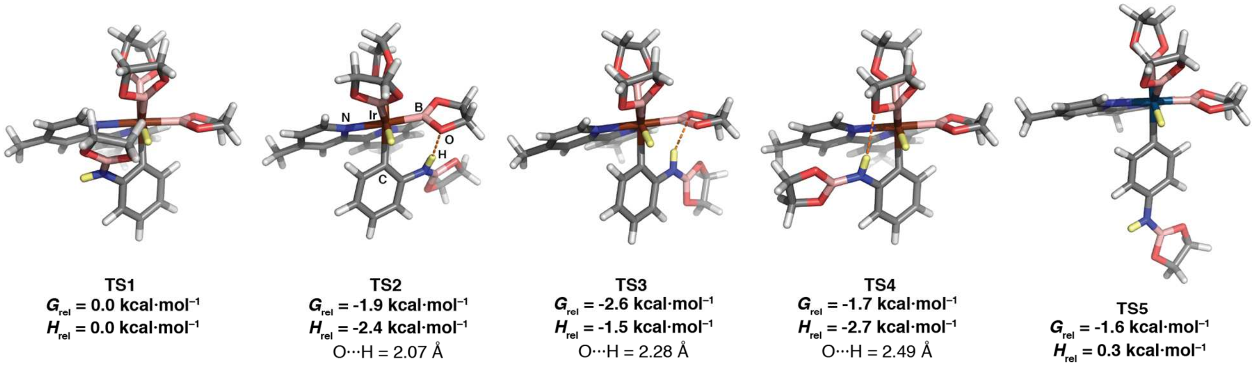
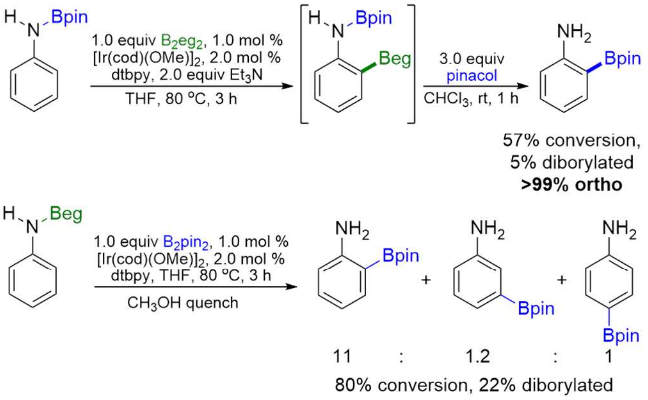


Figure 3. Computed transition states for Ir-catalyzed CHB of PhN(H)Beg with B_2eg_2. The N–H hydrogen and the C–H hydrogen in the bond being cleaved are yellow. Dashed orange lines indicate hydrogen bonding interactions. G_{rel} and H_{rel} are $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values relative to **TS1**. DFT calculations were performed using the M06 functional and a split 6-31G*/SDD basis set for light and Ir atoms. An SDD core potential was used for Ir.

The TS for para CHB (**TS5**) was also located. Its Gibbs' energy was higher than all of the hydrogen-bonding TSs, and was separated from the lowest energy TS (**TS3**) by 1.0 kcal·mol^{-1}. Attempts to locate the TS for meta CHB yielded a structure with one imaginary frequency (**TS$_{\mathbf{meta}}$**, p. S33-S34 of the SI), but the respective RMS and maximum displacements were 10X and 34X greater than software default convergence criteria. The theoretical $\Delta\Delta G^{\ddagger}$ value of 1.0 kcal·mol^{-1} between **TS3** and **TS5** predicts an ortho:para ratio of 8.2:1. While the ortho:para ratio of 26:1 predicted from calculated $\Delta\Delta H^{\ddagger}$ values match experiment more closely, both $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ predictions fall short of observed experimental selectivity. This is not uncommon in combined experimental/computational studies.

The computational results predict that Beg outperforms Bpin because the N(H)Beg substituent and Beg ligands can adopt optimal hydrogen bonding configurations with minimal steric interference. CHBs of PhN(H)Bpin with B_2eg_2 and PhN(H)Beg with B_2pin_2 were performed as an experimental test of this hypothesis (Scheme 3).

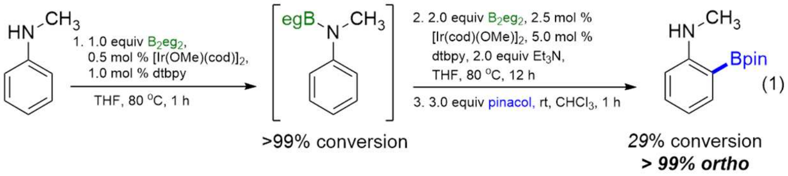
Scheme 3. Aniline CHBs of PhN(H)Bpin with B_2eg_2 and PhN(H)Beg with B_2pin_2.



CHB of PhN(H)Bpin exhibits the same high ortho selectivity when B_2eg_2 is the borylating agent as is observed for CHB of aniline with B_2eg_2. When the NBeg in the structure of **TS3** is converted to NBpin and the syn bipyridine Me is converted to ^{t}Bu, the closest C···C contact (4.31 Å) is longer than the closest C···C contact (3.96 Å) in the crystal structure of $Ir(Bpin)_3$(dtbpy)(coe) (coe = cyclooctene).[23] Consequently, retention of high ortho selectivity for the NBpin/B_2eg_2 combination is not surprising.

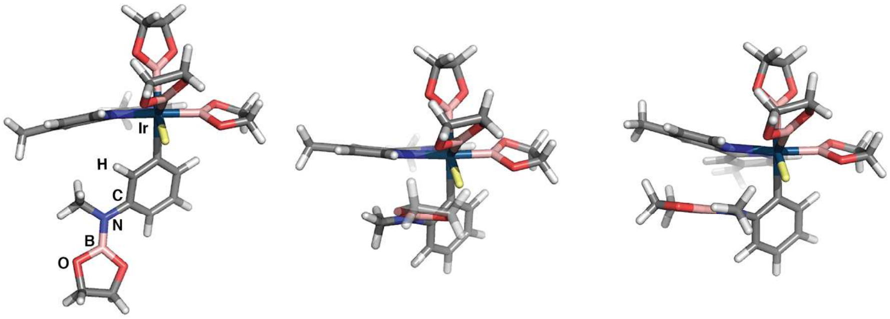
In contrast, ortho selectivity erodes when PhN(H)Beg is borylated with B_2pin_2, although the ortho:meta:para ratio of 11:1.2:1 is better than the 2.5:1.5:1 ratio for Ir-catalyzed CHB of aniline with HBpin.[12] The TSs for the PhN(H)Beg/Ir–Bpin structures are not calculated. However, it is not unreasonable to expect that the calculated steric destabilization from changing Beg to Bpin in phenol ortho CHB transition states would translate to aniline CHBs.[38] The experiments in Scheme 3 demonstrate that the B substituents on the boryl ligands, and thus the CHB reagent, have the greater influence on ortho selectivity.

Meta and para CHB of *N*-methylaniline would further support the hypothesis that hydrogen-bonding is responsible for the high ortho selectivity of B_2eg_2 in aniline CHBs since PhN(Me)Beg lacks an NH moiety. Remarkably, CHB on PhN(H)Me yields only the ortho isomer, albeit at only 24% conversion. In operando NMR spectroscopy shows that PhN(H)Me is fully converted to PhN(Me)Beg before CHB ensues (eq 1). Even though the conversion of PhN(Me)Beg to borylated products is low, the ortho product is the only CHB isomer detected.



(1)

This surprising result raises an obvious question. Would calculations also favor ortho CHB when hydrogen bonding is not an option? The calculated TS structures for meta CHB (**TS6**) and ortho CHB with anti (**TS7**) and syn (**TS8**) dispositions of the Beg group relative to bipyridine ligand are shown in Figure 4.



TS6
G_{rel} = 0.0 kcal·mol⁻¹
H_{rel} = 0.0 kcal·mol⁻¹

TS7
G_{rel} = -0.3 kcal·mol⁻¹
H_{rel} = -1.0 kcal·mol⁻¹

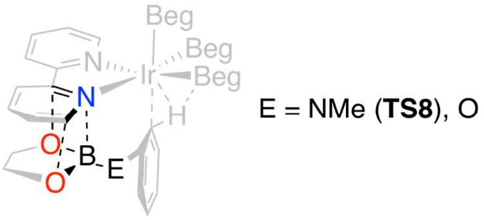
TS8
G_{rel} = 2.3 kcal·mol⁻¹
H_{rel} = -0.4 kcal·mol⁻¹

Figure 4. Computed transition states for Ir-catalyzed CHB of PhN(CH_3)Beg with B_2eg_2. The hydrogen in the C–H bond being cleaved is pale yellow. G_{rel} and H_{rel} are $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values relative to **TS6**.

$$\angle_{\sigma} = 180 - \angle C4_{\mathrm{py}} - N_{\mathrm{py}} - Ir \qquad (2)$$

In line with phenol ortho CHBs, the Gibbs' energy of the syn TS (**TS8**) is higher than the anti TS (**TS7**). Other shared features of **TS8** with the syn phenol TS include short contacts between the NBeg, N, and, O atoms with the bipyridine N and flanking C atoms, and a distortion of the pyridine Ir–N bond. This distortion reduces σ-overlap of the pyridine N lone pair with Ir and is best quantified by $\angle_{\sigma}$, which is defined in eq 2. When the Ir atom lies in the pyridine plane, σ-overlap is maximized and $\angle_{\sigma} = 0$. The N_{py}–B_{Beg} distances, C_{py}–O distances, and $\angle_{\sigma}$ values for the phenol and aniline TSs are summarized in Table 2. The N–B and C–O distances in **TS8** are 0.05-0.13 Å longer than the corresponding values in phenol ortho-borylation TS. The negative charge on the EBeg group (E = NMe, O) will be smaller for NMe than for O. Consequently, the electrostatic interaction will be weaker, which is consistent with the elongation of the EBeg contacts with the syn pyridine of the bipyridine ligand when E = N(Me)Beg. The 6.5° decrease in $\angle_\sigma$ when E is switched from NMe to O also supports weakening of the electrostatic interaction between N(Me)Beg and the syn pyridine.

Table 2. Structural comparisons between syn TSs in 4-C_6H_4OBeg and $C_6H_5NMe(Beg)$ CHBs.



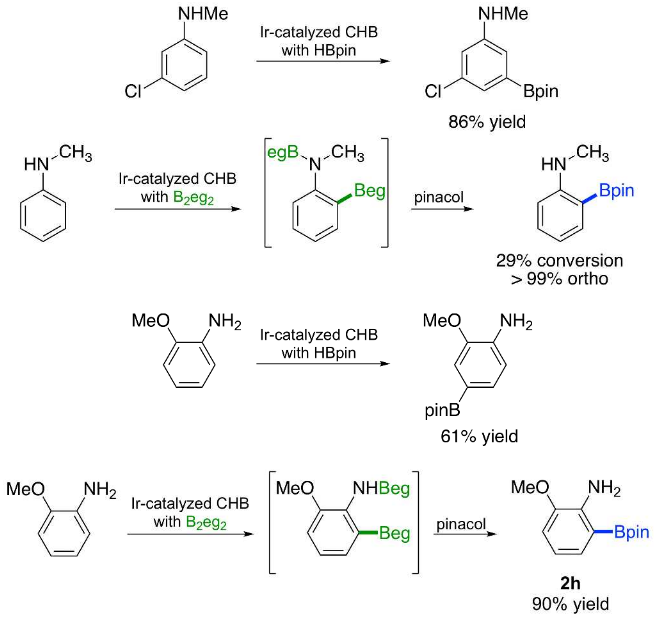
E	N–B (Å)	C–O (Å)	$\angle_\sigma$ (°)
NMe	3.10	3.14, 3.33	11.8
O[a]	2.97	3.09, 3.24	18.5

[a] Data from **TS5-OBeg**$_{\textbf{syn-dtbpy}}$ in Figure 3 of ref. 36

The G_{rel} and H_{rel} values ($\Delta\Delta G^\ddagger$ and $\Delta\Delta H^\ddagger$ values relative to **TS6**) in Figure 4 predict that the ortho CHB **TS7**, where the Beg group is anti to the bipyridine ligand, has the lowest energy. The theoretical $\Delta\Delta G^\ddagger$ value between of -0.3 kcal·mol^{-1} predicts an ortho:meta ratio of 1.5:1, and the $\Delta\Delta H^\ddagger$ value predicts a higher ortho:meta ratio of 4.1:1. Although the ortho isomer is predicted to be the major one, the actual selectivity is much higher. While the trend in the computed ratio correlates with the experimental results, future studies at a higher level of theory are warranted. Overall, the experimental findings show that hydrogen bonding is not required for ortho selectivity for *N*-methyl aniline when the CHB reagent is switched from B_2pin_2 to B_2eg_2.

In addition to removing previous limitations for ortho CHBs of anilines with B_2pin_2 and HBpin, CHBs with B_2eg_2 can complement selectivities for aniline CHBs with commonly used boron reagents. Scheme 4 shows two examples highlighting the most dramatic differences in CHB selectivities.

Scheme 4. Regiochemical consequences of Beg and Bpin reagents in aniline CHBs.



CONCLUSIONS. The important findings of this study are listed below.

- By changing the boron reagent from HBpin or B_2pin_2 to bis-(ethyleneglycolato)diboron (B_2eg_2), ortho CHBs can now be accomplished wide variety of anilines. Substrates whose previously poor (or altered) regioselectivity is now overcome include (i) anilines with no substituents at the 4-position, (ii) 2-substituted anilines, (iii) 3-substituted anilines, and (iv) *N*-methylaniline.
- CHB ortho to NH_2 in 2-methylquinolin-6-amine is possible.
- The substituents on the Ir boryl ligands have the greatest impact on selectivity.
- The ortho-borylated isomer is the only product observed in the Ir-catalyzed CHB of *N*-methylaniline with B_2eg_2. ^1H NMR studies show that PhN(H)Me is fully converted to

PhN(Beg)Me before CHB ensues. Thus, hydrogen bonding in the TS cannot account for ortho selectivity.

- For Ir-catalyzed CHB of PhN(H)Beg, computational studies revealed three NH···O hydrogen bonding transition states where the aniline N(Beg)H interacted with an Ir-Beg ligand. The NH···O TSs have lower Gibbs' energies than an ortho CHB TS that lacks hydrogen bonding.
- The three NH···O TSs Gibbs' energies are also lower than that for para CHB TS of PhN(H)Beg.
- Of three TSs calculated for Ir-catalyzed CHB of PhN(Me)Beg, the ortho TS where the Beg moiety is anti to the bipyridine ligand has the lowest Gibbs' energy. This TS closely resembled the favored TS for CHB ortho to the OBeg of 4-F-C_6H_4OBeg, where selectivity is proposed to arise from electrostatic interactions between the OBeg unit and the proximal pyridine ring of the bipyridine ligand.

In summary, the diboron reagent B_2eg_2 lifts the limitations seen in Ir-catalyzed CHBs of anilines with HBpin. Experiment and theory are consistent with stabilization of hydrogen bonding TSs when Bpin Ir boryl ligands are replaced by less sterically encumbered Beg ligands. Further exploration of other diboron reagents and the synthetic utility of associated CHB products is underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:xxxxxxxxxxxxx.

Experimental details, product characterizations, computational methods, energies, and Cartesian coordinates (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail for M.R.S: smithmil@msu.edu

*E-mail for R.E.M: maleczka@chemistry.msu.edu

*E-mail for B.C: buddhadeb.c@cbmr.res.in

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

R.E.M. and M.R.S. own a percentage of BoroPharm, Inc.

ACKNOWLEDGMENT

B.C. thanks DST-SERB, New Delhi for Ramanujan Grant (SB/S2/RJN-45/2013) and Young Scientist Research Grant (SB/FT/CS-141/2014) to execute this project, and the Director, CBMR for providing research facilities. R.B. thank DST-SERB, New Delhi for the SRF Fellowship under the Ramanujan Grant and C.H. thanks the Young Scientist Research Grant for J.R.F. R.E.M. and M.R.S thank the NIH (GM63188) for support, and the Institute for Cyber-Enabled Research (ICER) at MSU for computational resources. We also thank the teams in the NMR and HRMS facilities at CBMR and MSU.

REFERENCES

(1) Travis, A. S. In *The Chemistry of Anilines*; John Wiley & Sons, Ltd, 2007; pp 715–782.

(2) Berliner, E. Electrophilic Aromatic Substitution Reactions. *Prog. Phys. Org. Chem.* **1964**, *2*, 253.

(3) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; Oxford University Press, 2012.

(4) Holleman, A. F.; Hartogs, J. C.; Van der Linden, T. Quantitative Untersuchungen über Die Nitrierung Des Anilins. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 704–728.

(5) Shen, H.; Vollhardt, K. P. C. Remarkable Switch in the Regiochemistry of the Iodination of Anilines by N-Iodosuccinimide: Synthesis of 1,2-Dichloro-3,4-Diiodobenzene. *Synlett* **2011**, *2012*, 208–214.

(6) Takagishi, S.; Katsoulos, G.; Schlosser, M. Fluorine and Trifluoromethyl Substituted Anilines: Site Selective Metalation and Electrophilic Substitution. *Synlett* **2002**, *1992*, 360–362.

(7) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *Angew. Chem. Int. Ed Engl.* **2004**, *43*, 2206–2225.

(8) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J.-C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. Iridium-Catalyzed C-H Activation versus Directed Ortho Metalation: Complementary Borylation of Aromatics and Heteroaromatics. *Chem. Eur. J.* **2010**, *16*, 8155–8161.

(9) Tischler, M. O.; Tóth, M. B.; Novák, Z. Mild Palladium Catalyzed Ortho C-H Bond Functionalizations of Aniline Derivatives. *Chem. Rec.* **2017**, *17*, 184–199.

(10) Fang, H.; Dou, Y.; Ge, J.; Chhabra, M.; Sun, H.; Zhang, P.; Zheng, Y.; Zhu, Q. Regioselective and Direct Azidation of Anilines via Cu(II)-Catalyzed C-H Functionalization in Water. *J. Org. Chem.* **2017**, *82*, 11212–11217.

(11) Allu, S.; Ravi, M.; Kumara Swamy, K. C. Rhodium(III)-Catalysed Carbenoid C(sp2)–H Functionalisation of Aniline Substrates with α-Diazo Esters: Formation of Oxindoles and Characterisation/Utility of an Intermediate-Like Rhodacycle. *Eur. J. Org. Chem.* **2016**, *2016*, 5697–5705.

(12) Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E., Jr.; Smith, M. R., III. A Traceless Directing Group for C-H Borylation. *Angew. Chem. Int. Ed.* **2013**, *52*, 12915–12919.

(13) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C-H Activation for the Construction of C-B Bonds. *Chem. Rev.* **2010**, *110*, 890–931.

(14) Hartwig, J. F. Borylation and Silylation of C-H Bonds: A Platform for Diverse C-H Bond Functionalizations. *Acc. Chem. Res.* **2012**, *45*, 864–873.

(15) Lee, C.-I.; Zhou, J.; Ozerov, O. V. Catalytic Dehydrogenative Borylation of Terminal Alkynes by a SiNN Pincer Complex of Iridium. *J. Am. Chem. Soc.* **2013**, *135*, 3560–3566.

(16) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. Pinacol Boronates by Direct Arene Borylation with Borenium Cations. *Angew. Chem. Int. Ed.* **2011**, *50*, 2102–2106.

(17) Légaré, M.-A.; Courtemanche, M.-A.; Rochette, É.; Fontaine, F.-G. Metal-Free Catalytic C-H Bond Activation and Borylation of Heteroarenes. *Science* **2015**, *349*, 513–516.

(18) Mazzacano, T. J.; Mankad, N. P. Base Metal Catalysts for Photochemical C-H Borylation That Utilize Metal-Metal Cooperativity. *J. Am. Chem. Soc.* **2013**, *135*, 17258–17261.

(19) Obligacion, J. V.; Semproni, S. P.; Chirik, P. J. Cobalt-Catalyzed C–H Borylation. *J. Am. Chem. Soc.* **2014**, *136*, 4133–4136.

(20) Furukawa, T.; Tobisu, M.; Chatani, N. Nickel-Catalyzed Borylation of Arenes and Indoles via C-H Bond Cleavage. *Chem. Commun.* **2015**, *51*, 6508–6511.

(21) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. Steric and Chelate Directing Effects in Aromatic Borylation. *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869.

(22) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr; Smith, M. R., III. Remarkably Selective Iridium Catalysts for the Elaboration of Aromatic C-H Bonds. *Science* **2002**, *295*, 305–308.

(23) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. Mild Iridium-

Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

(24) Jones, W. D.; Kosar, W. P. Carbon-Hydrogen Bond Activation by Ruthenium for the Catalytic Synthesis of Indoles. *J. Am. Chem. Soc.* **1986**, *108*, 5640–5641.

(25) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient Catalytic Addition of Aromatic Carbon-Hydrogen Bonds to Olefins. *Nature* **1993**, *366*, 529.

(26) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. Directed Ortho Borylation of Functionalized Arenes Catalyzed by a Silica-Supported Compact Phosphine-Iridium System. *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059.

(27) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. Ortho-C–H Borylation of Benzoate Esters with Bis(pinacolato)diboron Catalyzed by Iridium–phosphine Complexes. *Chem. Commun.* **2010**, *46*, 159–161.

(28) Ros, A.; Fernández, R.; Lassaletta, J. M. Functional Group Directed C–H Borylation. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243.

(29) Taube, H.; Posey, F. A. The Study of a System Involving Equilibrium Between Inner Sphere and Outer Sphere Complex Ions - $Co(NH_3)_5H_2O^{+++}$ and $SO_4^{=}$. *J. Am. Chem. Soc.* **1953**, *75*, 1463–1467.

(30) Boebel, T. A.; Hartwig, J. F. Silyl-Directed, Iridium-Catalyzed Ortho-Borylation of Arenes. A One-Pot Ortho-Borylation of Phenols, Arylamines, and Alkylarenes. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

(31) Davis, H. J.; Phipps, R. J. Harnessing Non-Covalent Interactions to Exert Control over Regioselectivity and Site-Selectivity in Catalytic Reactions. *Chem. Sci.* **2017**, *8*, 864–877.

(32) Haldar, C.; Hoque, E.; Bisht, R.; Chattopadhyay, B. Concept of Ir-Catalyzed CH Bond Activation/borylation by Noncovalent Interaction. *Tetrahedron Lett.* **2018**, *59*, 1269–1277.

(33) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E., Jr; Smith, M. R., III. Outer-Sphere Direction in Iridium C-H Borylation. *J. Am. Chem. Soc.* **2012**, *134*, 11350–11353.

(34) Bisht, R.; Chattopadhyay, B. Formal Ir-Catalyzed Ligand-Enabled Ortho and Meta Borylation of Aromatic Aldehydes via in Situ-Generated Imines. *J. Am. Chem. Soc.* **2016**, *138*, 84–87.

(35) Li, H. L.; Kuninobu, Y.; Kanai, M. Lewis Acid-Base Interaction-Controlled Ortho-Selective C-H Borylation of Aryl Sulfides. *Angew. Chem. Int. Ed Engl.* **2017**, *56*, 1495–1499.

(36) Li, H.-L.; Kanai, M.; Kuninobu, Y. Iridium/Bipyridine-Catalyzed Ortho-Selective C-H Borylation of Phenol and Aniline Derivatives. *Org. Lett.* **2017**, *19*, 5944–5947.

(37) Davis, H. J.; Genov, G. R.; Phipps, R. J. Meta-Selective C−H Borylation of Benzylamine-, Phenethylamine-, and Phenylpropylamine-Derived Amides Enabled by a Single Anionic Ligand. *Angew. Chem. Int. Ed.* **2017**, *56*, 13351–13355.

(38) Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E., Jr; Singleton, D. A.; Smith, M. R., III. Ir-Catalyzed Ortho-Borylation of Phenols Directed by Substrate-Ligand Electrostatic Interactions: A Combined Experimental/in Silico Strategy for Optimizing Weak Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 7864–7871.

(39) Yamamoto, T.; Ishibashi, A.; Suginome, M. Regioselective Synthesis of O-Benzenediboronic Acids via Ir-Catalyzed O-C-H Borylation Directed by a Pyrazolylaniline-Modified Boronyl Group. *Org. Lett.* **2017**, *19*, 886–889.

(40) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C-H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 12759–12762.

(41) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A Meta-Selective C-H Borylation Directed by a Secondary Interaction between Ligand and Substrate. *Nat. Chem.* **2015**, *7*, 712–717.

(42) The ligand for the Kanai-Kuninobu ortho CHB of aniline is prepared via a Suzuki cross-coupling of 5-bromo-2,2′-bipyridine ($14,000/mol) with 1-Bpin-4-(trifluoromethyl)benzene ($870/mol) in 73% yield. B_2pin_2 ($50/mol) is the borylating agent. Prices are the lowest per mole values of all commercial sources listed by SciFinder Scholar on 02/01/18.

(43) The yields for deprotection are given in an endnote in ref. 35. The products are not specified and experimental details were not reported. We presume that the deprotected compounds are *N*-acylated since all $ArN(Ac)(CH_2SMe)$ reactants were prepared from acylated anilines.

(44) The Ir ligand used in this work is dtbpy ($2,300/mol). B_2eg_2 is prepared from $B_2(OH)_4$ ($51/mol) and ethylene glycol ($0.22/mol) in 91% Yield.

(45) Robbins, D. W.; Hartwig, J. F. A C-H Borylation Approach to Suzuki-Miyaura Coupling of Typically Unstable 2-Heteroaryl and Polyfluorophenyl Boronates. *Org. Lett.* **2012**, *14*, 4266–4269.

(46) Bartlett, R. K.; Turner, H. S.; Warne, R. J.; Young, M. A.; Lawrenson, I. J. The Reaction of Primary Amines with Boron Halides. Part II. Arylamines. The Effect of Ortho-Substitution: Formation of Di-B-Halogenoborazoles. *J. Chem. Soc. A* **1966**, No. 0, 479–500.

(47) Thanthiriwatte, K. S.; Hohenstein, E. G.; Burns, L. A.; Sherrill, C. D. Assessment of the Performance of DFT and DFT-D Methods for Describing Distance Dependence of Hydrogen-Bonded Interactions. *J. Chem. Theory Comput.* **2011**, *7*, 88–96.

(48) Parthasarathi, R.; Subramanian, V. Characterization of Hydrogen Bonding: From van Der Waals Interactions to Covalency. In *Hydrogen Bonding—New Insights*; Grabowski, S. J., Ed.; Springer Netherlands: Dordrecht, 2006; pp 1–50.

Table of Contents