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REGIOSELECTIVE IRIDIUM CATALYZED C-H ACTIVATION/
BORYLATION OF 2-SUBSTITUTED INDOLES

presented by

Sulagna Paul

has been accepted towards fulfillment
of the requirements for the

Master of Science degree in CHEMISTRY

Major Professor's Signature

07/31/07

Date

REGIOSELECTIVE IRIDIUM CATALYZED C–H ACTIVATION / BORYLATION OF 2–SUBSTITUTED INDOLES

By

Sulagna Paul

A THESIS

Submitted to
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ABSTRACT

IRIDIUM CATALYZED REGIOSELECTIVE C–H ACTIVATION/ BORYLATION OF 2–SUBSTITUTED INDOLES

By

Sulagna Paul

The catalytic functionalization of hydrocarbons has long been a challenge in homogeneous and heterogeneous catalysis. Since synthetic applications of arylboronic esters are broad, the transformation of aryl halides or aromatic feedstocks to aryl boronate esters has great appeal.

In 1999, our group demonstrated the first thermal, catalytic aromatic C-H activation/borylation reaction catalyzed by $Cp^*Ir(PMe_3)(H)(BPin)$. Later on, our laboratory as well as the Hartwig, Ishiyama and Miyaura laboratories developed even more reactive and remarkably selective (Ind)Ir(COD) and Ir(OMe)(COD) precatalysts. In our investigations of indole borylation, we noted small amounts of a single diborylated isomer formed from iridium catalyzed C–H activation borylation reaction with HBPin. Further investigation revealed that the second borylation occurs at the 7–position of indole, which is one of the difficult positions of the indole core to functionalize. A range of the 2–substituted indole substrates and conditions have been examined. The reaction is highly regioselective with a wide range of functional group tolerance. A unique chelate directed pathway is believed to be responsible for this unprecedented selectivity. The compounds synthesized employing C–H activation/ borylation protocol have been isolated in good to excellent yields (45—92%) and have been fully characterized using ^{1}H, ^{13}C, ^{11}B, IR, GC–MS, High resolution MS and elemental analysis.

To my parents and husband for their support and love

ACKNOWLEDGEMENTS

First, I would like to thank my research advisor, Dr. Milton R. Smith III, for his guidance and assistance. Often humorous, always honest and insightful, as an advisor he is appreciated by all.

Second, I am thankful to Dr. Robert E. Maleczka, Jr. for his valuable advice and discussions during our joint group meetings and Dr. Baker and Dr. Odom for their assistance being the members of my guidance committee.

I feel very lucky to work with some talented people in my lab. My thanks go out to Ghayoor Abbas Chotana for his patient teaching as a senior graduate student during my first year as a graduate student. I am thankful to Edith for her valuable time and experience, she shared with me. I have also made couple good friends, Venkata A. Kallepalli (Appi) and Aparajita Banerjee.

Finally, I would like to thank to my best friend, my senior, my husband Sanjit for his intellectual conversation and the lab experiences we shared. I would like to express my appreciation and love to my family in India: Dad, Mom, and my elder brother for their love, encouragement and emotional support.

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LIST OF ABBREVIATION

HBPin	4,4,5,5-tetramethyl-1,3,2-dioxaborane/ Pinacolborane
dtbpy	Di-*tert*-bipyridyl
B_2Pin_2	Bis(pinacolato)diboron
COD	Cyclooctadiene
COE	Cyclooctene
DMG	Directed metallation group
Ind	Indenyl
MMO	Methane monooxygenase
EAS	Electrophilic aromatic substitution
D*o*M	Directed *ortho* metallation
HBCat	Catecholborane
TNT	Trinitrotoluene
THF	Tetrahydrofuran
GC-FID	Gas Chromatography-Flame Ionization Detector
GC/MS	Gas Chromatography-Mass Spectroscopy
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
br	Broad
s	Singlet
d	Doublet
t	Triplet

q	Quartet
LRMS	Low Resolution Mass Spectroscopy
HRMS	High Resolution Mass Spectroscopy

CHAPTER 1

INTRODUCTION

C–H Bond Activation:

C–H bond activation followed by carbon–carbon bond formation is emerging as an important new method in organic synthesis.[1] In contrast to most of the carbon–carbon bond formation reactions, selective transformation of C–H bonds to C–C bonds or other functional groups has long been a challenge in homogeneous and heterogeneous catalysis. Saturated hydrocarbons such as methane are quite abundant in Nature and exist as the major constituents of natural gas and petroleum. Owing to their chemical inactivity, selective introduction of functional groups to hydrocarbons has been difficult and at the same time a topic of great interest. This chemical inertness arises from their constituent atoms all being held together by strong and relatively nonpolar C–C and C–H bonds.

Many of the world's established natural gas resource locations are remote, in sites where there is little or no local demand. Exploitation of such resource is impeded by high cost of gas transportation. Methane, the principle component of natural gas is difficult to store, while the oxidized product methanol is easy to store and transport. A variety of enzymes[2] efficiently and selectively catalyze alkane oxidation at ambient temperature and pressure, usually via hydroxylation. For methane conversion, the effective enzyme is methane monooxygenase (MMO). While enzymes like MMO operate well for a particular substrate, they often are poor catalysts for substrate analogues. Hence, there are relatively few economically viable and environmentally benign methods known to convert hydrocarbons directly to more valuable chemicals. Despite the fact that C–H bonds are relatively more difficult to cleave than C–halogen bonds, C–H bonds are not completely inert. The problem in methane is the C–H bonds in it are all chemically equivalent and selective conversion of methane to methanol is that methanol is more prone to oxidation than methane, leading to over oxidation products like CO_2.

One functional transformation in hydrocarbons that is well known is aromatic substitution. Regioselectivity in electrophilic aromatic substitution (EAS) was established over one hundred years ago, an early example being the reaction of arenes with nitric acid.[3] The regioselectivities for EAS are determined by the number, type and relative position of the substitution on the arene. As classified by Holleman,[4] arene substituents fall into two classes: (i) ortho, para-directors that typically activate the aromatic system and (ii) meta-directors that operate by deactivating the ortho/para positions. An example

Figure 1: Oxidation of methane

of regioselective EAS is the conversion of 4–cyano bromobenzene to 2–bromo–3-cyano nitrobenzene.[5]

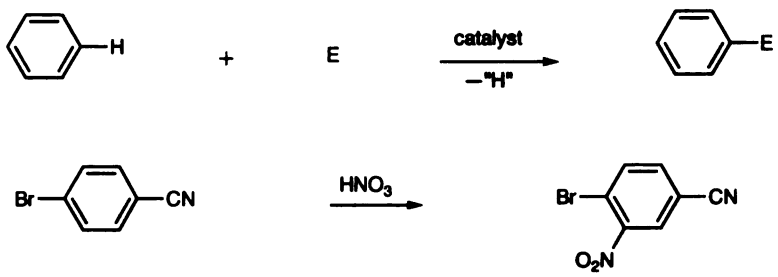


Figure 2: Electrophilic aromatic substitution

In practice, EAS gives high regioselectivities in relatively few cases, depending on the electronic nature of the substituents. For example, nine regioisomers are possible for all combinations of ortho/para and meta directors for a disubstituted benzene (Figure 3). In only two of these isomers do the directing effects, enforce high selectivity for

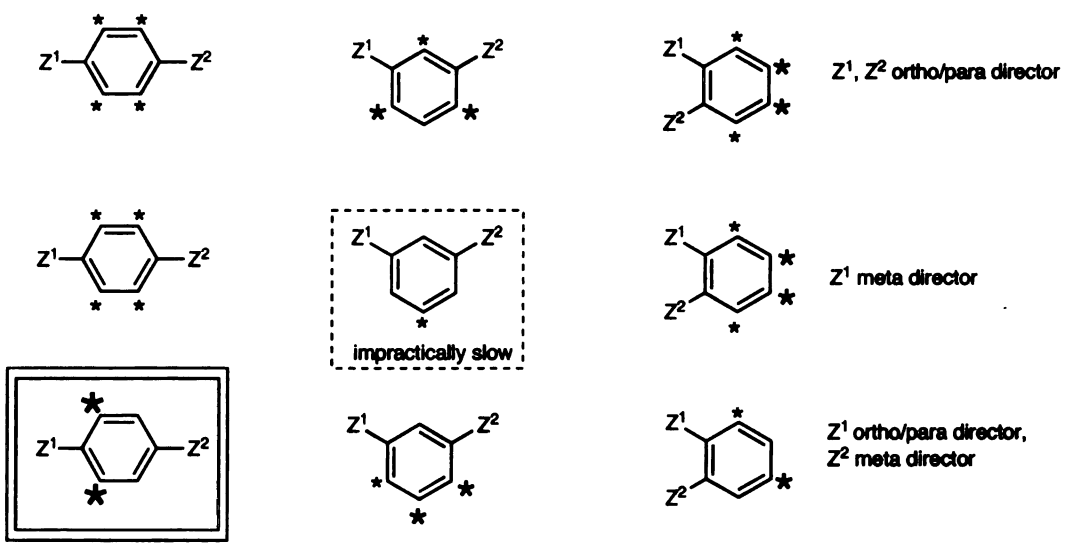


Figure 3: Selectivity in electrophilic aromatic substitution

subsequent electrophilic aromatic substitution. One of these two is the classic case of meta disposed meta–directors, where the arene is deactivated toward subsequent electrophilic substitution. Hence, only one out of the nine possible combinations is

practical and gives high regioselectivity in aromatic electrophilic substitution! Consequently, syntheses of 1,3,5–trisubstituted arenes are quite challenging (Figure 4).[6]

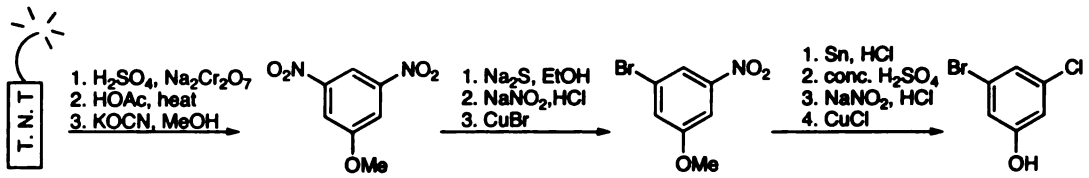


Figure 4: Synthesis of 3–bromo–5–chloro phenol

For a process to complement the regioselectivity of electrophilic aromatic substitution, it must harness another type of directing effect. Directed ortho metallation (D*o*M) constitutes such an approach and is widely applied in synthesis. While steric effects are widely invoked to rationalize selectivities in chemical reactions, they have been exploited in aromatic substitution to only a limited extent,[7] even though, sterically directed chemistry potentially complements regioselectivities for EAS and D*o*M (Figure 5).

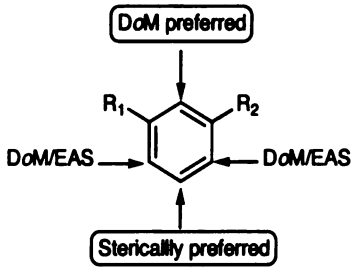


Figure 5: Directing effects in electrophilic aromatic substitution

In 1976, Ittel and coworkers[8] reported iron complexes that underwent rapid, reversible insertions into aromatic C–H bonds. In the presence of excess toluene a 2:1 ratio of meta and para C–H insertion products results and none of the *o*–tolyl isomer was observed. This is the regioselectivity expected if steric effects dominate over electronic effects for C–H insertion (Figure 6). Thus, transition metal insertion into C–H bonds potentially offer selectivity that complements electrophilic aromatic substitution and D*o*M.

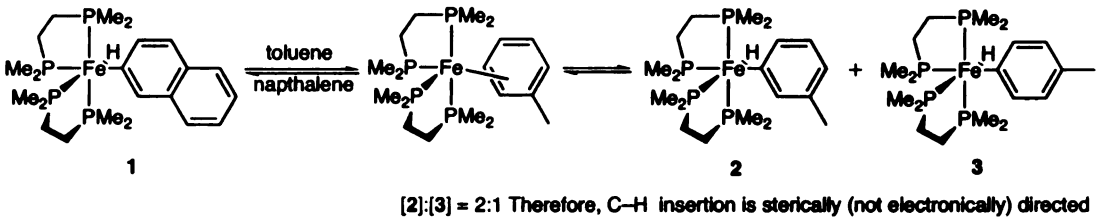


Figure 6: Sterically directed C-H activation

In 1982, Bergman[9] and Graham[10] reported that photochemically generated Rh and Ir systems were capable of intermolecular oxidative addition of C–H bonds in saturated hydrocarbons (Figure 7). Subsequently, C–H activation was heavily studied by

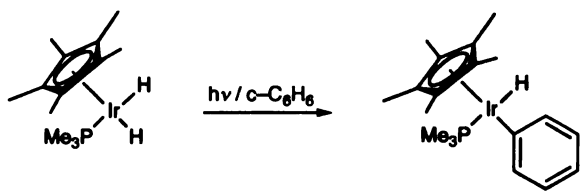


Figure 7: C–H activation of aromatic compound by Ir-complex

Bergman,[1a] Jones,[1b] Crabtree,[1c] and others with specifics of C–H insertion being the main focus. Ultimately, the C–H activation has not been the greatest challenge. Rather, the

difficult task has been the further transformation of the metal–carbon bonds that arise from the C–H insertion, preferably in a catalytic process.

When catalytic functionalization of C–H bonds was about to emerge, Jones et. al[11] reported the activation of benzylic sp^3-hybridized C–H bonds using a Ru catalyst. Their catalytic indole synthesis relied on intramolecular trapping of the newly formed Ru–C bond in the form of isocyanide insertion (Figure 8).

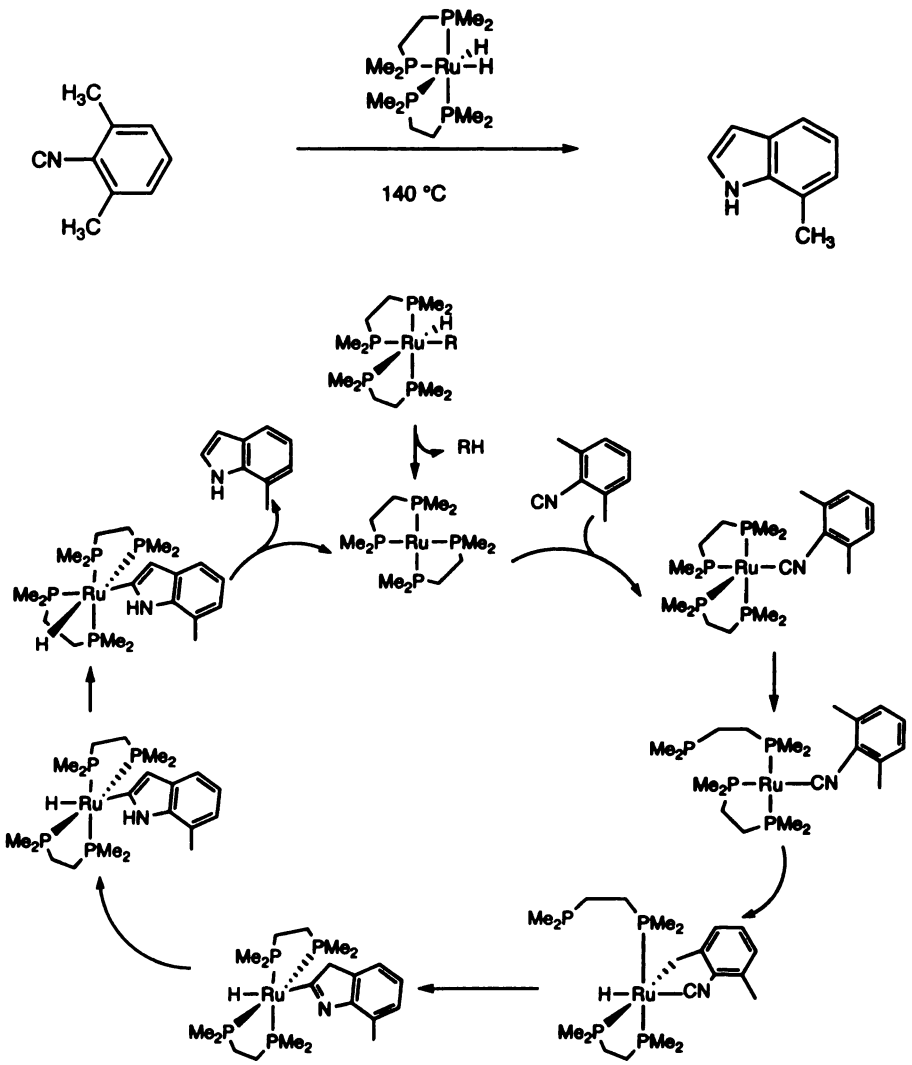


Figure 8: Ru-catalyzed intramolecular functionalization of C-H bond

Berry and coworkers[12] established one of the first catalytic example of intermolecular meta functionalization route. Based on the transfer dehydrogenative coupling of triethylsilane with an arene in the presence of a rhodium catalyst (Figure 9), an arene–silicon bond was generated. The reaction must be heated to 150 °C to produce the thermodynamic product aryl silane from the kinetic product the carbosilane dimer. Unfortunately, the substrate scope for this system is limited.

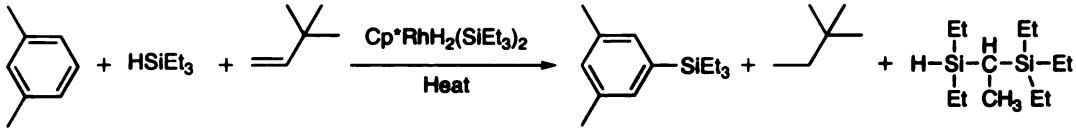


Figure 9: Rh–catalyzed synthesis of arylsilane

Organoborane compounds are important, versatile reagents. The popularity of alkylboranes in organic synthesis is due to H. C. Brown[13] recognizing that they could be prepared from borane and hydrocarbon precursors. Forming the organoborane in a single step, greatly improved access to this class of compounds whose prior syntheses paralleled those still in force for preparing arylboron analogs (Figure 10). Arylboron reagents

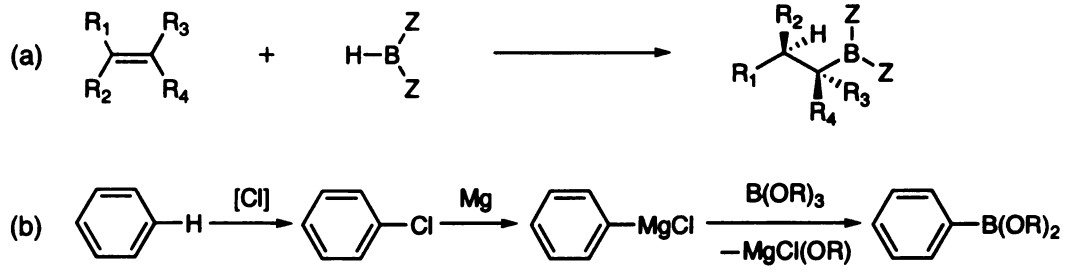


Figure 10: Traditional synthesis of (a) alkyl and (b) aryl boron compounds

usually require a multi-step synthesis (Figure 10). In 1997, Hartwig[14] reported that transition–metal–boryl complex (M = Fe, Ru, W) produce terminal organoboranes when reacted with alkanes under photochemical followed by thermal reaction conditions.

From their mechanistic analysis, they believe ligand dissociation is induced photochemically and that thermal reaction of the resulting intermediate occurs with alkanes. Later on, they developed a photochemical rhenium–catalyzed version of synthesizing terminal organoboranes from alkanes and B_2Pin_2 (Figure 11).[15]

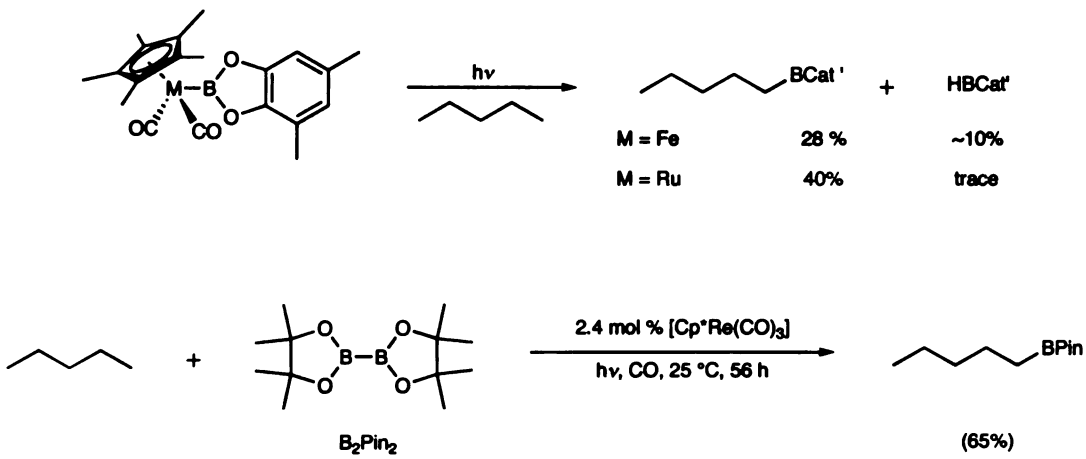


Figure 11: Regioselective borylation of saturated hydrocarbon

However, thermochemical and computational data establishes that the reaction of an alkane with HBCat to give an alkyl–boron compound is essentially thermoneutral,[16] which indicates that photolysis should not be necessary with a more appropriate catalyst (Figure 12).

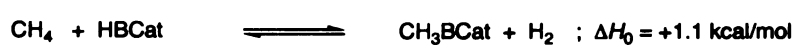


Figure 12: Enthalpy of formation of organoborane compounds

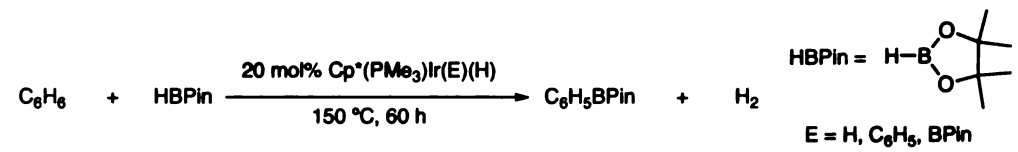


Figure 13: Ir-catalyzed C-H activation/borylation

Thermal Ir–catalyzed borylation was first reported by our group in 1999 (Figure 13).[17] In reaction of $Cp^*(PMe_3)Ir(H)(Ph)$ and pinacolborane, substantial amounts of aryl boranes were produced. The major metal containing product in this reaction,

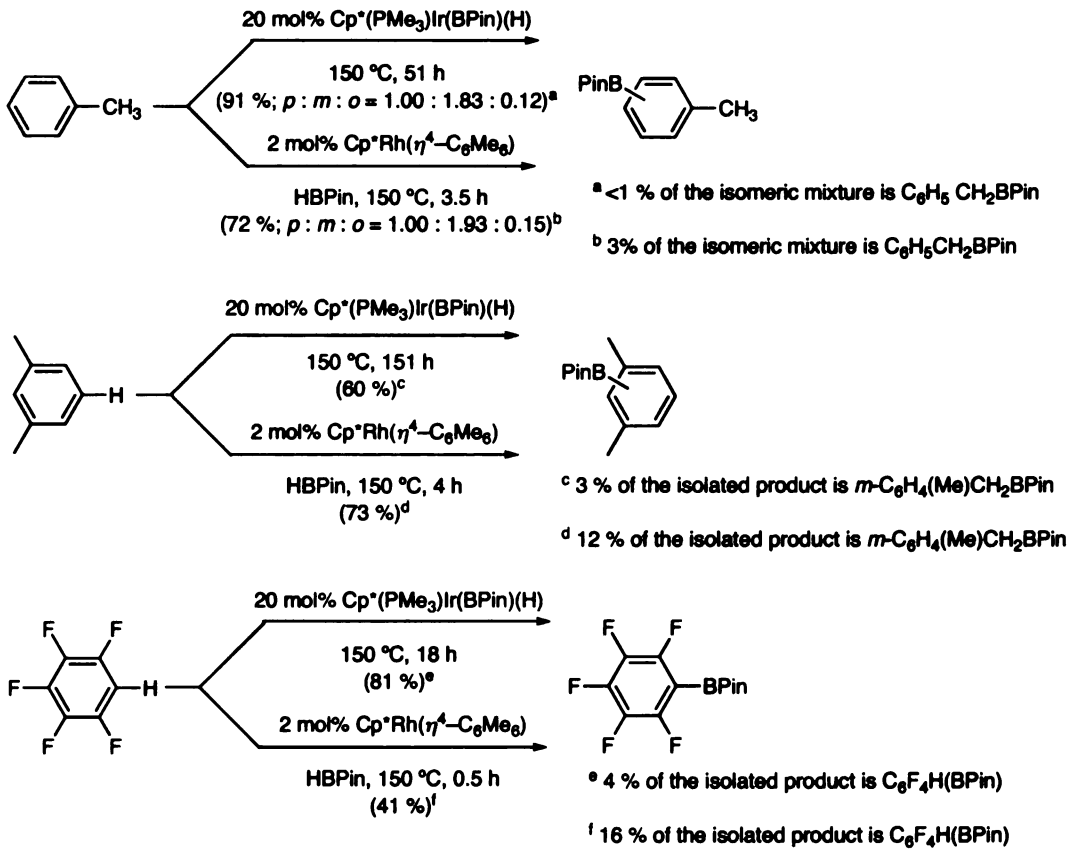


Figure 14: Steric directed regioselective borylation

$Cp^*(PMe_3)Ir(H)(BPin)$ was a precatalyst for benzene borylation with relatively low turnover number corresponding to three molecule of PhBPin per molecule of

$Cp^*(PMe_3)Ir(H)(BPin)$. Shortly thereafter, Hartwig and co-workers described a Rh–system capable of functionalizing alkane as well as benzene C–H bonds.[18] In the following year, our group extended this chemistry to a wider range of aromatic compounds to describe the functional group tolerance and regioselective activation.[19] The Ir system was more chemoselective, giving significantly less benzylic C–H and aryl C–F derived products. In addition, regioselectivity of borylation was found to be sterically controlled compared to traditional aromatic substitution where electronic effects determine the regioselectivity (Figure 14).

Ir–catalyzed borylation is more sensitive to steric rather than electronic effects, following a steric hierarchy where H < F < CN < Cl < Br ~ CH_3. Thus selective borylation adjacent to F or CN groups can be achieved in many cases (Figure 17) which complements to electronic direction in EAS in presence of larger substituents.[20]

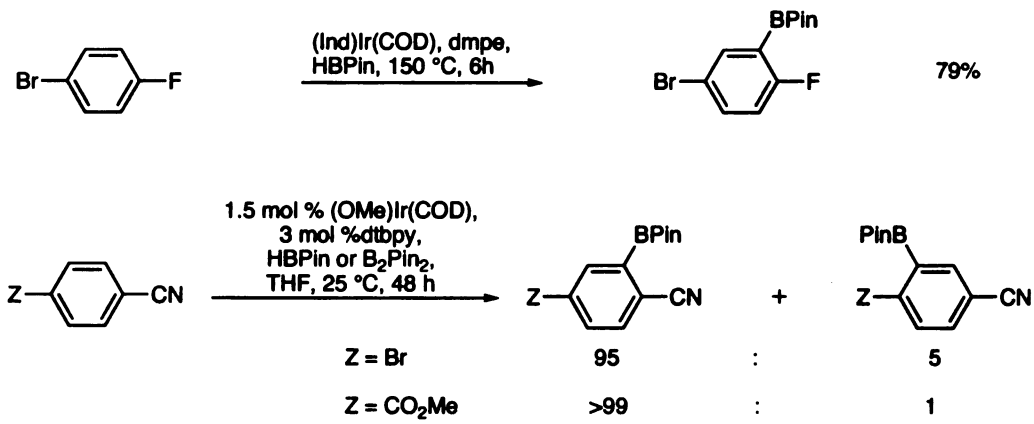


Figure 15: Regioselective borylation of 1,4-substituted arenes

The turning point of our chemistry was to identify the active Ir species, one or multiple, responsible for catalysis. In the year 2002, our group showed that addition of

phosphines or related donor ligands to Ir catalysts (Ind)Ir(COD) or (η^6–mesitylene)Ir(BPin)$_3$ gave much higher turnover numbers, making Ir catalyzed borylation a potentially practical attractive method for arene functionalization. [21] A variety of arenes have been converted to arylboronic esters when reacted with pinacolborane, where the arene is the limiting reagent. This methodology has also been successfully applied to aryl halides and heteroaromatic compounds.[22] The reaction protocol consists of heating a H–BPin/arene mixture with (Ind)Ir(COD) [Ind = Indenyl, COD = Cyclooctadiene] and 1,2–bis(dimethylphosphino)ethane (dmpe) at 150 °C or 1,2–bis(diphenylphosphino)ethane at 100 °C until the borylation is complete by GC–FID.[18,23] In 2003, Hartwig, Miyaura, Ishiyama and co-workers reported very similar chemistry of an iridium(III) complex generated from 1/2[Ir(OMe)(COD)]$_2$ and 4,4′–di–*tert*–butyl–2,2′–bipyridine (dtbpy) as the catalyst for a regioselective, stoichiometric and room temperature borylation reaction of five–membered heteroarenes.[24]

The mechanism of these catalytic cycles would involve an oxidative addition to and reductive elimination from $Ir^{I/III}$ and/or $Ir^{III/V}$ intermediates (Figure 16). However, differences in stoichiometric reactivities of Ir(I) and Ir(III) boryl complexes and the dependence of the reaction on the equivalents of phosphine added favors $Ir^{III/V}$ mechanism. Very recently our supposition was confirmed by Hartwig and coworkers by mechanistic the studies of the functionalization of arenes with B_2Pin_2 catalyzed by the combination of dtbpy and olefin–ligated iridium halide or alkoxide complexes [Ir(dtbpy)(COE)(BPin)$_3$] (COE =cyclooctene).[25] Kinetic studies show that this complex enters into the catalytic cycle after reversible dissociation of COE to form a reactive intermediate, [Ir(dtbpy)(BPin)$_3$], which then cleaves the arene C—H bond.

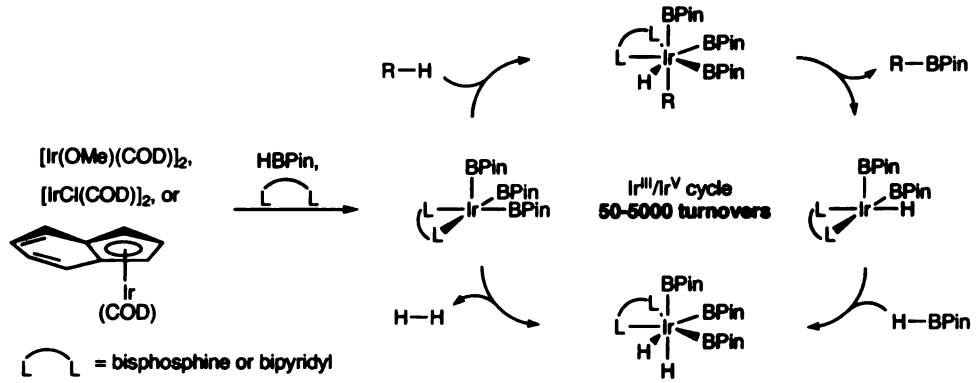


Figure 16: Catalytic cycle of Ir-catalyst

The advantages of this method are preparation of highly versatile arylboronic esters with unique regioselectivity of borylation in one operational step from commercially available arenes, good functional group tolerance (halogen, ether, ester, amide). The inert byproducts of the reaction allow subsequent transformations to be

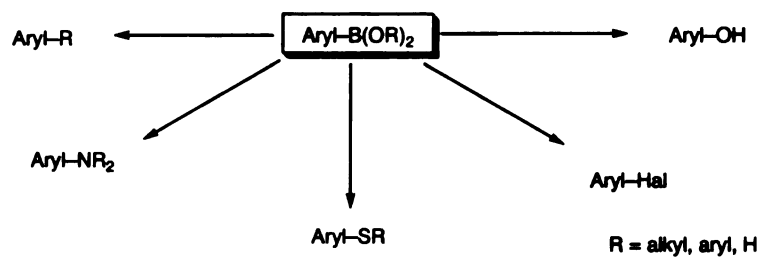


Figure 17: Possible synthetic transformations from arylboranes

carried out without separation or purification of the arylboronic ester. Thus, C–C and C–O bonds can be generated from C–H bonds (Figure 17).[26]

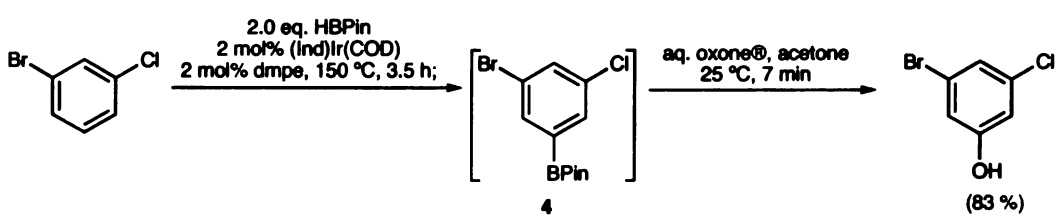


Figure 18: A convenient route to 3–bromo–5–chloro phenol

A particularly interesting example is the one-pot preparation of aforementioned 3–bromo–5–chlorophenol from 3–chloro bromobenzene, an important substrate (Figure 18) because it is a meta-substituted phenol bearing ortho/para directing groups.[23] The regioselectivity of the borylation is the key as the intermediate boronate ester (4) provides direct access to the phenol. Thus, utilizing the unique regioselectivity of borylation and subsequent oxidation, the phenol that was previously prepared in ten steps from TNT is accessible in two steps from the parent hydrocarbon. Similarly, one pot borylation/

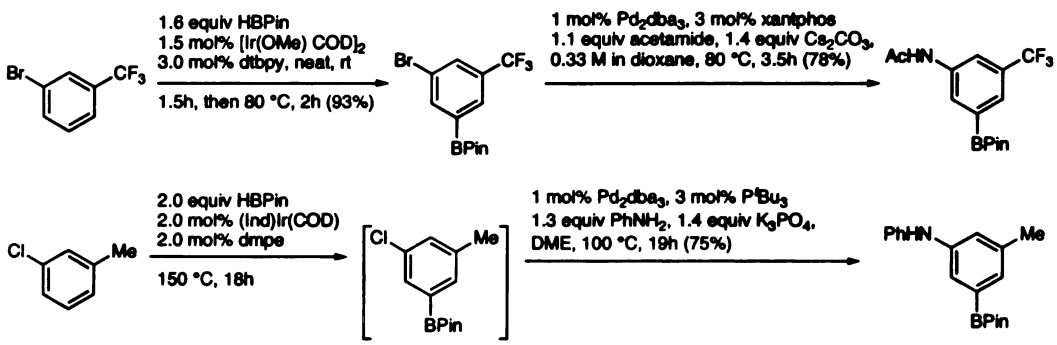


Figure 19: Several transformations of boronic esters

amidation[27] and one pot borylation/ amination[21a] have also been established.

The arylboronic ester has become a potential tool for making aromatic building blocks and our chemistry has been shown to be relatively less complex and a time saving way to make synthetically useful building blocks (Figure 8) such as aryl amines, phenol, biaryls.[21,23,26,27]

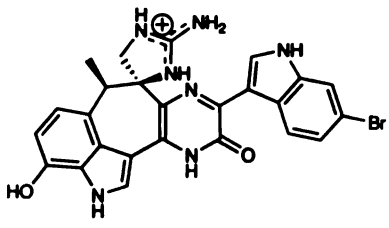
CHAPTER 2

RESULTS AND DISCUSSION

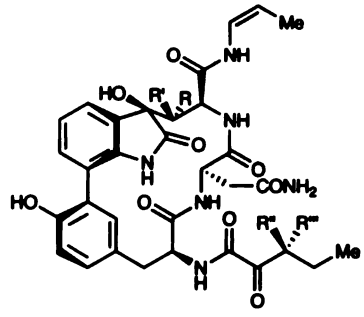
Ir–catalyzed regioselective borylation of 2–substituted indoles.

Indoles are pervasive heterocycles with important biological functions. The synthesis of substituted indoles can be classified into two traditional methods: first, direct functionalization of indole moiety and second, construction of indole ring from other substrate. Examples of the former are electrophilic addition and metallation.[7,28] A classic example of the latter method is the Fischer indole synthesis.[29] While these methods are still useful, recent metal mediated C–H functionalization of indoles are particularly

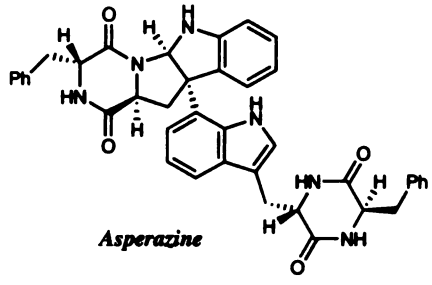
attractive in the sense that they allow subsequent modification on indole framework and this elaboration does not require protection of the indole N–H bonds.[30]



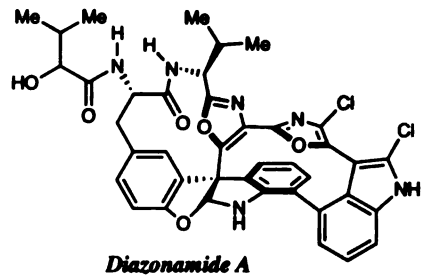
Dragmacidin E



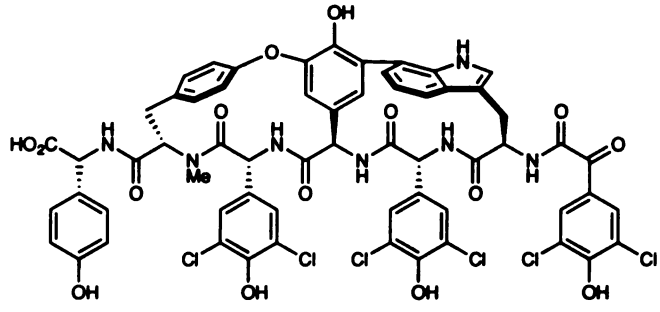
TMC-95	R	R'	R"	R"'
A	OH	H	Me	H
B	OH	H	H	Me



Asperazine



Diazonamide A



Chloropeptin I

Figure 20: Natural products containing 7–substituted indole substructures

Of all the positions of the indole substructure, the 7–position is one of the most difficult to functionalize selectively. In addition, several intriguing natural products are known having substitution at 7–position, such as asperazine,[31a] chloropeptin I,[31b] diazonamide,[31c] dragmacidins[31d] and TMC–95A and B (Figure 20).[31e]

There is only one example of functionalization exclusively at 7–position of indole itself. Chloroperoxidase, a bacterium from marine organism *Pseudomonas pyrrocinia*, produces 7–chloroindole with other isomers (Figure 21).[32]

Figure 21: Enzymatic chlorination at the 7–position of indole

For substituted N–unprotected indoles, functionalization exclusively at 7–position are rare. For example, bromination at the 7–position of indole substrate containing an –OH group at the 4–position shows poor selectivity, whereas protecting the –OH group with a benzyl group produced good selectivity.[33] The regioselectivity in this example

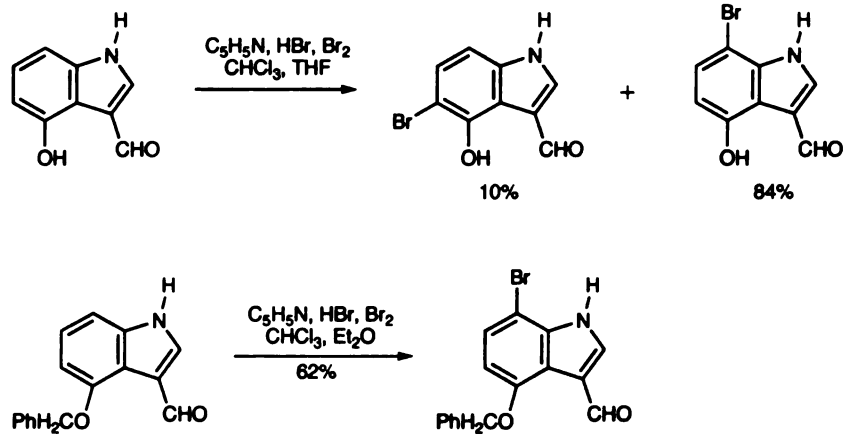


Figure 22: Functionalization at the 7–position of indoles driven by EAS

follows the rules of EAS, where the ortho/para directing group at 4–position directs the substitution at 7–position, which draws a limitation towards the variety and position of substituents on phenyl ring of the starting material (Figure 22).

An attempted acylation of indole substrate[34] (Figure 23) utilizing N, N–dimethylacetamide and phosphoryl chloride gave the 7–acetylindole in 65% yield along with its regioisomer 2–acetylindole in 20% and the 2,7–diacetylindole in 8% yield.

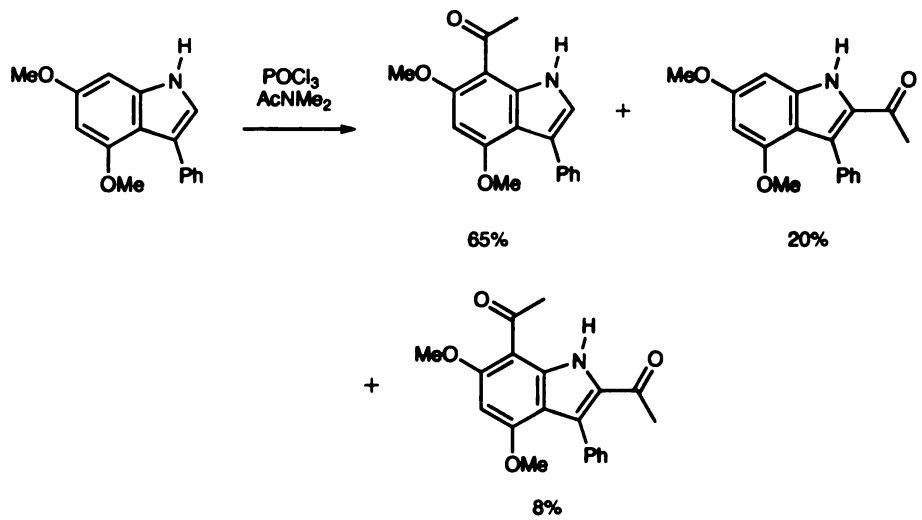


Figure 23: Functionalization at the 7–position of indoles driven by EAS

Another example of preparing 7-substituted indole is methylation of 4-nitro indole, which leads to the unselective formation of 7-methyl indole, with the 5-regioisomer being the major product (Figure 24).[35]

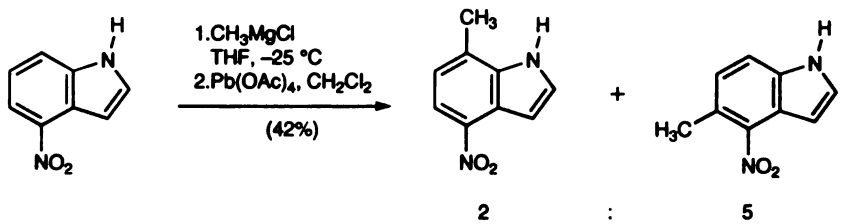


Figure 24: Methylation of 4-nitro indole

Outside enzymatic halogenations, there is only one report of an unprotected indole whose six-member ring is unfunctionalized, is derivatized at the 7–position. 2–methyl indole has been converted to 7–ethyl–2–methyl indole in the presence of aluminum anilide (Figure 25). The reaction needed high temperatures, 300 °C.[36]

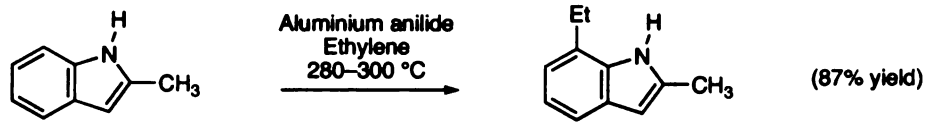


Figure 25: Synthesis of 7–ethyl–2–methyl indole

The only approach to 7–functionalization of indoles at the 7–position with any generality is that developed by Snieckus and coworkers.[7] His approach requires N–protection with a Directed Metallation Group (DMG) and is outlined in Figure 26. Specifically, in this method the N–H is protected as the *t*-butyl phosphinoyl derivative. The phosphinoyl group directs *n*–BuLi for deprotonation at the 7–position, the metallated

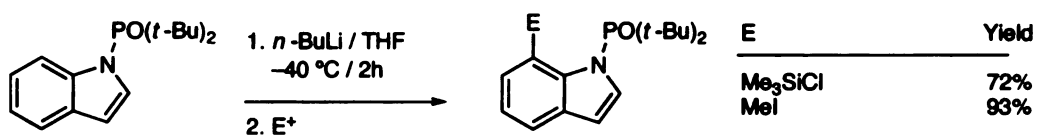


Figure 26: Synthesis 7–substituted indole via DMG

intermediate is then quenched with an electrophile affording the N–protected 7–substituted indole. A significant drawback of this approach is that the protecting group can only be cleaved with $LiAlH_4$ in refluxing toluene.

On the other hand, when the N–amide protected indole was subjected to a sequential one pot C–2 metallation, silylation, C–7 metallation and electrophilic quench,

the 7–substituted–2–silylated–N–protected indole was obtained (Figure 27). Subsequent N–$CONEt_2$ (and simultaneous 2–TMS) cleavage was carried out to provide the corresponding 7–substituted indole.

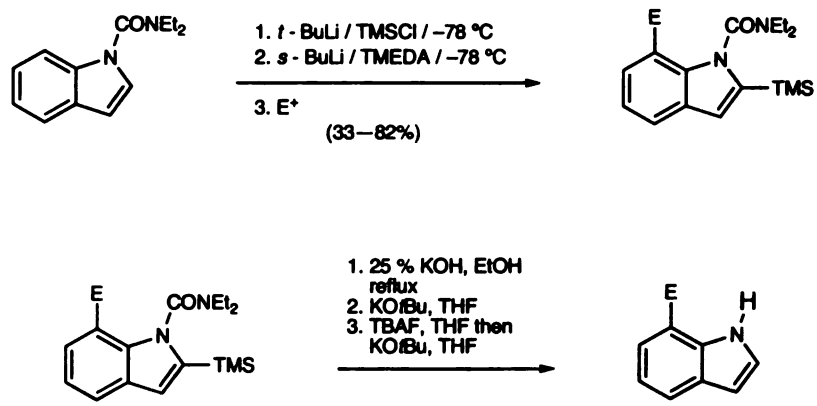


Figure 27: General approach of synthesizing 7–substituted indole

Clearly, methods for functionalizing indoles at 7–position that obviate the N–protection would reduce the number of steps. Rainier[37] has claimed a Rh–catalyzed C–H insertion method to functionalize at the 7–position of N–unprotected indole. Exposure of

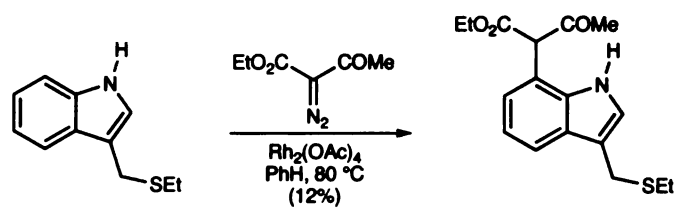


Figure 28: Rh-catalyzed synthesis of 7–substituted indole

the thioether to diazoketoester and $Rh_2(OAc)_4$ resulted in a low yield of the 7–substituted indole (Figure 28), though the spectroscopic analysis to prove the regiochemistry of the compound is not quite satisfactory and is inconsistent with the assigned regiochemistry.

Hetero aromatic boronic acids and esters are useful intermediates for the synthesis of natural products, medicinal compounds and functional materials. Previously, our group and the Hartwig–Miyaura group have reported monoborylation of heteroaryl substrates such as pyrroles, furans, thiophenes, indoles.[22,24] In the course of exploring the scope of borylations for heterocycles, we noted small quantities of diborylated products (Figure 29) formed when indole borylation was carried out with slight excess of HBPin. A series of NMR experiments (HMQC, HMBC) conclusively identified the 7–position as the site of the second borylation (see chapter 3 for details). The general protocol for these reaction is addition of HBPin (2.0 equiv) with 3 mol % of the Ir–catalyst and ligand in *n*–

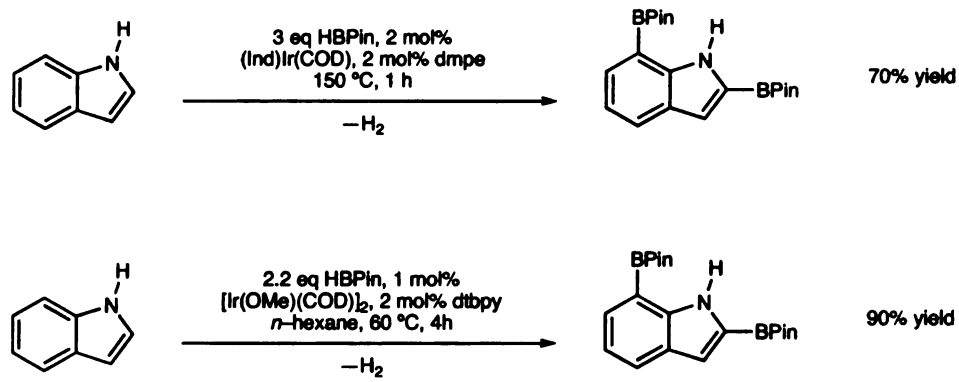
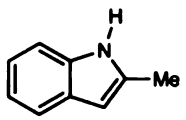
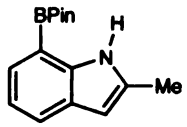
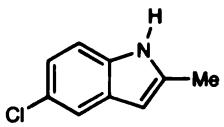
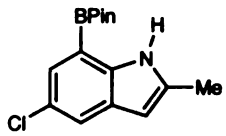
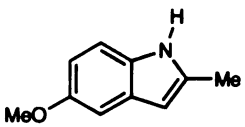
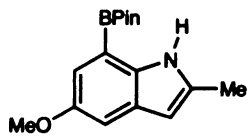
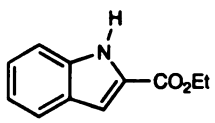
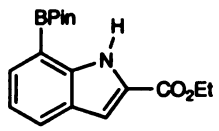
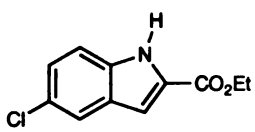
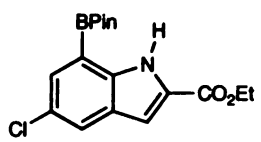
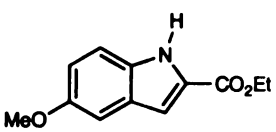
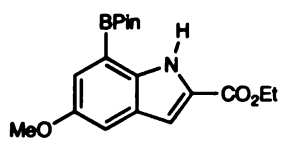
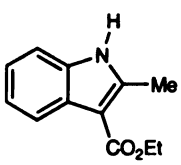
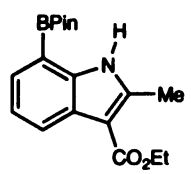
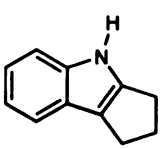
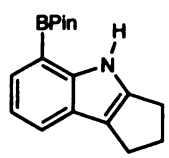


Figure 29: Diborylation of indole

hexane to indole.[38] Then the solution is heated at 60 °C for 4 h under a nitrogen atmosphere (open to nitrogen flow).

By changing both the precatalyst from (Ind)Ir(COD) to $[Ir(OMe)(COD)]_2$ and the co-ligand from dmpe to dtbpy while lowering the temperature from 150 °C to 60 °C, the yield has been found to increase from 70% to 90%. For the high temperature catalyst-system, (Ind)Ir(COD)/dmpe, the reduced yield was due in part to production of

Table: 1

Entry	Indole	Product	%Yield
1			78
2			91
3			88
4			87
5			83
6			82
7			64
8			45

significant amounts of triborylated indole. With $[Ir(OMe)(COD)]_2$ triborylation was nominal and 90% of the diborylated product could be isolated.[39]

To explore the scope of the reaction, borylation was carried out with several 2–substituted indoles using a range of conditions. Most of the indole reagents are sparingly soluble in nonpolar solvents like *n*–hexane. Initially THF was used to dissolve the indole starting materials, but solvents containing donor atoms have been found to slow down the reaction for some of the indole substrates. This problem was solved by pregenerating the catalyst in *n*–hexane and adding this solution to a flask containing the indole substrate. The partial solubility of the indole substrates in *n*–hexane was sufficient enough for the starting material to be completely consumed. For example, borylation of ethyl 5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole-2-carboxylate in a mixture of *n*–hexane / THF (3:1) gave a 67% yield of the product after heating at 60 °C for 4.5 h. On the other hand, in the absence of THF the reaction was complete in 6 h yielding 83% of the product (Table 1; entry 5).

Borylation of 5-methoxy-2-methylindole, when subjected to react with HBPin, $[Ir(OMe)(COD)]_2$ and dtbpy in a sealed air-free flask, gave 45% of the isolated borylated product and substantial amounts of the indole starting material, even though the GC-FID showed complete conversion of the starting material. In order to address this problem, the reaction was run in sealed NMR tube and monitored by ^{11}B NMR. In addition to the product peak at δ32 ppm, a major resonance at δ25 ppm was seen. This was assigned to the N-borylated product. The lower isolated yield of this reaction is assumed to be due to result of N-borylation, which hydrolyzes on work up to yield the starting indole. Inside a closed air–free flasks, we can assume that the byproduct of the reaction, the reactive hydrogen gas, can interfere in the actual catalytic cycle by generating equilibrium to form

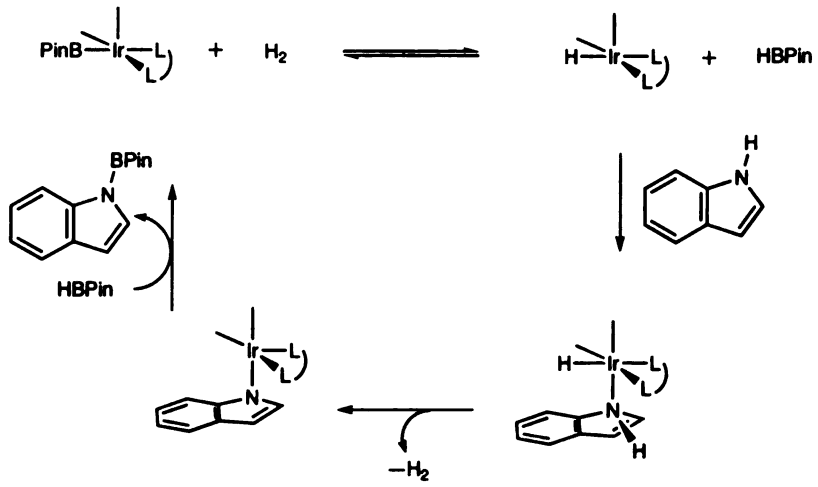


Figure 30: Possible mechanism of N–borylation

a metallic hydride species which leads to the formation of N–borylated product (Figure 30). If this hypothesis is correct, the formation of N-borylated species could be minimized by running the reaction in an open system. Indeed, 2-methyl-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)- indole was obtained in 88% yield (Table 1; entry 3), a substantial improvement, when the reaction was run under nitrogen in an open system.

Borylation of ethyl-2-methylindole-3-carboxylate for the preparation of ethyl 7--(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole-3-carboxylate both (Ind)Ir(COD) and $[Ir(OMe)(COD)]_2$ catalytic system, irrespective of closed or open system, with HBPin gave poor yields (~32%). The major indole species under these conditions were N–borylated products. The formation of competing N–borylated and C–borylated product can be monitored by ^{11}B NMR, when the reaction ran in an NMR tube under open system, the peak at around 25 ppm in ^{11}B NMR corresponds to N–B bond while peak at around 30–32 ppm corresponds to C–B bond (Figure 31). When N–borylation becomes a problem in an open system, changing HBPin to B_2Pin_2 as boron reagent would be a

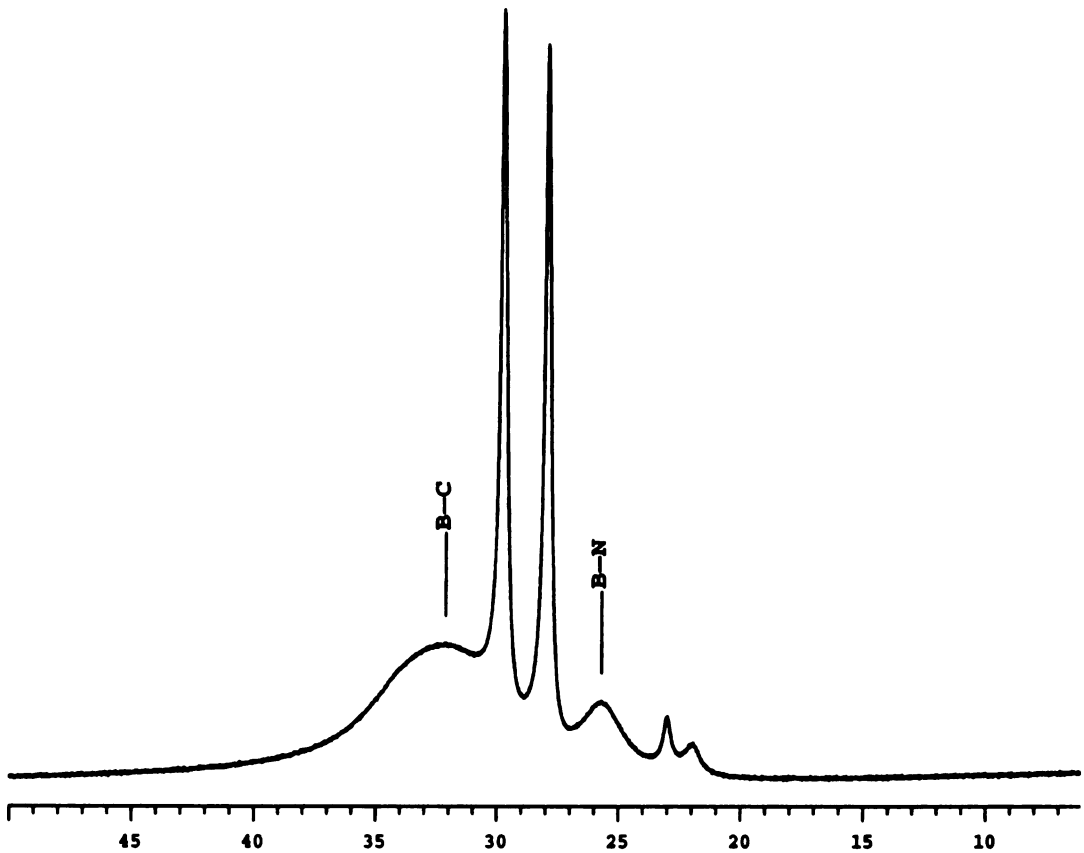


Figure 31: B-11 NMR of N-borylation of ethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole-3-carboxylate.

possible solution. Since the possible byproduct produced with B_2Pin_2 is HBPin and hence the formation H_2 can be avoided (Figure 32). Using B_2Pin_2 as boron reagent with $[Ir(OMe)(COD)]_2$ as catalyst, C–borylation was found to be major isomer, and the yield was increased to 64% (Table 1; entry 7).

During the course of developing this chemistry, some indole substrates, appeared to be less reactive under the conditions of Ir–catalyzed borylation. The synthesis of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-1,2,3,4–tetrahydrocyclopent[*b*]indole never went to full completion. The conversion was practically stopped after 36 h with a starting

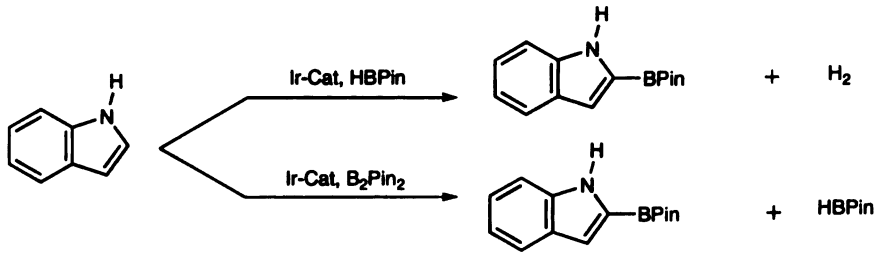


Figure 32: Byproducts of borylation reaction

When the reaction is incomplete, chromatography can be employed to separate the unreacted starting material and product from the crude mixture. For 2-Methyl indole, borylation with HBPin in presence of $[Ir(OMe)(COD)]_2$ and dtbpy at 65 °C for 20 h gave 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole in 66% yield after column chromatography (hexane/ethyl acetate, 90:10). However, when the reaction was carried out at 60 °C for 4 h, under same catalytic loading, 78% of the product could be isolated by eluting through a short plug of silica with CH_2Cl_2 from the mixture of starting material and product (Table 1; entry 1).

Crystallization of crude mixtures from *n*–hexane was found to be a convenient way to separate and isolate the more polar borylated–product from the remaining starting material. Passing the crude mixture through a short plug of silica with CH_2Cl_2 prior to crystallization is recommended in some cases. For example, direct crystallization from the crude mixture afforded 63% product while short plug of silica/crystallization method affords 88% of the pure product for 5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole (Table 1; entry 3).

Sequential borylations at positions flanking the indole N hint at its participation in the reaction. Three possibilities that we envision are depicted in figure 33. In the first pathway (eq1, Figure 33), initial N–H scission afford an Ir–N intermediate. Subsequent Ir

insertion into the C–H bond at the 7–position of indole would precede product formation. In the second pathway (eq2, Figure 33) hydrogen bonding between the hydrogen on the indole nitrogen and a pinacolate oxygen directs C–H insertion. In the third mechanism (eq3, Figure 33) coordination of the indole N to Ir directs C–H insertion. An intriguing alternative to this latter mechanism could be the coordination of the indole N to B in one

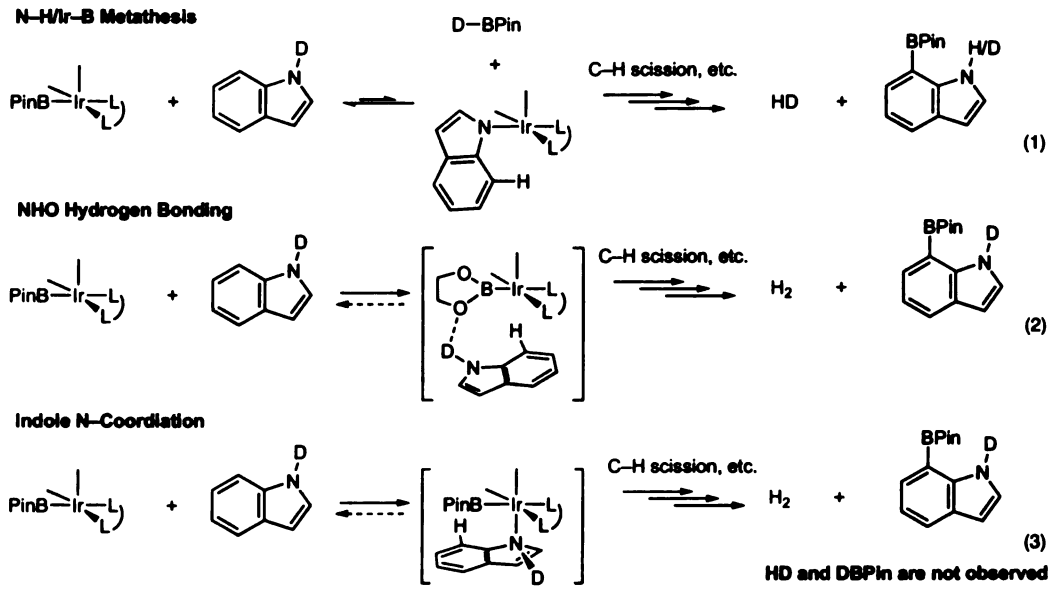


Figure 33: Possible mechanisms of C-borylation

of the boryl ligands.

Catalytic borylation on N–d_1–5–chloro–2–methylindole and HBPin showed no deuterium incorporation after 50% conversion, as was evident in HBPin and H_2 by ^1H and ^{11}B NMR. This eliminates the first mechanism (eq.1) of figure 32, since any N-D activation should be traced out by formation of N-H or N-BPin.

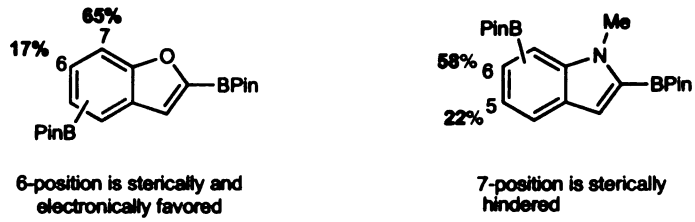


Figure 34: Regioselectivity of borylation of benzofuran and N-methyl indole

Diborylation of N-methyl indole, lacking the heteroatom attached proton, was carried out to examine the importance of H-bonding in borylation.[39] Though initial borylation at C2 predominated, 58 and 22% of the second borylation occurred at C6 and C5, respectively (Figure 34). This outcome could be construed as support for H-bonding, but a N-coordination could be sensitive to steric due to methylation. Benzofuran which is an isosteric analog to indole absent the heteroatom–attached proton produces 2,7–diborylated regioisomer as the major product (Figure 34).[39] This indicates that the hydrogen bonding is not required for the observed regioselectivity and hence the possibility of second mechanism (eq2) is not strong. Since, oxygen of benzofuran is less basic than the nitrogen of indole, the regioselectivity for 7-borylation is decreased. As chelate directing effect directs borylation at 2– and 7–position, the opposing steric effect and EAS directs the second borylation at 6–position.

Kinetic experiments have been carried out with N–H and N– d_1–indole. N–deuterated indole afforded 2–borylated product with retention of isotopic label as judged by ^{1}H and ^{11}B NMR. This weakens the possibility of N–H scission mechanism (eq1, Figure 33). Under pseudo first–order conditions at 25 °C, k_H/k_D was found to be 0.62 (Figure 35).[40] Inverse isotope effect arise when vibrational zero–point energies in the transition state or an intermediate that precedes the rate determining step are greater than those for corresponding modes in the ground state.

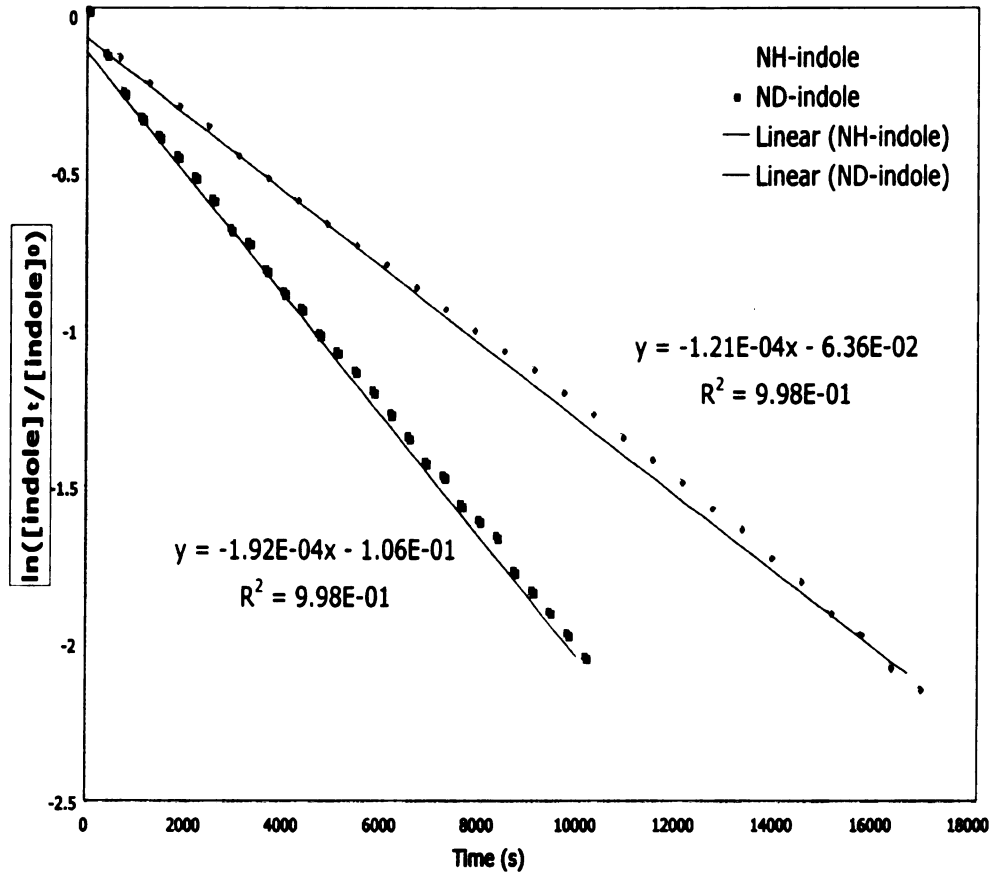


Figure 35: Kinetic experiment of indole

According to Streitwieser's[41] model for a C–H bond attached to a carbonium ion, the out of plane bending mode for sp^3 and sp^2 hybridized bonds differ by 540 cm^{-1}. Because the deuterium zero point energy is lower than those for hydrogen in a C–H bond, deuterium will result in a faster rate when the frequencies for the sites of isotopic substitution increase in the transition state relative to the ground state. Thus, an sp^2 to sp^3 hybridization leads to the inverse isotope effect when the α–positions are deuterated. A similar situation can be assumed for our system as depicted in Figure 36.[42] From the measured value for out of plane bending for indole[43] and the ~700 cm^{-1} increase in the low frequency mode in amines on protonation,[42] we can calculate $k_H/k_D \sim 0.65$, which is

very close to the value we measured. An inverse isotope effect is consistent with the third mechanism (eq3, Figure 33) where N–coordination is accompanied by rehybridization from sp^2 to sp^3.

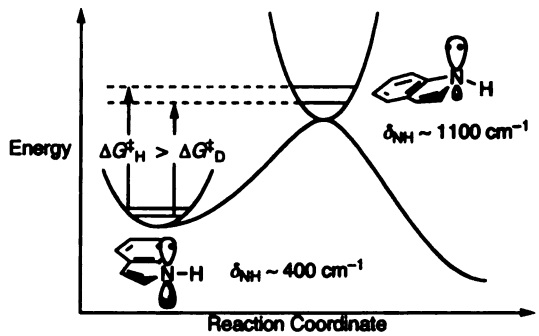


Figure 36: Inverse isotope effect for borylation at 2–position of indole

This reflects that the mechanism of borylation reaction is quite different than the arylation at 2-position of indole as described by Sames and coworkers,[30a] which follows an electrophilic palladation pathway. They measured the kinetic isotope effects for C–arylation of 2-*deutero*-1-methylindole and of 3-*deutero*-1-methylindole. A surprisingly large k_H/k_D value, 1.6 for the 3-positon where the substitution does not occur while a smaller k_H/k_D value 1.2 for the 2-position was observed. These suggest that the reaction follows an electrophilic palladation of indole, accompanied by a 1,2-migration of intermediate palladium species.

We measured kinetic isotope effects for borylation of 2 and 3–deuterated indoles. For borylation at 2–position, the corresponding k_H/k_D were found to be ~2.09 and ~0.98 respectively. This result indicates that C–H bond at 3–position has no involvement in the course of the reaction and C–H bond activation could be the rate-determining step, hence a chelate directing mechanism is quite possible. Similar chelate directing effect can also

be addressed in case of other heterocycles, where borylation occurs adjacent to the heteroatom (Figure 37).[44]

For E = NH, O, S

For E^1 = NH, O

E^2 = CH, N

Figure 37: Chelate directing effect for other heterocycles

A recent study raises doubts that products in Table 1 might perform poorly in Suzuki–Miyaura cross-coupling reaction,[45] Thus, one pot borylation/Suzuki–Miyaura cross–coupling transformation was attempted with 5–bromo–*m*–xylene. The crude

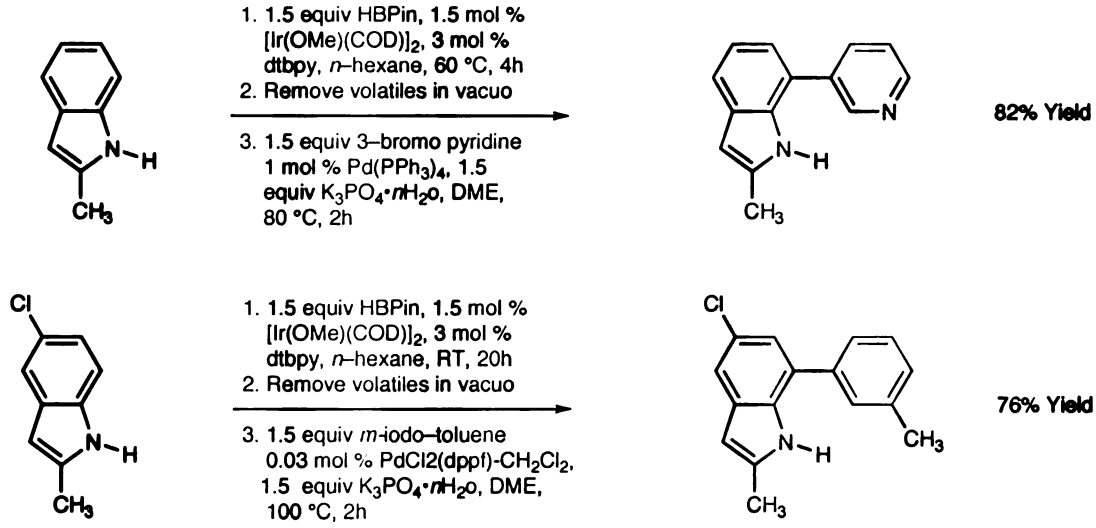
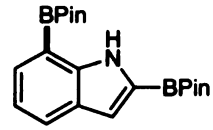


Figure 38: One pot borylation/Suzuki-Miyaura cross-coupling reaction

product from Ir–catalyzed borylation was subjected to Pd–catalyzed coupling reaction with an aryl iodide. The arylated products were isolated in high yields (Figure 38), bolstering the synthetic prospects of the borylated products.

CONCLUSIONS

Indoles are important heterocycles with biological functions. Functionalization on indole moiety occurs at 3–position when subjected to electrophilic aromatic substitution. Out of all different position on indole substructure, functionalization at 7–position perhaps is perhaps most challenging. Ir–catalyzed borylation appears to be the first general approach to functionalizing unprotected 2–substituted indoles directly at 7–position. The reaction shows high level of regioselectivity (Figure 39), which we attribute



>99% isomeric purity

Figure 39: High level of regioisomeric purity of diborylated indole

to a chelate directed mechanism associated with the coordination of N with either Ir or B in the C-H cleaving step. Future work is planned to validate this mechanism.

CHAPTER 3

EXPERIMENTAL METHODS

General Methods:

Pinacolborane (HBPin) was generously supplied by BASF and B_2Pin_2 by Frontier Scientific. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) [Ir(OMe)(COD)]$_2$ was prepared per literature procedure.[46] 4,4′-Di-*t*-butyl-2,2′-bipyridine (d'bpy) was purchased from Aldrich. Ethyl indole-2-carboxylate, 1,2,3,4-tetrahydrocyclopent[*b*]indole, 2-methylindole, 5-chloro-2-methylindole, ethyl 2-methylindole-3-carboxylate, 5-methoxy-2-methylindole, ethyl 5-methoxyindole-2-carboxylate were purchased from Aldrich. Ethyl 5-chloroindole-2-carboxylate was purchased from Lancaster. 3-*Deutero*-indole and 2-*deutero*-indole were prepared per literature procedure.[47] All substrates were purified before use. Solid substrates were sublimed under vacuum. Pinacolborane (HBPin) was distilled before use. *n*-Hexane was refluxed over sodium, distilled, and degassed. Tetrahydrofuran was distilled and then passed through a dry still packed with activated alumina and degassed before use. Silica gel was purchased from EMD™ (230-400 Mesh).

Unless otherwise specified, all reactions were carried out at 60 °C in air free flasks under a nitrogen atmosphere. All reactions were monitored by a Varian CP-3800 GC-FID (column type: WCOT Fused silica 30m × 0.25mm ID coating CP-SIL 8 CB). GC-FID

method: 70 °C, 2 min.; 20 °C/min, 9 min.; 250 °C, 20 min.; All reported yields are for isolated materials.

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-300 (300.11 and 75.47 MHz respectively), Varian VXR-500 or Varian Unity-500-Plus (499.74 and 125.67 MHz respectively) spectrometer and chemical shifts are referenced to residual solvent signals. ^{11}B spectra were recorded on a Varian VXR-300 operating at 96.29 MHz and were referenced to neat $BF_3 \cdot Et_2O$ as the external standard. All coupling constants are apparent *J* values measured at the indicated field strengths. All 2-dimensional experiments were run using *z*-axis pulse field gradients. Elemental analyses were performed at Michigan State University using a Perkin Elmer Series II 2400 CHNS/O Analyzer. GC-MS data were obtained using a Varian Saturn 2200 GC/MS (column type: WCOT Fused silica 30m × 0.25mm ID coating CP-SIL 8 CB). Melting points were measured on a MEL-TEMP® capillary melting apparatus and are uncorrected.

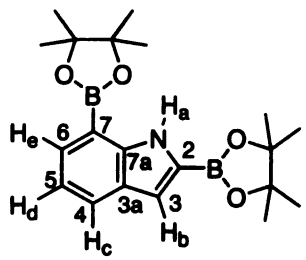
General Procedure

In a glove box, a Schlenk flask, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (10.0 mg, 0.015 mmol, 3 mol% Ir), excess HBPin (typically, 1.5 to 2 equivalents of boron), and d'bpy (8.1 mg, 0.03mmol, 3 mol%). These reagents were dissolved in 2 mL of *n*–hexane. The corresponding indole (1 mmol, 1 equivalent) was dissolved in 1 mL of THF and added to the *n*-hexane solution. The mixture was stirred at 60 °C until the reaction was judged complete by GC-FID. At this time, solvent was removed under reduced pressure, and the crude material was purified

either by column chromatography or crystallization to furnish the desired borylated product.

Experimental Details and Spectroscopic Data:

Diborylation of Indole.



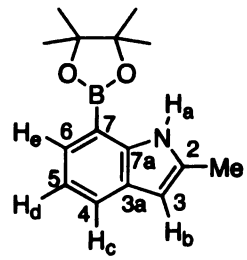
The general procedure was applied to indole (234 mg, 2 mmol, 1 equiv) and HBPin (638 μL, 563 mg, 4.4 mmol, 2.2 equiv) using 2 mol % [Ir] catalyst loading at 60 °C for 4 h. Upon cooling to room temperature and transferring to a vial, crystallization took place. The supernatant liquid was removed via pipette and the remaining solid was washed with hexanes (2 × 1 mL). The off-white solid diborylated product was dried under high vacuum (372 mg). ^{1}H NMR spectrum of this solid product was clean. The mother liquor and hexane washings were combined and the volatile materials were removed under reduced pressure. The resulting mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford additional diborylated product (293 mg) as a white solid, mp 147-148 °C. Combined yield (665 mg, 90%). ^{1}H, ^{13}C NMR, gHMQC and gHMBC spectroscopy were used to assign the diborylated product as 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.34 (br s, 1 H, H_a), 7.76 (dt, J =

7.9, 1.0 Hz, 1 H, H_c), 7.68 (dd, J = 7.0, 1.2 Hz, 1H, H_e), 7.10 (d, J = 2.1 Hz, 1 H, H_b), 7.08 (dd, J = 7.9, 7.0 Hz, 1 H, H_d), 1.40 (br s, 12 H, CH_3 of BPin), 1.37 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 143.1 (C, *C7a*), 131.3 (CH, *C6*), 127.3 (C, *C3a*), 125.1 (CH, *C4*), 119.3 (CH, *C5*), 113.8 (CH, *C3*), 84.0 (2 C), 83.8 (2 C), 25.0 (4 CH_3 of BPin), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.1; FT-IR (neat): 3455, 2978, 1593, 1543, 1371, 1327, 1302, 1262, 1143, 1130, 970, 854, 819, 756, 700, 679 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+ 369 (100), 312 (4), 285 (7), 269 (4), 254 (2), 226 (2), 212 (4), 184 (3), 169 (3); Anal. Calcd for $C_{20}H_{29}B_2NO_4$: C, 65.09; H, 7.92; N, 3.80. Found: C, 65.24; H, 8.05; N, 3.65.

^1H, ^{13}C NMR, gHMQC and gHMBC spectroscopy showed the single diborylated product to be 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole as follows. The ^1H NMR spectrum showed that proton H_d is ortho coupled to protons H_c and H_e. This ruled out the possibility of second borylation taking place on C5 or C6. Hence the second borylation took place either at C4 or C7. gHMQC spectrum showed that proton H_b (which is coupled to NH proton H_a) is attached to C3 at 113.8 ppm. C3 showed a three bond cross peak to proton H_c in the gHMBC spectrum. This could only be possible if proton H_c is attached to C4. This ruled out the possibility of second borylation taking place at C4. In the ^{13}C spectrum of starting indole (and mono borylated indole), carbon C7 is present at 111 ppm. A sharp resonance for C7 was not seen in the ^{13}C NMR spectrum of the diborylated product due to broadening from and coupling with boron. Instead quaternary carbon C7 was observed as a broad hump at 111 ppm in the ^{13}C spectrum of diborylated product. A three bond cross peak from C7 to proton H_d in the gHMBC spectrum was seen as expected for the C7 borylated isomer. Three cross peaks

from quaternary carbon C8 to protons H_b, H_c and H_e and one cross peak from quaternary carbon C9 to proton H_d in the gHMBC spectrum were also consistent with the second borylation taking place at C7.

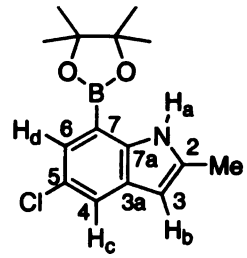
Table 1, Entry 1: Borylation of 2–methylindole.



The general procedure was applied to 2-methylindole (262 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3 mmol, 1.5 equiv) at 60 °C for 4 h. Volatile materials were removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the borylated product (201 mg, 78% yield) as a colorless oil. ^1H and ^{13}C NMR spectroscopy were used to assign the borylated product as 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.85 (br s, 1 H, H_a), 7.62 (d, J = 7.8 Hz, 1 H, H_e), 7.55 (dd, J = 7.2, 1.2 Hz, 1 H, H_c), 7.06 (dd, J = 7.8, 7.2 Hz, 1 H, H_d), 6.21-6.19 (m, 1 H, H_b), 2.48 (d, J = 0.9 Hz, 3 H, CH_3), 1.39 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ 141.3 (C), 134.9 (C), 128.0 (CH), 127.9 (C), 123.0 (CH), 118.9 (CH), 99.8 (CH), 83.6 (2C), 24.8 ($4CH_3$ of BPin), 13.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.6; FT-IR (neat): 3451, 2978, 1604, 1560,

1493, 1431, 1371, 1277, 1136, 974, 850, 802, 752, 679, 636 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+ 257 (100), 200 (24); Anal. Calcd for $C_{15}H_{20}BNO_2$: C, 70.06; H, 7.84; N, 5.45. Found: C, 69.68; H, 8.07; N, 5.28.

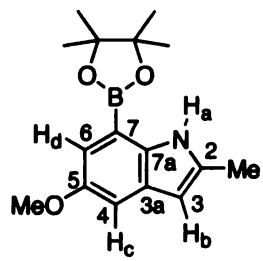
Table 1, Entry 2: Borylation of 5–chloro–2–methylindole.



The general procedure was applied to 5–chloro–2–methylindole (165 mg, 1 mmol, 1 equivalent) and HBPin (218 μL, 192 mg, 1.5 mmol, 1.5 equiv) at room temperature for 20 h. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the borylated product (264.0 mg, 91%) as a white solid, mp 106-110 °C. ^1H and ^{13}C NMR spectroscopy were used to assign the borylated product as 5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-2-methylindole. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.82 (br s, 1 H, H_a), 7.55 (d, J = 1.9 Hz, 1 H, $H_{c/d}$), 7.49 (d, J = 1.9 Hz, 1 H, $H_{c/d}$), 6.14 (m, 1 H, H_b), 2.47 (d, J = 0.7 Hz, 3 H, CH_3), 1.39 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ 139.7 (C), 136.7 (C), 129.5 (C), 127.6 (CH), 125.0 (C), 122.3 (CH), 99.6 (CH), 84.2 (2C), 25.0 ($4CH_3$ of BPin), 14.0 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.0; FT-IR (neat): 3443, 2978, 1558, 1464, 1427, 1387, 1130, 952, 881, 850, 758, 679, 640 cm^{-1}; GC-MS *m/z* (%

relative intensity): M^+ 291 (100), 234 (63), 191 (33); Anal. Calcd for $C_{15}H_{19}BClNO_2$: C, 61.79; H, 6.57; N, 4.80. Found: C, 62.06; H, 6.89; N, 4.78.

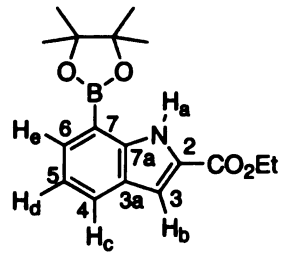
Table 1, Entry 3: Borylation of 5–methoxy–2–methylindole.



The general procedure was applied to 5-methoxy-2-methylindole (161 mg, 1 mmol, 1 equivalent) and HBPin (218 μL, 192 mg, 1.5 mmol, 1.5 equivalents) at 60 °C for 4 h. Volatile materials were removed under reduced pressure and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to yield borylated product as a light yellow solid (274 mg, 95%) containing 3% starting indole. Crystallization from hexanes at -30 °C afforded the desired product (253 mg, 88% yield) as a white solid, mp 72-74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.72 (br s, 1 H, H_a), 7.21 (d, J = 2.4 Hz, 1 H, $H_{c/d}$), 7.16 (d, J = 2.44, 1 H, $H_{c/d}$), 6.14 (m, 1 H, H_b), 3.86 (s, 3 H, OCH_3) 2.47 (d, J = 0.7 Hz, 3 H, CH_3), 1.39 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 153.6 (C), 136.8 (C), 135.9 (C), 128.8 (C), 115.8 (CH), 107.1 (CH), 99.4 (CH), 83.8 (2C), 56.2 (OCH_3), 24.9 (4CH_3 of BPin), 13.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.3; FT-IR (neat): 3455, 2980, 1483, 1373, 1326, 1282, 1217, 1126, 1041, 852, 752 cm^{-1}; GC-MS

m/z (% relative intensity): M^+ 287 (100), 187 (42); Anal. Calcd for $C_{16}H_{22}BNO_3$: C, 66.92; H, 7.72; N, 4.88. Found: C, 66.68; H, 7.56; N, 4.86.

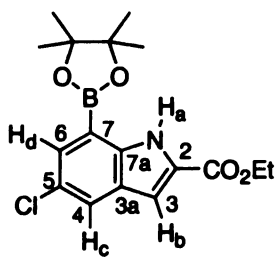
Table 1, Entry 4: Borylation of ethyl indole–2–carboxylate.



The general procedure was applied to ethyl indole-2-carboxylate (189 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.5 mmol, 1.5 equiv) at 60 °C for 1 h. Volatile materials were removed under reduced pressure and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the pure product (274 mg, 87% yield) as a white solid; mp 82-84 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.69 (br s, 1 H, H_a), 7.80-7.77 (m, 1 H, H_c), 7.76 (dd, J = 7.0, 1.2 Hz, 1 H, H_e), 7.20 (d, J = 2.2 Hz, 1 H, H_b), 7.19–7.14 (dd, J = 8.1, 7.1 Hz, 1 H, H_d), 4.40 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 1.41 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.39 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 162.0 (C=O), 141.6 (C), 132.7 (CH), 127.4 (C), 126.4 (C), 126.0 (CH), 120.3 (CH), 108.1 (CH), 84.0 (2C), 60.8 (CH_2), 24.9 (4CH_3 of BPin), 14.3 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.3; FT-IR (neat): 3449, 2982, 1711, 1593, 1535, 1421, 1371, 1290, 1232, 1132, 976, 850, 752, 677 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+ 315 (100), 258 (49),

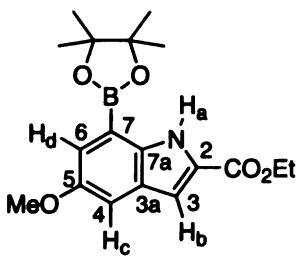
230 (14), 215 (17), 169 (23). Anal. Calcd for $C_{17}H_{22}BNO_4$; C, 64.78; H, 7.04; N, 4.44. Found: C, 64.45; H, 7.20; N, 4.62.

Table 1, Entry 5: Borylation of ethyl 5–chloroindole–2–carboxylate.



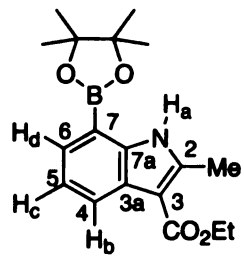
The general procedure was applied to ethyl 5-chloroindole-2-carboxylate (224 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2 mmol, 2 equiv) at 60 °C for 6 h. Volatile materials were removed under reduced pressure and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the pure product (290 mg, 83% yield) as a white solid, mp 112-114 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.64 (s, 1 H, H_a), 7.73 (dd, J = 2.1, 0.7 Hz, 1 H, H_c) 7.69 (d, J = 2.1 Hz, 1 H, H_d), 7.11 (d, J = 2.3 Hz, 1 H, H_b), 4.40 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 1.41 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.38 (s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 161.6 (C=O), 139.7 (C), 132.5 (CH), 128.6 (C), 127.5 (C), 126.2 (C), 124.8 (CH), 107.3 (CH), 84.4 (2C), 61.0 (CH_2), 24.8 (4CH_3 of BPin), 14.3 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.9; FT-IR (neat): 3449, 1709, 1641, 1300, 1233, 1142, 851, 752, 713, 677 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+ 349 (100), 351 (32), 334 (14), 292 (63); Anal. Calcd for $C_{17}H_{21}BClNO_4$ C, 58.4; H, 6.05; N, 4.01. Found: C, 58.15; H, 5.79; N, 4.33.

Table 1, Entry 6: Borylation of ethyl 5-methoxyindole-2-carboxylate.



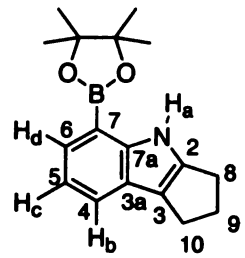
The general procedure was applied to ethyl 5-methoxyindole-2-carboxylate (219 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2 mmol, 2 equiv) at 60 °C for 3 h. Volatile materials were removed under reduced pressure and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the pure product (282 mg, 82% yield) as a white solid; mp 79 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.56 (br s, 1 H, H_a), 7.44 (d, J = 2.4 Hz, 1 H, H_d), 7.20 (dd, J = 2.4, 0.5 Hz, 1 H, H_c), 7.11 (d, J = 2.3 Hz, 1 H, H_b), 4.40 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.83 (s, 3 H, OCH_3), 1.41 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.38 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 162.0 (C=O), 154.3 (C), 137.1 (C), 127.8 (C), 127.1 (C), 122.9 (CH), 107.5 (CH), 107.3 (CH), 84.1 (2C), 60.7 (CH_2), 55.9 (OCH_3), 24.9 (4CH_3 of BPin), 14.3 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.0; FT-IR (neat): 3453, 2978, 1705, 1597, 1533, 1446, 1421, 1230, 1213, 1140, 1039, 850, 752 cm^{-1}; GC-MS m/z (% relative intensity): M^+ 345 (100), 330 (5), 299 (26), 245 (8), 213 (9), 199 (14); Anal. Calcd for $C_{18}H_{24}BNO_5$: C, 62.63; H, 7.01; N, 4.06. Found: C, 62.69; H, 7.18; N, 4.20.

Table 1, Entry 7: Borylation of ethyl 2–methylindole–3–carboxylate.



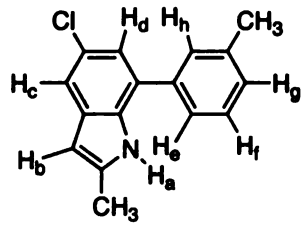
The general procedure was applied to ethyl 2-methylindole-3-carboxylate (203 mg, 1 mmol, 1 equiv) and B_2Pin_2 (254 mg, 1 mmol, 1 equiv) at 60 °C for 18 h. Column chromatography (hexanes/ethyl acetate 90:10) furnished the desired product (210 mg, 64% yield) as a white solid, mp 96-98 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.23 (br s, 1 H, H_a), 8.19 (m, 1 H, $H_{b/d}$), 7.61 (dd, J = 7.1, 1.2 Hz, 1 H, $H_{b/d}$), 7.20 (dd, J = 8.0, 7.1 Hz, 1 H, H_c), 4.38 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 2.78 (s, 3 H, CH_3), 1.43 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.39 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 166.1 (C=O), 143.8 (C), 139.8 (C), 129.4 (CH), 126.2 (C), 124.8 (CH), 121.2 (CH), 104.2 (C), 84.0 (2C), 59.3 (CH_2), 25.0 (4 CH_3 of BPin), 14.6 (CH_3), 14.3 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 32.1; FT-IR (neat): 3429, 2978, 1689, 1591, 1549, 1495, 1373, 1278, 1132, 1093, 846, 804, 756, 680, 652 cm^{-1}; GC-MS m/z (% relative intensity): M^+ 329 (100), 314 (4), 300 (9), 284 (16), 272 (21), 184 (18); Anal. Calcd for $C_{18}H_{24}BNO_4$: C, 65.67; H, 7.35; N, 4.25. Found: C, 65.47; H, 7.42; N, 4.58.

Table 1, Entry 8: Borylation of 1,2,3,4–tetrahydrocyclopent[*b*]indole.



The general procedure was applied to 1,2,3,4-tetrahydrocyclopent[*b*]indole (157 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2 mmol, 2 equiv) at 60 °C for 36 h. Column chromatography (hexanes/ethyl acetate 90:10) furnished the desired product (127 mg, 45% yield) as a white solid, mp 135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.96 (s, 1 H, H_a), 7.58 (d, J = 7.7 Hz, 1 H, H_d), 7.57 (d, J = 7.1 Hz, 1 H, H_c), 7.1 (dd, J = 7.8, 7.2 Hz, 1 H, H_c), 2.96-2.91 (m, 2 H, CH_2), 2.87-2.83 (m, 2 H, CH_2), 2.58-2.52 (m, 2 H, CH_2), 1.41 (s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 146.3 (C), 143.7 (C), 127.5 (CH), 123.6 (C), 121.9 (CH), 119 (C), 118.8 (CH), 83.7 (2C), 28.7 (CH_2), 26.0 (CH_2), 24.9 (4CH_3 of BPin), 24.4 (CH_2); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.3; FT-IR (neat): 3453, 3018, 2982, 1414, 1265, 1215, 1136, 929, 848, 767, 669, 623, 509 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+ 283 (100), 226 (26), 183 (33); HRMS (EI): *m/z* 283.1743 [(M^+); Calcd for $C_{17}H_{22}NO_2B$: 283.1744].

One-pot borylation/Suzuki coupling of 5–chloro–2–methylindole.



The general borylation procedure was applied to (165.21 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.5 mmol, 1.5 equiv) at room temperature for 20 h. The GC-FID showed 100% consumption of the starting indole. The reaction mixture was pumped down under high vacuum for 1 h to remove the volatile materials. The Schlenk flask was brought into the glove box, where dichloro[1,1′–bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct [$PdCl_2$(dppf)-CH_2Cl_2] (24.5 mg, 0.03 mol %), *m*-iodo toluene (192 μl, 327 mg, 1.5 mmol, 1.5 equiv) and DME (3 mL) were added. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. K_3PO_4 (319 mg, 1.5 equiv) and water (1 mL) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 100 °C for 2 h. The flask was cooled down to room temperature and 5 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (10 mL × 3). The combined ether extractions were washed with brine (10 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure. Column chromatography (hexane/CH_2Cl_2 = 4 : 1) furnished the desired product (195 mg, 76% yield) as a white solid, mp 84–86 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (br s, 1 H, H_a), 7.43 (d, J = 2.0 Hz, 1 H, $H_{c/d}$), 7.38 (m, 3 H among H_e, H_g, H_h, H_f), 7.21–7.23 (m, 1 H, among H_e, H_f , H_g, H_h), 7.07 (d, J = 2.0 Hz, 1 H, $H_{c/d}$), 6.20 (dd, J = 2.2, 2.2 Hz, 1 H, H_b), 2.44 (s, 3 H, CH_3 of toluene), 2.41 (d, J = 0.7 Hz, 3 H, CH_3 of indole); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 139.0 (C), 138.2 (C), 136.7 (C), 132.3 (C), 130.4 (C), 129.01 (CH), 128.9 (CH), 128.6 (CH), 126.0 (C), 125.6 (C), 125.1 (CH), 120.9 (CH), 118.1 (CH), 100.7 (CH), 21.5 (CH_3), 13.8 (CH_3); FT-IR (neat): 3439, 3030,

2920, 1604, 1579, 1560, 1489, 1488, 1389, 1323, 1290, 1080, 887, 853, 787, 708, 635, 607 cm^{-1}; GC-MS *m/z* (% relative intensity): M^+; HRMS (EI): *m/z* 255.0815 [(M^+); Calcd for $C_{16}H_{14}NCl$: 255.0815].

Kinetics Experiments:

Preparation of 2-deuterio indole:[47]

A solution of 1–phenylsulphonylindole (10 g, 38.0 mmol) in dry THF (150 mL) was cooled to –78 °C. To this solution *n*–butyl lithium (32 mL; 2.3 M in hexane) was added dropwise with vigorous stirring under nitrogen atmosphere. The resulting orange solution was allowed to warm to 20 °C and stirred for 2 h before cooling to –78 °C (during which solid was separated out) and D_2O (5 mL, 0.25 mol) was added. The mixture was allowed to warm to 20 °C and 400 mL dry ether was added followed by anhydrous K_2CO_3. When the ethereal layer was clear the solid was filtered off and filtrate was evaporated under reduced pressure to give, after two crystallization from ether, 1–phenylsulphonyl–[2–^{2}H] indole as crystals, (98%, mp. 81 °C).

A mixture of 1–phenylsulphonyl–[2–^{2}H] indole (5 g, 19.3 mmol) in 75 mL methanol and 2M NaOH solution (20 mL) was heated to reflux under nitrogen atmosphere for 2 h. The mixture was cooled and poured into 90 mL water and extracted with ether, dried to give a solid. Recrystallization from ether–hexane (1:3) solution, provided 95% of pure product (mp. 49 °C)

Preparation of 3-deuterio indole:[47]

A suspension of indole (1 g, 8.5 mmol) in 0.01 M DCl–D_2O (10 mL) was stirred for 4 h at 60 °C under nitrogen atmosphere. The mixture was cooled to 20 °C and indole was recovered by extraction with ether. The solvent was evaporated under reduced pressure. The residue was treated twice with fresh deuteriating solution. The mixture was then stirred with 10 mL of water and 5 mL of ether at 20 °C for 2 h followed by extraction from ether. Recrystallized from ether–hexane (1:2) solution to obtain the desired product as plates (99%; mp. 48 °C).

General Procedure for Kinetics Experiments:

Kinetic experiments with 2 & 3-d_1-indole were carried out on NMR scale. The data were processed by mass spectroscopy. 1mL of 1 M stock solution of 1:1 mixture of [^{1}H] and [^{2}H]–indoles in C_6D_6 was prepared and 100 μL of this stock solution (contains 0.1 mmol of substrates) was transferred into the NMR tube. Excess HBPin (5 eq, 78 μL) and C_6D_6 (482 μL) were added into the NMR tube. $[Ir(OMe)(COD)]_2$ (100 mg, 0.15 mmol) and dtbpy (81mg, 0.3 mmol) was dissolved in mesitylene and volume was diluted to 4 mL. 40 μL of this stock solution (containing 3 mol % [Ir–ligand], 1.0 mg, 0.0015 mmol of $[Ir(OMe)(COD)]_2$ and 0.81 mg, 0.003 mmol of d^{t}bpy in 40 μL of mesitylene) was added into the NMR tube and the total volume becomes 700 μL. The reaction was monitored by ^{1}H NMR.

2-d_1-Indole: The kinetic isotope effect of [2–^{2}H] indole was analyzed by GC-MS. GC–MS were taken to determine the ratio of [^{1}H]-indole and [2–^{2}H]-indole by the abundance of their molecular ions.

From GC–MS of pure [^{1}H]–indole, *m/z* 117: *m/z* 118 = 1: 0.10.

From GC–MS of pure [2–^{2}H] indole, *m/z* 117: *m/z* 118 = 0.11: 1.

Let n_1 be the mol fraction of [^{1}H]–indole and n_2 be the mol fraction of [2–^{2}H] indole.

The *m/z* 117 peak is contributed by two means, (1) the M^+ peak for *m/z* 117 and of [^{1}H]–indole (2) the $[M-1]^+$ peak for *m/z* 118 of [2–^{2}H]–indole. Hence for [^{1}H]-indole, M^+ = 100 and for [2–^{2}H] indole, $[M-1]^+ = 11$. The *m/z* 117 peak intensity, $I_{117} = n_1 + 0.11n_2$. Similarly, *m/z* 118 peak intensity $I_{118} = 0.10n_1 + n_2$. From initial GC–MS, ratio of I_{117} to I_{118} peaks in the mixture are 1: 0.95.

Hence, $I_{117}/ I_{118} = [n_1 + 0.11n_2]/[0.10n_1 + n_2] = 1/0.95 = 1.05$

Putting the value of $n_2 = (1 - n_1)$, we get, $[n_1 + 0.11(1-n_1)]/[0.10n_1 + (1-n_1)] = 1.05$

$[0.89\, n_1 + 0.11] / [1 - 0.90n_1] = 1.05$

Or, $0.89n_1 + 1.05(0.90\, n_1) = 1.05 - 0.11$. Therefore, $n_1 = 0.51$; $n_2 = 0.49$.

When 35% starting material was remaining (determined by NMR),

$I_{117}/ I_{118} = [n_{1t} + 0.11n_{2t}]/[0.10n_{1t} + 1n_{2t}] = 0.56$

Therefore, $n_{1t} = 0.32$; $n_{2t} = 0.68$.

Putting these values in the first order rate equation, $k = -[\ln (A_t/A_0)/t]$, we get,

$k_H/k_D = \ln [([^1\text{H-indole}]_t/[^1\text{H-indole}]_0)](0.35)/ \ln [([^2\text{H-indole}]_t/[^2\text{H-indole}]_0)](0.35)$

[Where %indole remaining = 0.35]

$k_H/k_D = \ln [(0.32)(0.35) / (0.51)] / \ln [(0.68)(0.35) / (0.51)] = 2.09.$

From repetition of this work, k_H / k_D value obtained is 1.98. The k_H / k_D value is 2.03 ± 0.5.

3-d_1-Indole: The kinetic isotope effect of [3–^{2}H] indole was analyzed by GC-MS. GC–MS were taken to determine the ratio of [^{1}H]–indole and [3–^{2}H] –indole by the abundance of their molecular ions.

From GC–MS of [^{1}H]–indole, *m/z* 117: *m/z* 118 = 100: 10.

From GC–MS of [3–^{2}H] –indole, *m/z* 117: *m/z* 118 = 17: 100.

The peak intensities for *m/z* 117 (I_{117}) and *m/z* 118 (I_{118}) were calculated as before.

From the initial GC–MS, intensity ratio, I_{117}: I_{118} was 1.18.

Hence, $I_{117}/ I_{118} = [n_1 + 0.17n_2]/[0.10\, n_1 + n_2] = 1.18$

Putting the value of $n_2 = (1 - n_1)$, we get, $[0.83n_1 + 0.17] / [1 - 0.90\, n_1] = 1.18$

Therefore, $n_1 = 0.53$; $n_2 = 0.47$.

When 67% starting material was remaining (determined by NMR),

$I_{117}/ I_{118} = [1n_{1t} + 0.17n_{2t}]/[0.10n_{1t} + 1n_{2t}] = 1.15$. Therefore, $n_{1t} = 0.52$; $n_{2t} = 0.48$.

Putting these values in the first order rate equation, $k = -[\ln (A_t/A_0)/t]$, we get,

$k_H/k_D = \ln [([^1\text{H-indole}]_t/[^1\text{H-indole}]_0)](0.67)/ \ln [([^2\text{H-indole}]_t/[^2\text{H-indole}]_0)](0.67)$

[Where %indole remaining = 0.67]

Or, $k_H/k_D = \ln [(0.52)(0.67) / (0.53)] / \ln [(0.48)(0.67) / (0.47)] = 0.98$.

From repetition of this work, same k_H / k_D value, 0.98 was obtained.

General Procedure for NMR Tube Reaction—Kinetic Experiments for N–H/N–D.

Preparation of N-d_1-indole:

Inside the glove box, 1 g of indole is weighed out in a test tube. 2 mL of dry THF was added to dissolve and to transfer the starting material to an air-free flask (AFF)

equipped with a magnetic stir bar. The AFF was stoppered and brought out of the glove box and attached to a Schlenk line. 2 mL of D_2O was added to the Schlenk flask under nitrogen flow. The AFF was stoppered and heated at 70 °C for 1 h. All volatile materials were removed under vacuo for 2 h. The AFF was again taken inside the glove box, and additional 2 mL of THF were added and the rest of the procedure was repeated. The N-d_1-indole was transferred to a dry sublimator inside the glove box. The N-d_1-indole was sublimed and collected (0.57 g, 57% yield) under nitrogen atmosphere.

Kinetic experiments with N-H and N-d_1-indole were carried out on NMR scale. General procedure was followed to make the stock solution of [Ir-ligand] in mesitylene.1 mL of 1 M stock solution of [^{1}H] and [^{2}H]–indoles in C_6D_6 were prepared separately. In the NMR tube first 100 µl of indole (either [^{1}H] or [^{2}H]) stock solution was added. Then excess HBPin (5 eq, 78 µL) was added followed by 3.5 µL of $(Me_3Si)_2O$ was added as an internal standard. C_6D_6 (478.5 µL) was added to bring volume of the reaction to 700 µL. The NMR tube was then capped with a Suba-seal and wrapped with Para film tape. The NMR tube was then brought outside of the glove box. The NMR sample was then locked and shimmed properly and settings were made to run in an arrayed ^{1}H–NMR experiment.[40] 40 µL of [Ir-ligand] stock solution (containing 3 mol% [Ir–ligand] (1.0 mg, 0.0015 mmol of $[Ir(OMe)(COD)]_2$ and 0.81 mg, 0.003 mmol of d'bpy in 40 µL of mesitylene) was taken in a syringe to bring it out of the glove box. The NMR tube was then ejected from the NMR machine and the catalyst solution was added into tube through the Suba-seal immediately. The tube was shaken and reinserted into the NMR machine, locked and shimmed. The arrayed experiment was then run for 4 h. The integral values of the starting material and product were plotted using Microsoft Excel (version

office Mac 10.0) and 1st order rate equations were calculated. From the rate equation for N-H & N-d_1-indole k_H / k_D were calculated as 0.62, indicating an inverse isotope effect.

SPECTROSCOPIC DATA

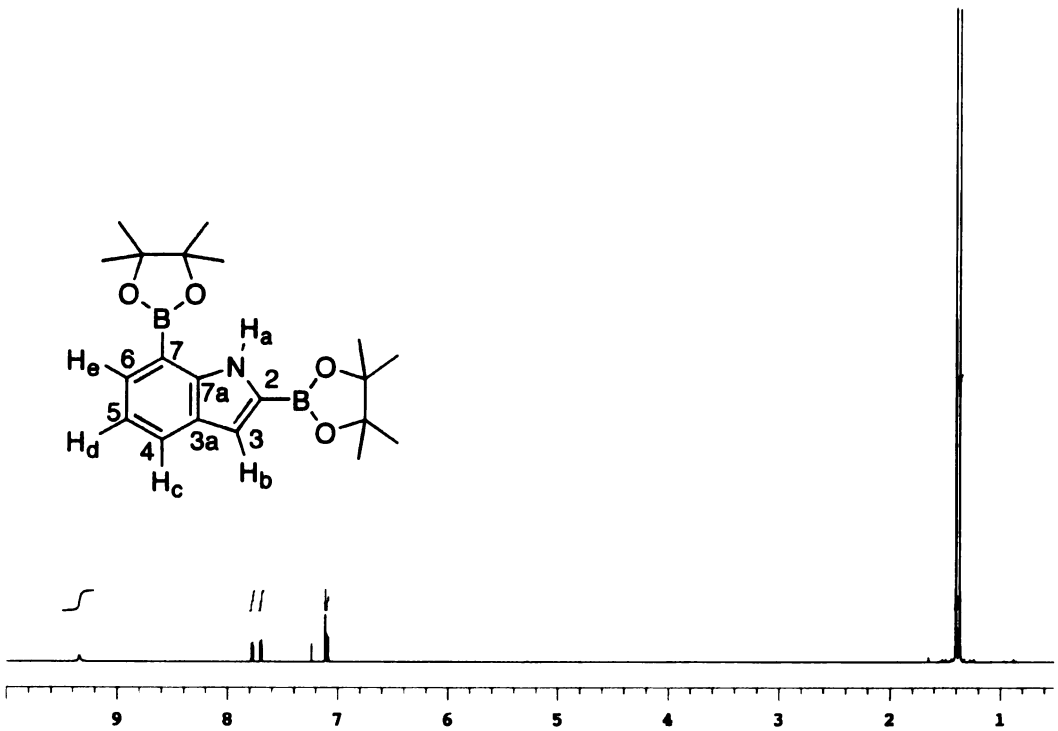


Figure 40: ^{1}H spectrum of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole

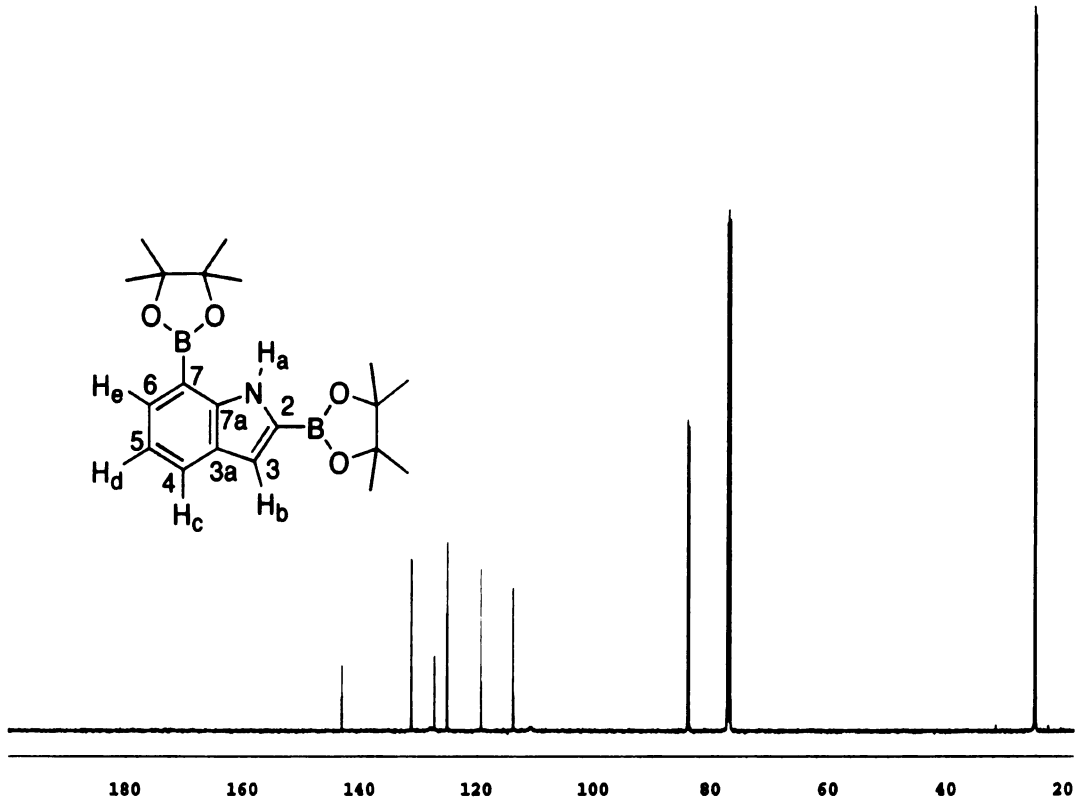


Figure 41: ^{13}C spectrum of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

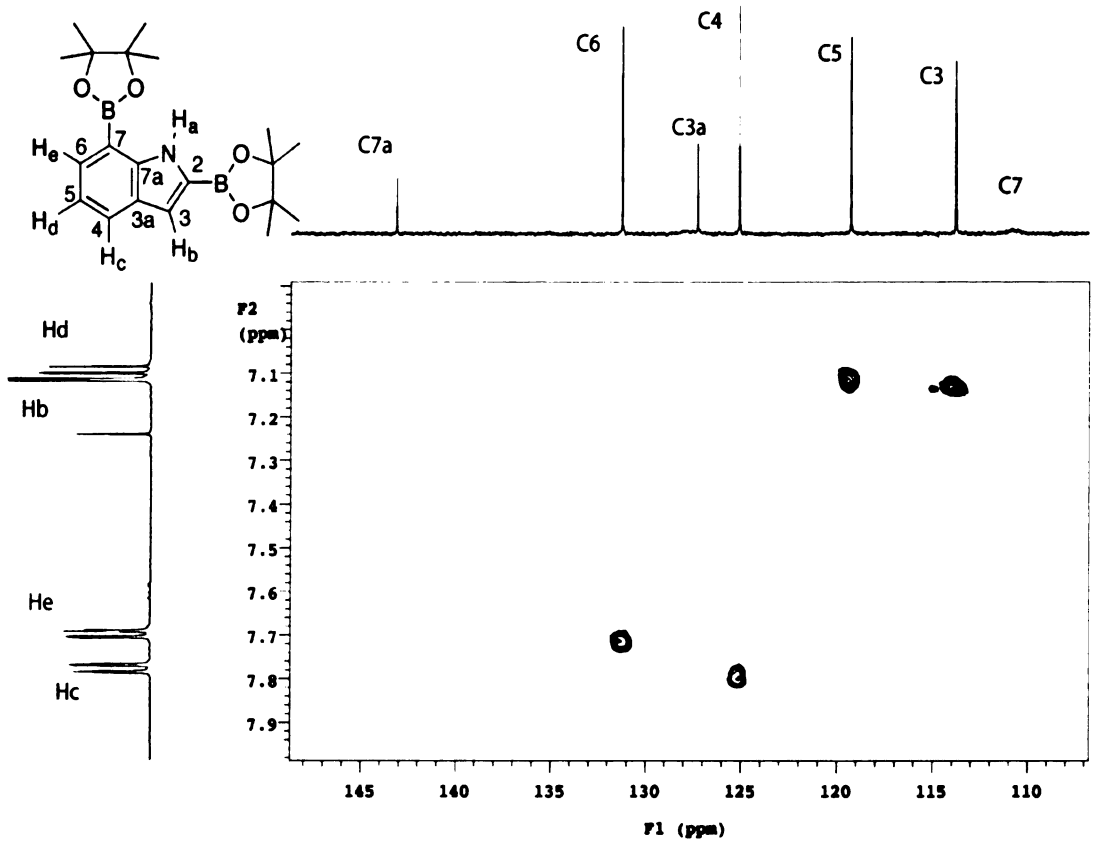


Figure 42: gHMQC spectrum of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

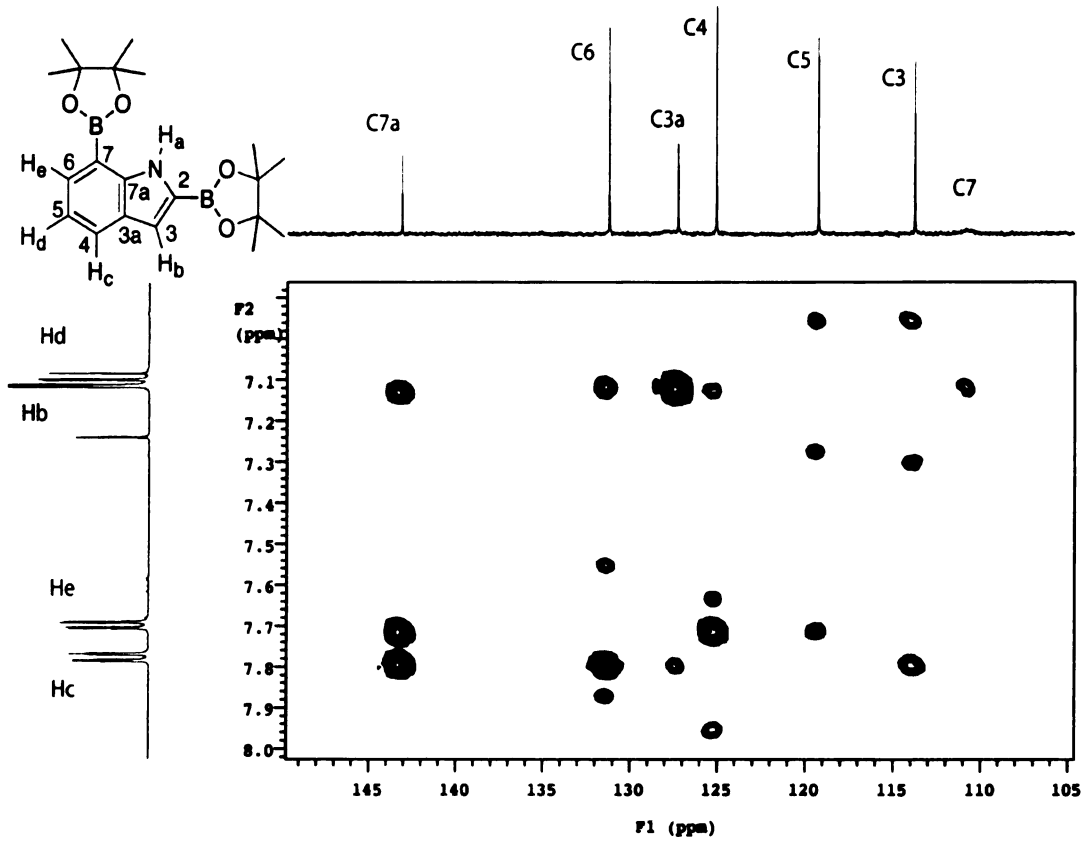


Figure 43: gHMBC spectrum of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

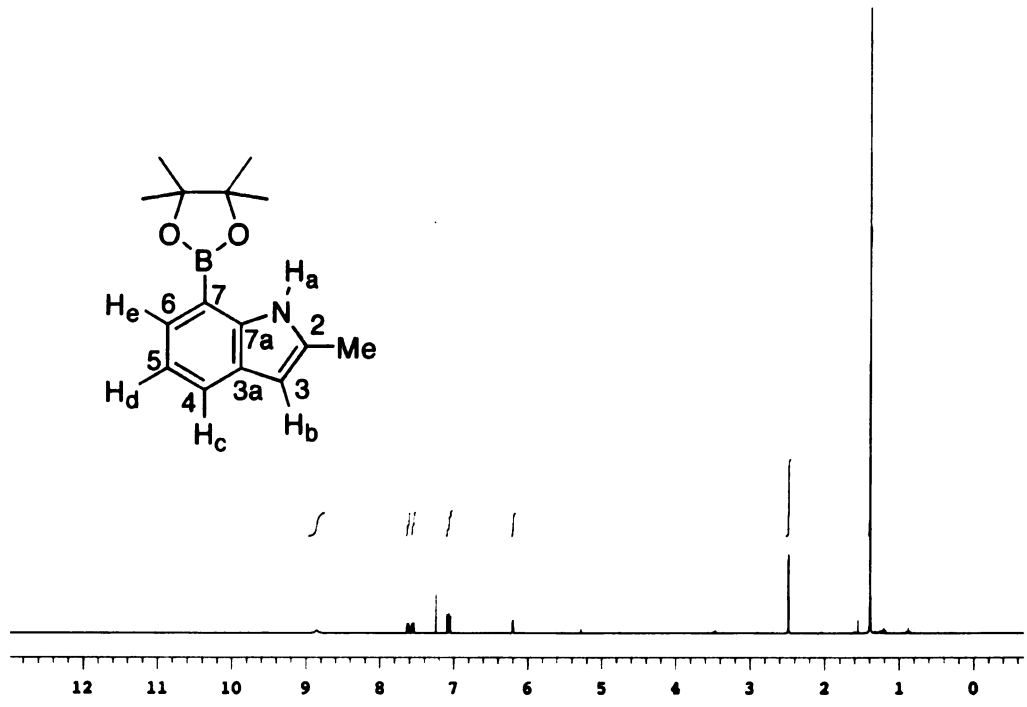


Figure 44: ^{1}H spectrum of 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

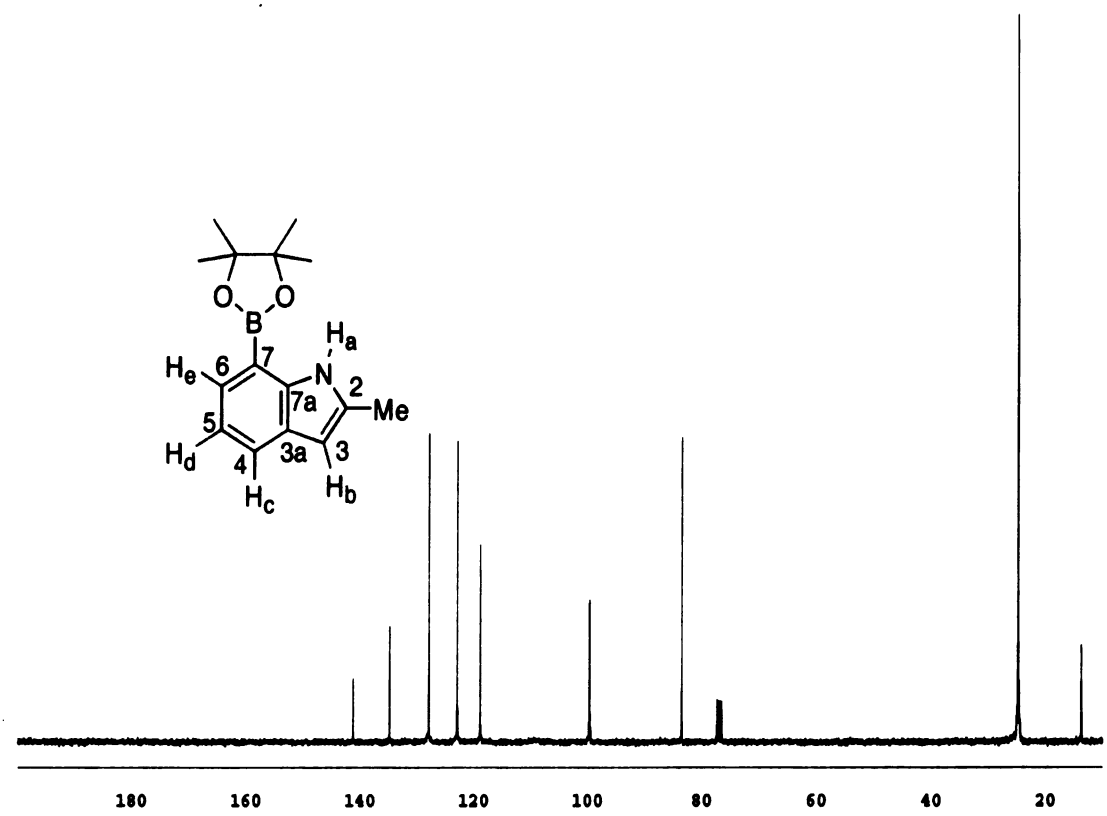


Figure 45: ^{13}C spectrum of 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

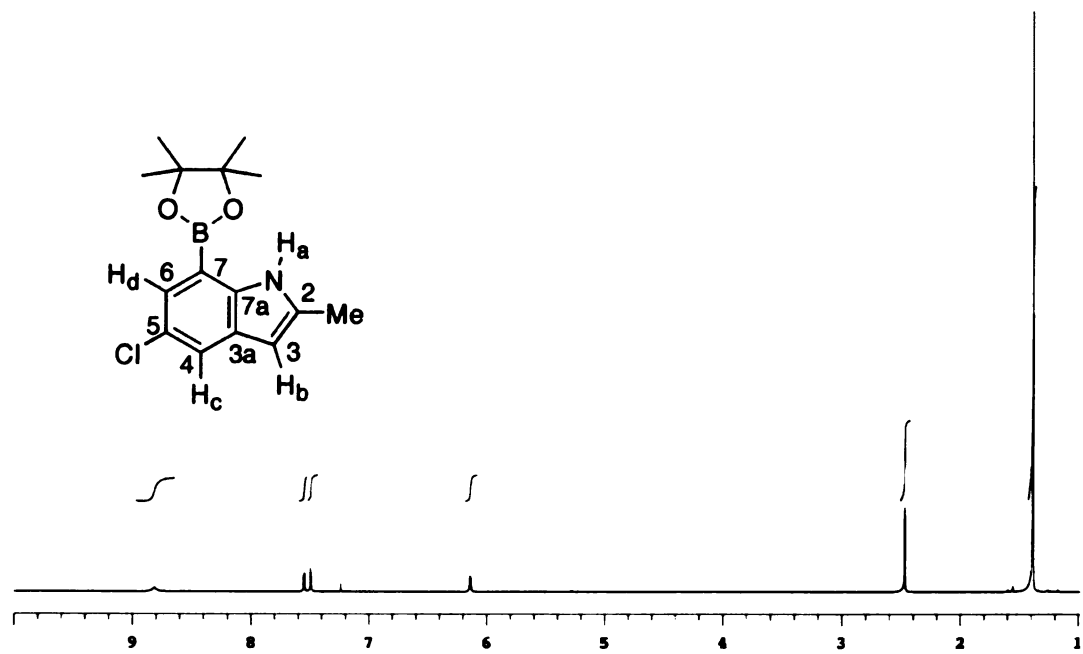


Figure 46: ^{1}H spectrum of 5-chloro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

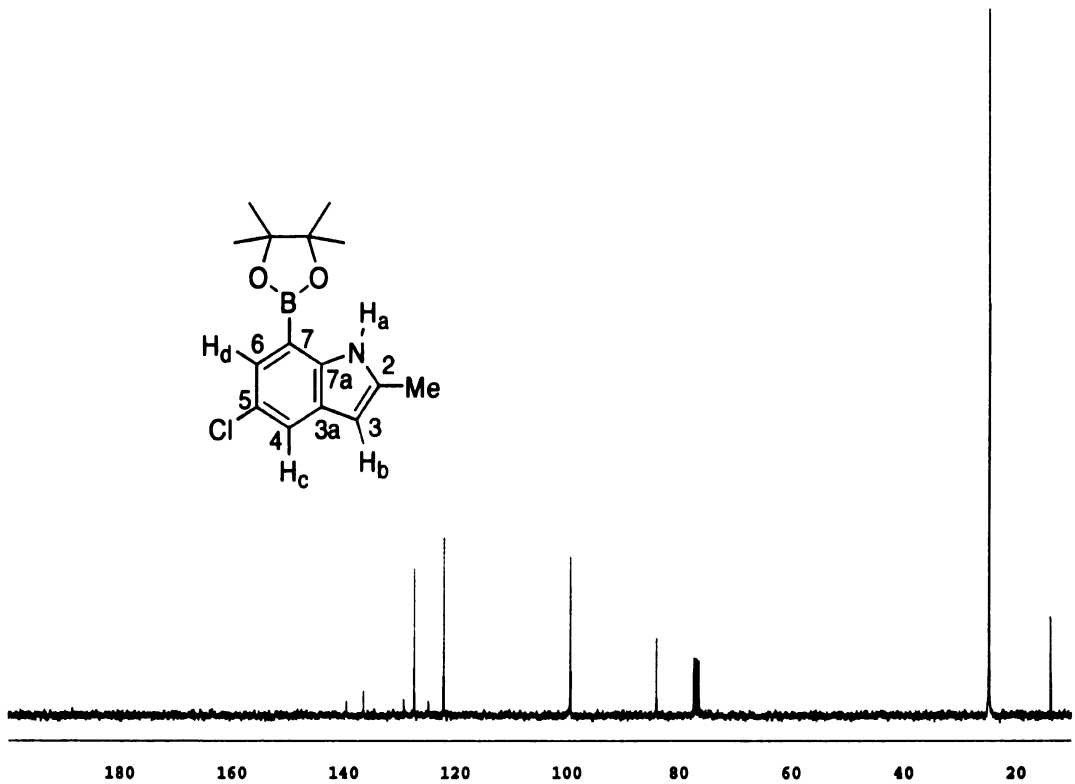


Figure 47: ^{13}C spectrum of 5-chloro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

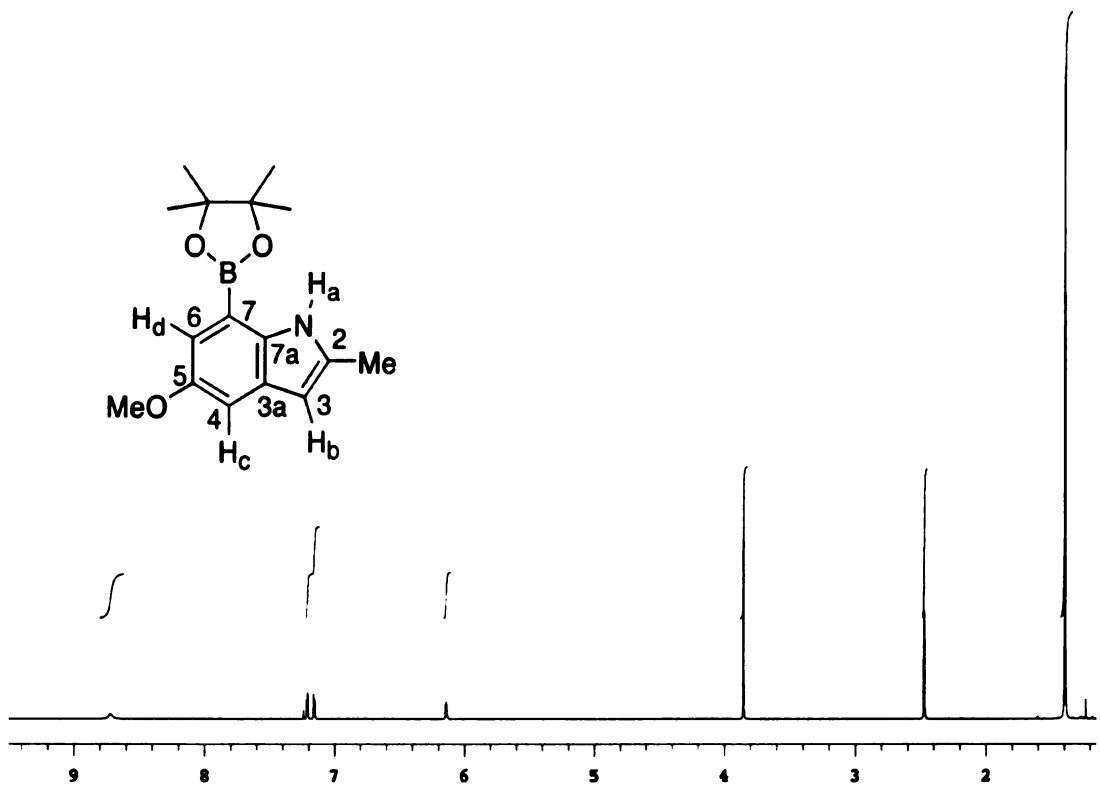


Figure 48: ^{1}H spectrum of 5-methoxy-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

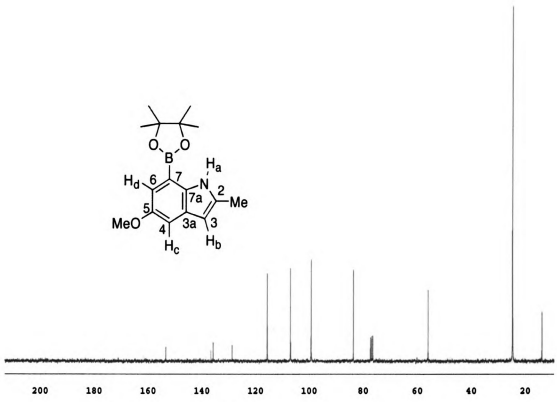


Figure 49: ^{13}C spectrum of 5-methoxy-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole.

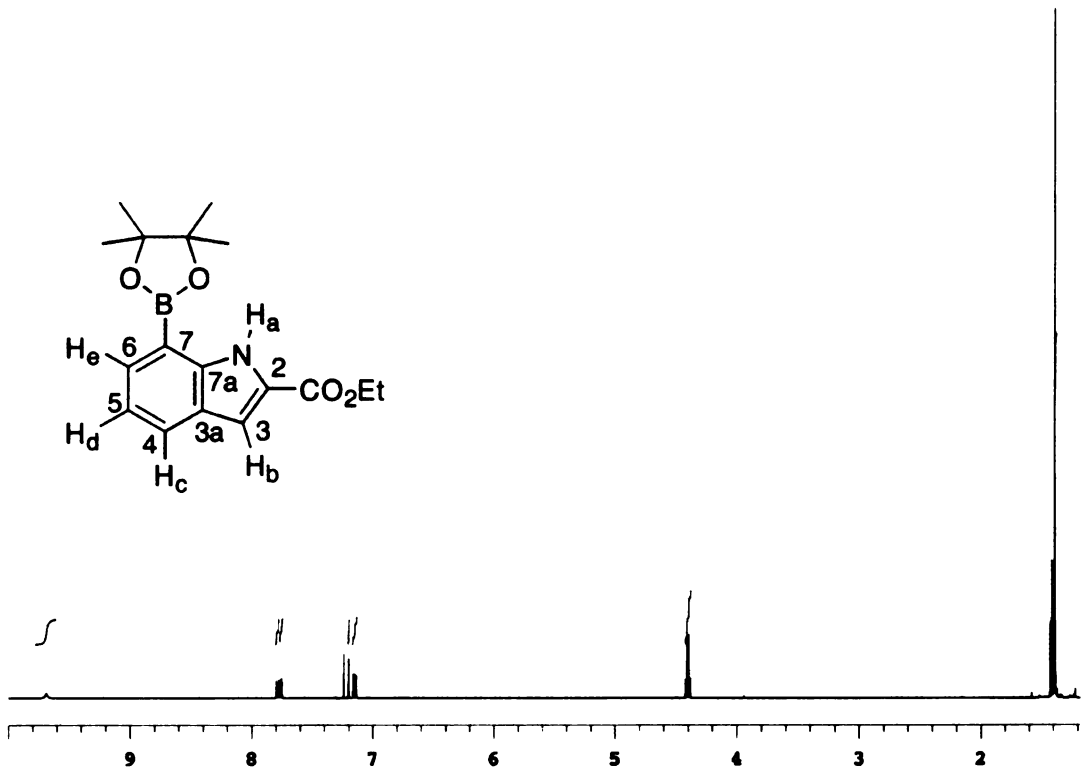


Figure 50: ^{1}H spectrum of ethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole-2-carboxylate.

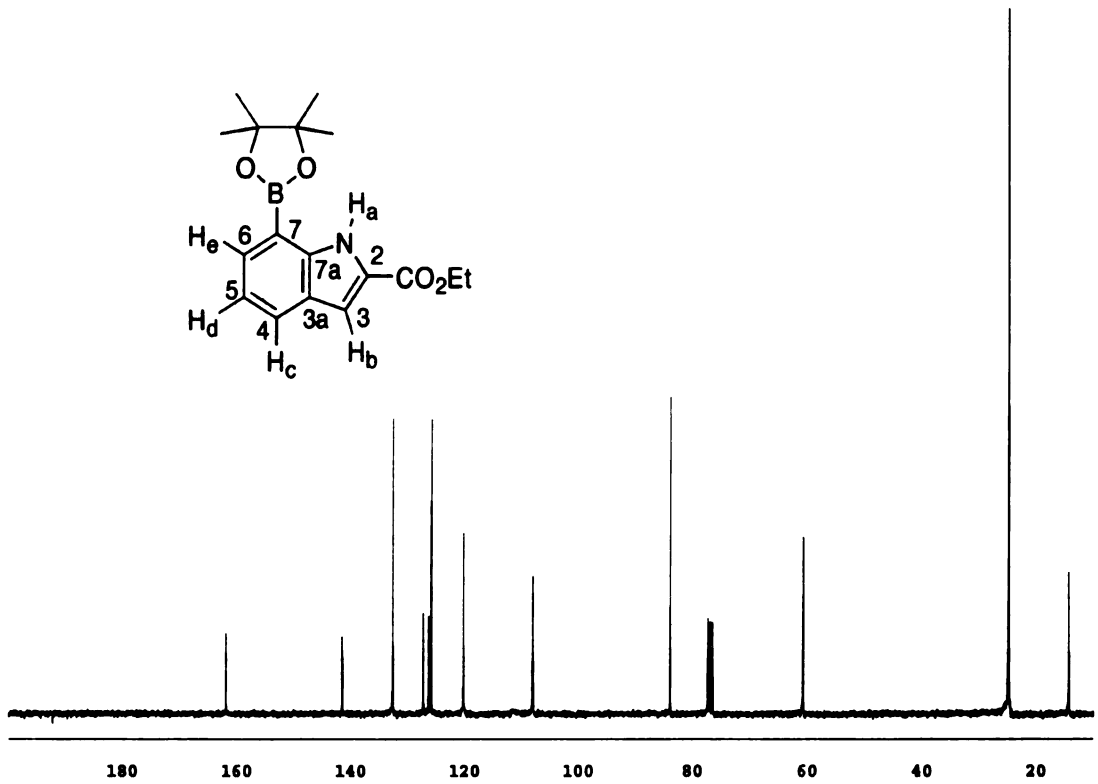


Figure 51: ^{13}C spectrum of ethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole-2-carboxylate.

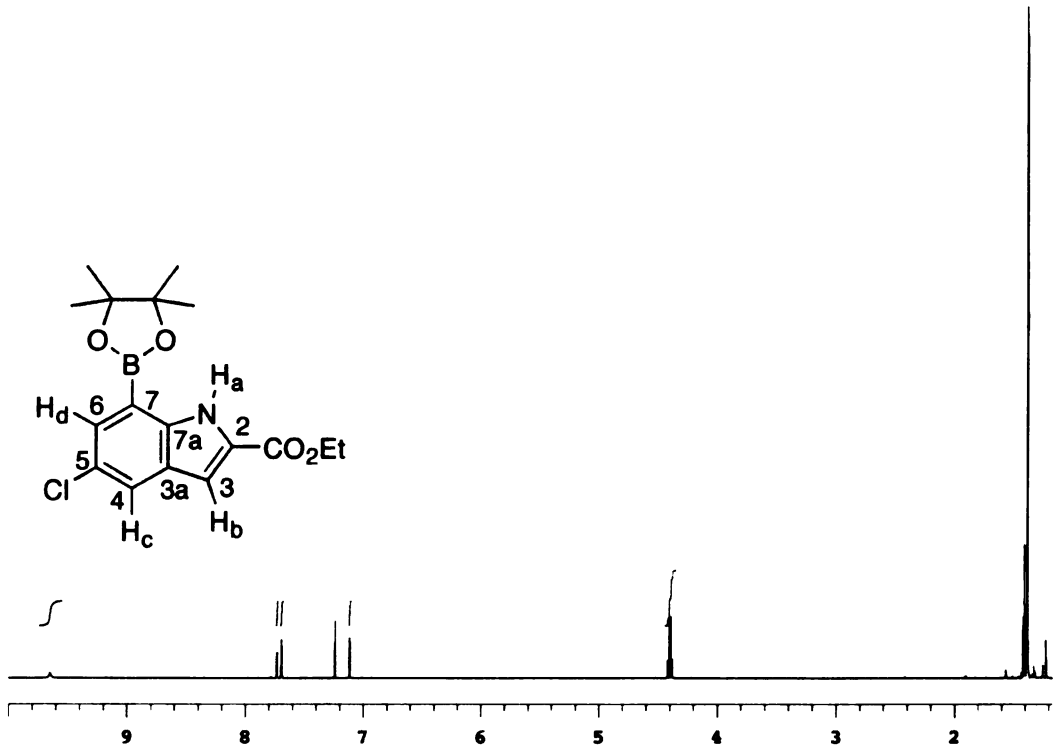


Figure 52: ^1H spectrum of ethyl 5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole-2-carboxylate.

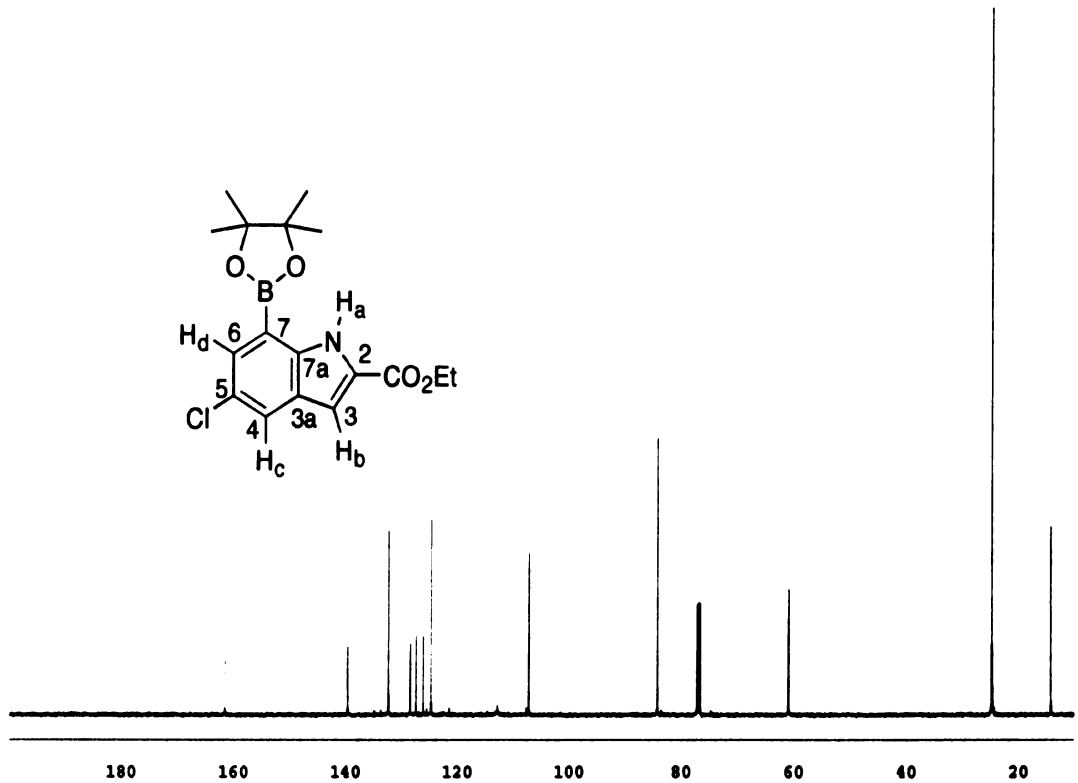


Figure 53: ^{13}C spectrum of ethyl 5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-indole-2-carboxylate.

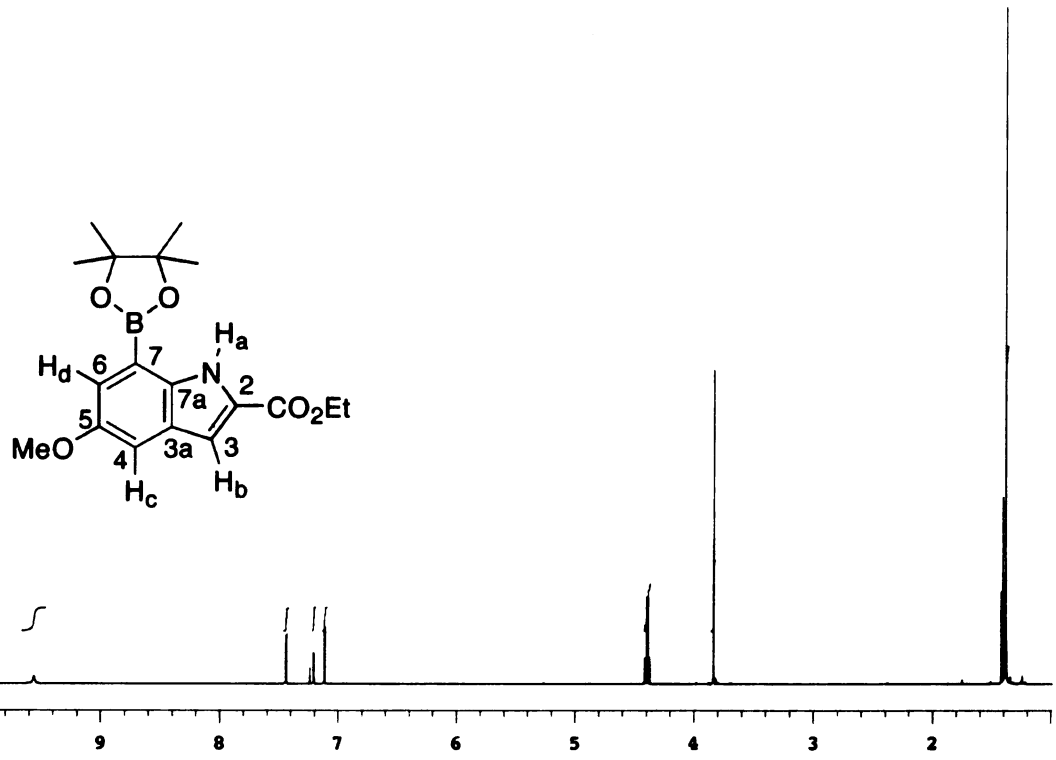


Figure 54: ^{1}H spectrum of ethyl 5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl) -indole-2-carboxylate.

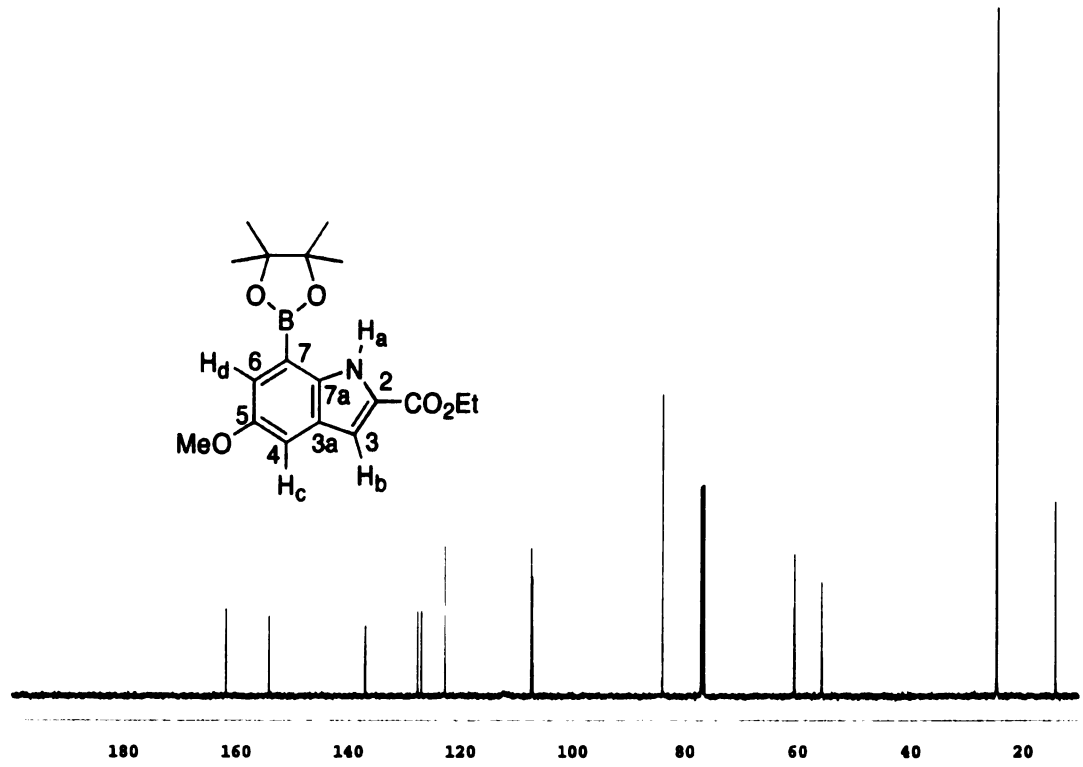


Figure 55: ^{13}C spectrum of ethyl 5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl) -indole-2-carboxylate.

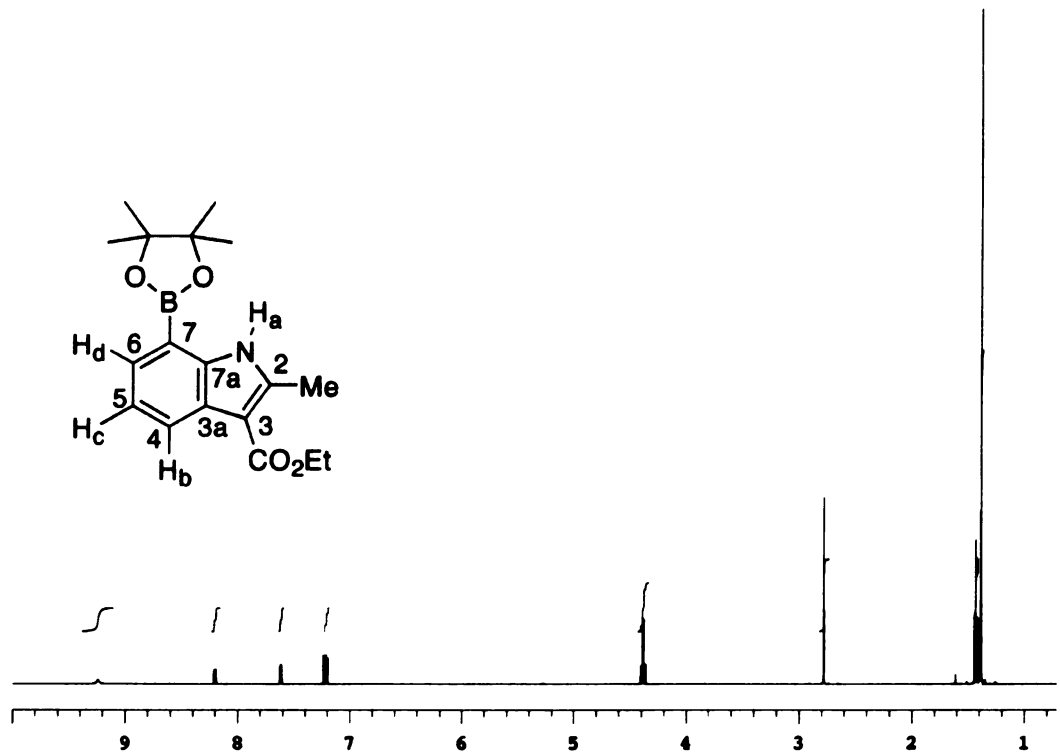


Figure 56: ^{1}H spectrum of ethyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl) -indole-3-carboxylate.

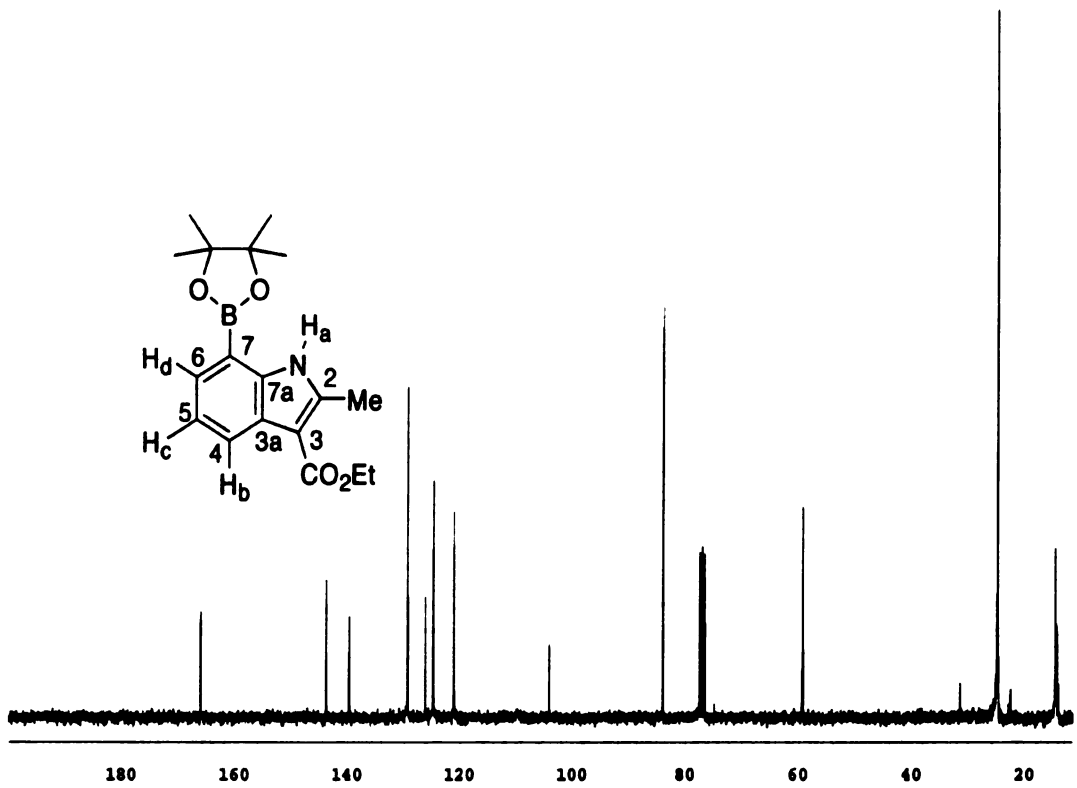


Figure 57: ^{13}C spectrum of ethyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl) -indole-3-carboxylate.

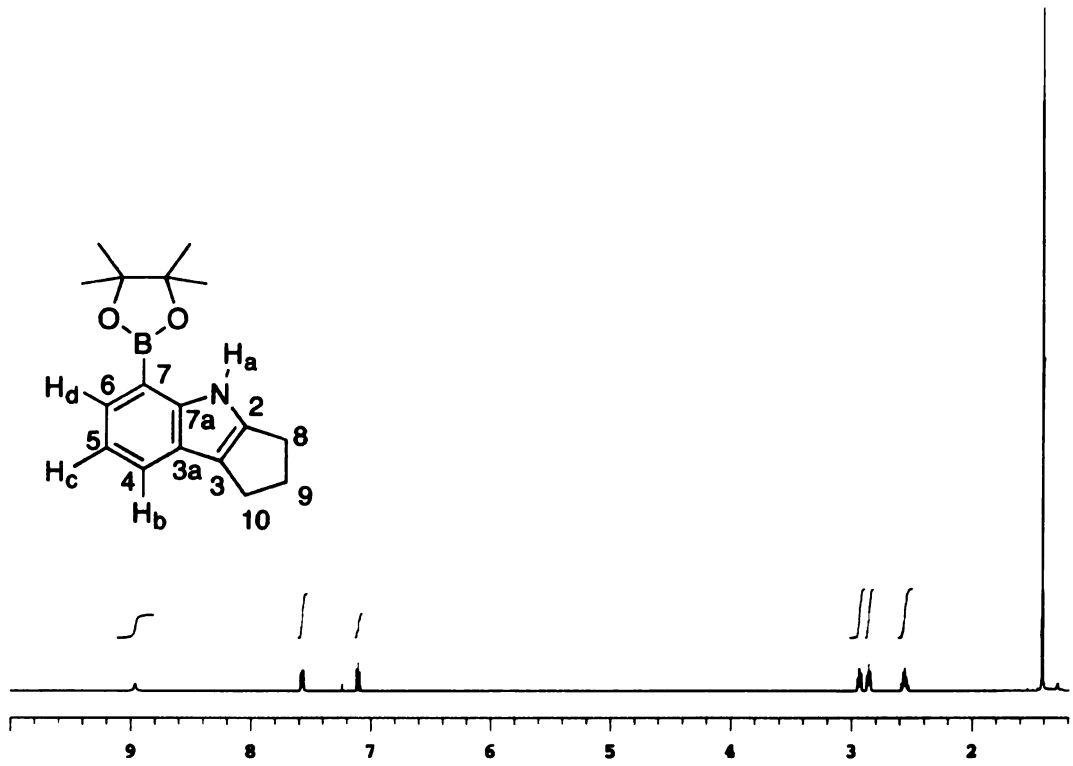


Figure 58: ^{1}H spectrum of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-1,2,3,4-tetrahydrocyclopent[*b*]indole.

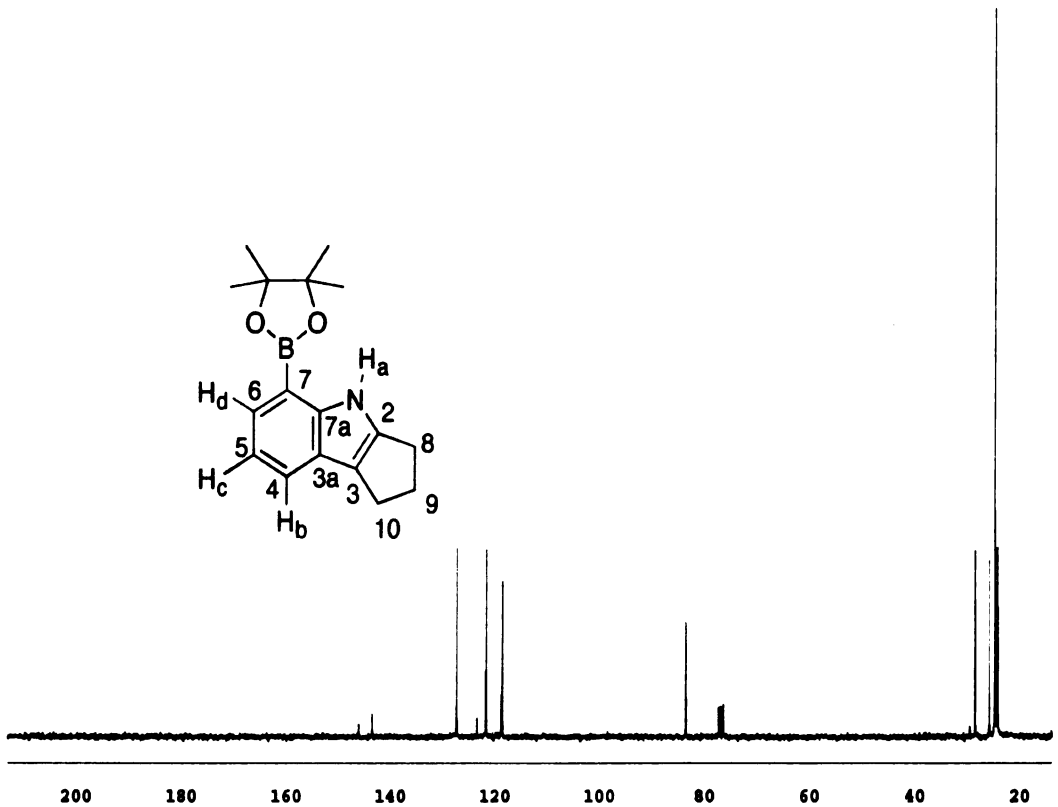


Figure 59: ^{13}C spectrum of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-1,2,3,4-tetrahydrocyclopent[*b*]indole.

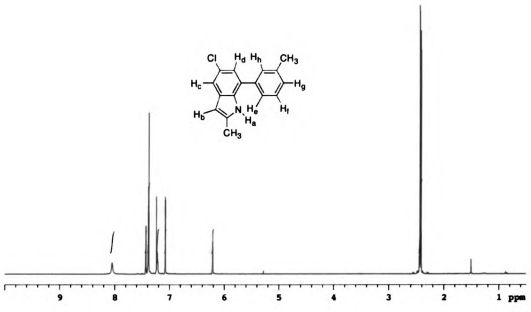


Figure 60: ^{1}H spectrum of Suzuki product of 5–chloro–2–methylindole.

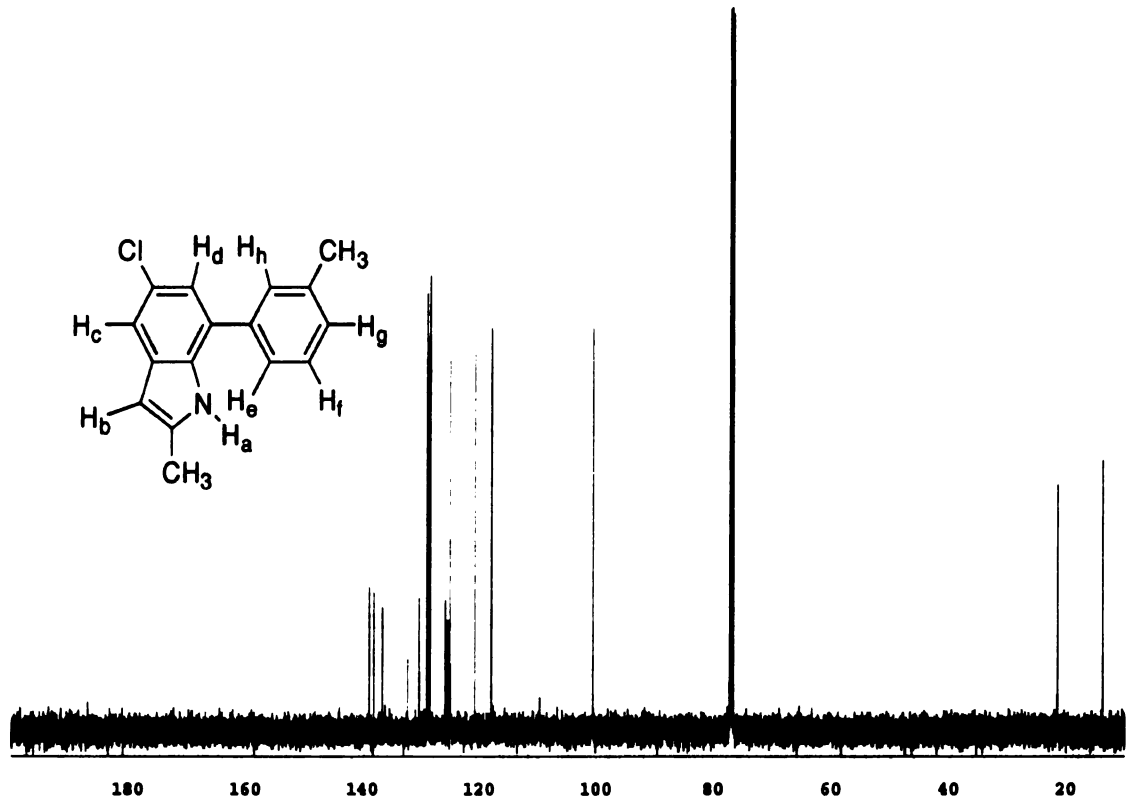


Figure 61: ^{13}C spectrum of Suzuki product of 5–chloro–2–methylindole.

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