A General Entry to C7-Borono Indole Derivatives

by

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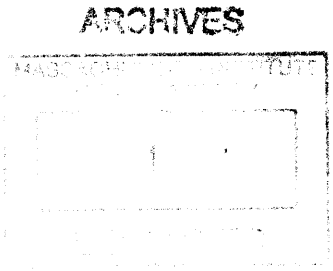

Submitted to the Department of Chemistry
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IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

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Signature of Author .....
Department of Chemistry
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Accepted by .....
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Chairman, Department of Committee on Graduate Students

To my family, Paul, Nona, P.J., and Stefanie Fenton

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ABSTRACT

The development of a methodology to access C7 pinacolatoboron substituted indole derivatives is described. It has been applied to indole, tryptophan, and tryptamine derivatives. Further functionalization to a C7 phenolic tryptamine derivative is also described.

Thesis Supervisor: Mohammad Movassaghi

Title: Associate Professor of Chemistry

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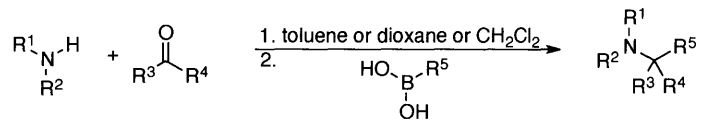
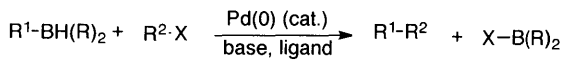
I: A General Entry to C7-Borono Indole Derivatives

Organoborons: Introduction and Uses

Organoborons, or organic molecules that contain carbon-boron bonds, have enjoyed a rich history in synthetic organic chemistry because of their utility in a number of important organic transformations. For example, their utility in the construction of carbon carbon bonds in such reactions as the Petasis Boronic Acid Mannich Reaction[1] and the Suzuki Cross Coupling[2] has proven incredibly valuable over the years. Boron containing proline derivatives have also been used in the asymmetric reduction of ketones in the Corey-Bakshi-Shibata Reduction,[3] and allylic borinic esters and trialkyl boranes have been utilized for the synthesis of optically active homoallylic alcohols in transformations such as the Roush Asymmetric Allylation.[4] General representations of the Petasis Reaction and Suzuki Cross Coupling can be found below in Scheme 1.



Petasis Boronic Acid-Mannich Reaction



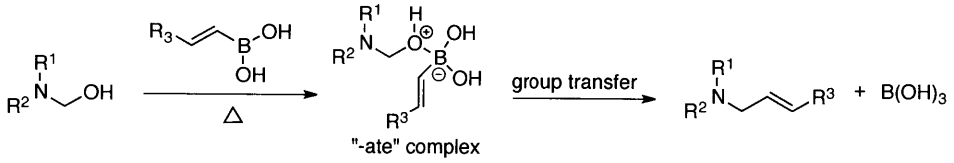
Suzuki-Cross Coupling Reaction

Scheme 1: Organoborons in synthetic transformations

While these four transformations all address different areas in synthetic organic chemistry, they are all mechanistically related through the intrinsic properties of boron as an atom. For example, boron is trivalent in its neutral state. As such, boron bears an empty p orbital in its neutral state that can readily behave as a Lewis acid to accept a lone pair of electrons. In fact, halogenated trivalent boron compounds including boron trifluoride and boron trichloride have been used extensively in organic synthesis as Lewis acids to promote the electrophilicity of certain reagents. Additionally, boron based Lewis acids have

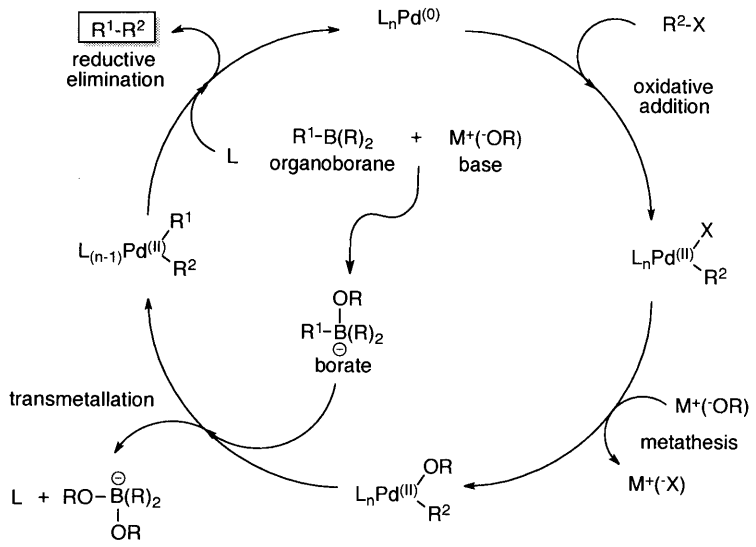
also been utilized to increase the acidity of certain protons, and as such, they have also been used in aldol chemistry. The high levels of diastereocontrol in said transformations has been attributed to the shortness of boron - oxygen bonds, a property of the system which increases the rigidity of the chair like transition state.

Interestingly, the formation of a fourth bond to boron induces a formal negative charge on said atom, and it is this property that accounts for many of the interesting mechanisms associated with organoboron compounds. This formally negatively charged boron compound is referred to as an "-ate" complex, and its negative character helps to enhance the nucleophilic character of groups that will readily migrate off of boron. For example, in the Petasis Reaction, the alkenyl, aryl, or heteroaryl group on the boronic acid or ester starting material will migrate to the hemiaminal carbon, ultimately displacing the hemiaminal oxygen and regenerating a neutral boron species (Scheme 2).



Scheme 2: "-Ate" complex formation in the petasis reaction

The formation of this "-ate" complex is also of vital importance to organometallic chemistry. For example, the addition of bases such as sodium carbonate or potassium phosphate promotes the formation of the "-ate" complex of the organoboron species in Suzuki cross couplings. The increased electron density at boron and the rehybridization of the atom from sp^2 to sp^3 increases the nucleophilicity of the alkyl/alkenyl/aryl group on boron, ultimately allowing for transmetallation to occur (Scheme 3). It is interesting to note that boronic acids by themselves will not transmetallate to palladium(II) species, further highlighting the importance of this "-ate" complex in synthetic transformations.

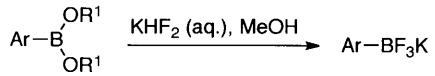


Scheme 3: "-Ate" complex transmetallation in Suzuki cross couplings

Even though the formation of these reactive "-ate" complexes accounts for much of the interesting *reactivity* of organoboron compounds, the formation of "-ate" complexes has also been used to impart *stability* to various organoboron species. As discussed, boron in its neutral state is sp^2 hybridized and bears a vacant p orbital. Therefore, a serious limitation of organoborons is that neutral boron functionalities are incompatible with many nucleophiles, bases, and oxidants (unless, of course, the desired reactivity is at the boron functionality). Although reordering the sequence of chemical reactions in a synthesis could circumvent this problem, it is sometimes impossible to change the order of events in a molecular synthesis. Additionally, this problem could detract from the efficiency and ease of the collective synthetic transformations.

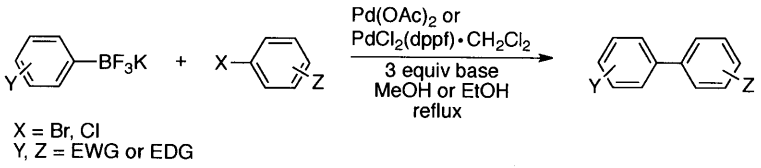
It is for this reason that Vedejs and Molander began to explore the utility of the potassium trifluoroborate salt.[5] Unlike trivalent boron complexes such as boronic acids and esters, potassium trifluoroborate salts are sp^3 hybridized and no longer bear the empty p orbital. Thus, potassium trifluoroborate salts are effectively protected synthetic analogues

of boronic acids and esters. These trifluoroborate salts are readily accessed through the reaction of boronic esters with potassium hydrogen difluoride in methanol to afford excellent yields of the desired products (Scheme 4).[5]



Scheme 4: Trifluoroborate salt synthesis

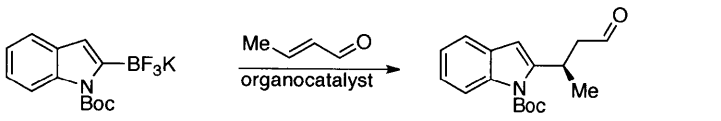
Interestingly, potassium trifluoroborate salts are bench stable to atmospheric oxygen and moisture. This implies that they can be prepared and stored in good scale without significant degradation. Excitingly, potassium trifluoroborate salts have also been shown to be viable partners in cross coupling chemistry despite their enhanced stability (Scheme 5).[6] While it is believed that these salts proceed through the same intermediate boronic acid as in a typical Suzuki cross coupling, the practicality of weighing out a crystalline solid that can readily be added to the reaction flask has greatly increased the versatility of the boronic acid/ester component in Suzuki cross couplings.



Scheme 5: Potassium trifluoroborates In Suzuki cross couplings

However, potassium trifluoroborate salts can be used as more than just protecting groups for trivalent organoboron species. For example, recent work from the MacMillan group has described the organocatalytic conjugate addition of vinyl and aryl trifluoroborate salts to enals (Scheme 6).[7] In their report, they rationalize that trifluoroborate salts increase the reaction scope with respect to the enal component because no exogenous base is necessary to form the "-ate" complex. Instead, the preformed

potassium trifluoroborate salt adds to the enal to form the desired carbon carbon bond linkage. Interestingly, the MacMillan group was able to override the innate C3 nucleophilicity of benzofuran and *N*-Boc protected indole using their methodology. As is well known, the most nucleophilic position on these substrates is their respective C3 carbon. Therefore, this finding is particularly exciting because it demonstrates that unnatural regioselection could be achieved on the furan or azole portion of these important heterocycles.

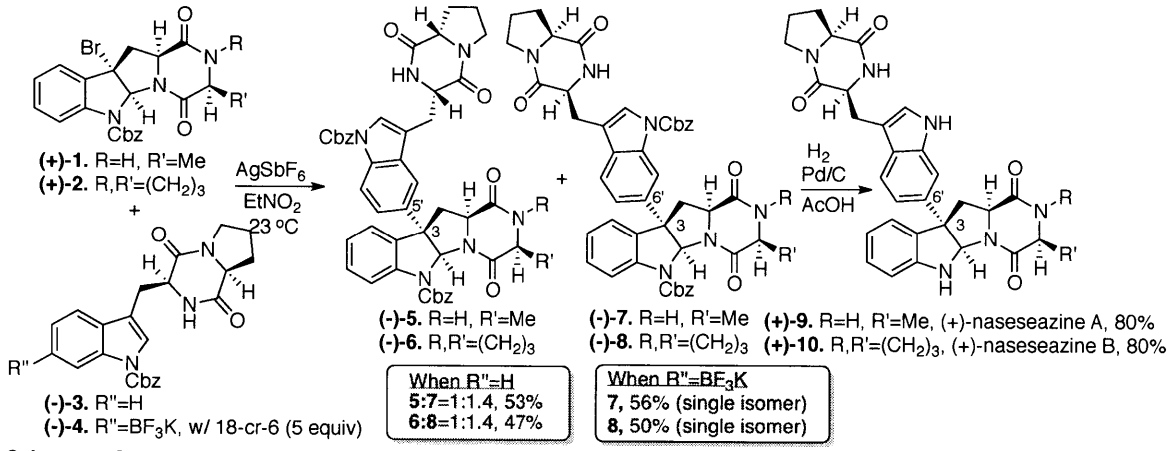


79% yield, >99:1 regiocontrol, 91% ee

Scheme 6: MacMillan's trifluoroborate couplings

In fact, potassium trifluoroborate salts were critical in our groups' recent synthesis of (+)-naseseazines A and B which utilizes a directed ipso attack methodology (Scheme 7).[8] In our study, the trifluoroborate salt was used as a means to attain complete regioselection in the late stage coupling of two highly elaborated molecular fragments. In this reaction, the preformed "-ate" complex both enhanced the nucleophilicity of the relevant components and helped stabilize the cationic character generated in the transition state of this Friedel-Crafts coupling. As illustrated in Scheme 7, treating a solution of *endo* tetracyclic bromide (+)-**1** and diketopiperazine (–)-**3** with $AgSbF_6$ in nitroethane at room temperature afforded a 1:1.4 mixture of C5' and C6' regioisomeric dimers (–)-**5** and (–)-**7** in 53% combined yield. Similarly, treatment of a solution of (+)-**2** and diketopiperazine (–)-**3** under identical reaction conditions provided a 1:1.4 mixture of C5' and C6' regioisomeric dimers (–)-**6** and (–)-**8** in 47% combined yield. However, treatment of tetracyclic bromide (+)-**1** with potassium trifluoroborate diketopiperazine (–)-**4** in the presence of 18-crown-6 and $AgSbF_6$ in a polar aprotic solvent at 23 °C afforded (–)-

7 in 56% yield as a single regioisomer. Under identical conditions, pentacyclic bromide (+)-**2** was treated with potassium trifluoroborate diketopiperazine (–)-**4** to afford (–)-**8** in 50% yield as a single regioisomer. Hydrogenolysis of the carboxybenzyl groups in compounds (–)-**7** and (–)-**8** proceeded in 80% yield in both cases to afford (+)-naseseazine A (+)-**9** and (+)-naseseazine B (+)-**10**, respectively.



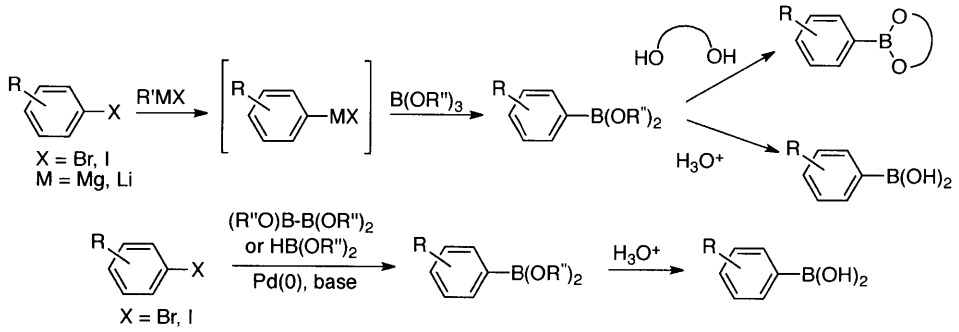
Scheme 7: Synthesis of (+)-naseseazines A and B *via* undirected and directed Friedel-Crafts chemistry

Thus, in accord with our group's recent completion of this synthesis, we are particularly invested in rapidly accessing borylated indole derivatives. By accessing these intermediates in a rapid and step economic manner, we will be able to apply our directed Friedel-Crafts methodology to the synthesis of other alkaloid natural products that bear this interesting Csp^2-Csp^3 structural motif. Regioselective borylation of the requisite indole derivatives would allow us one step access to the desired precursor of the trifluoroborate salt. This approach would be attractive because the synthesis of these types of structures typically requires an indole based synthesis followed by a Miyaura Borylation from a requisite halide. Therefore, the focus of this thesis will be on the incorporation of boron into indole derivatives. More specifically, due to our interest in a subclass of molecules with

C3sp^3-C7sp^2 bond connectivity, we sought a general method for accessing C7 borylated indole derivatives.

C-H Activation Strategies for the Synthesis of Arene-Organoboron Compounds

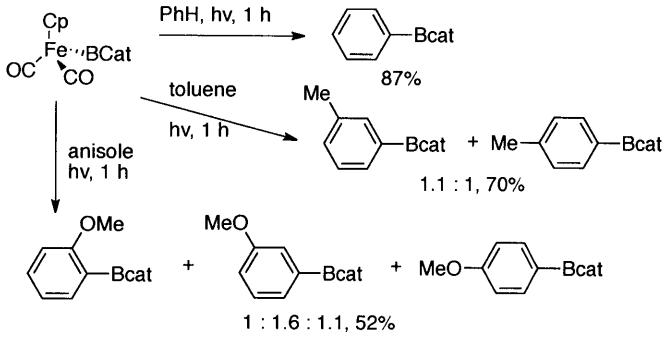
From a historical perspective, the formation of arene carbon-boron bonds has received a great amount of attention due to the vast utility of organoboron compounds. For example, powerful carbon-carbon bond forming reactions such as the Petasis reaction and the Suzuki cross coupling require an organoboron equivalent in the reaction. Two major strategies that were initially utilized for synthesizing arene carbon-boron bonds can be seen below in Scheme 8. The first of these methods relies on the conversion of an aryl halide to a Grignard or aryl lithium species followed by subsequent reaction with a trialkylboron compound. The second of these methods is the Miyaura-Borylation which utilizes palladium chemistry to couple a boron source with an aryl halide.[9] While both of these represent important means for constructing arene carbon-boron bonds, neither will be the focus of this dissertation.



Scheme 8: Historical access to aryl boron compounds

Although these two methods provide viable access to these versatile intermediates, aryl Grignard and aryl lithium formation is quite harsh. Additionally, the incorporation of halides into arenes and heteroarenes for Miyaura borylations can require excessive step count and other synthetic challenges. Due to these limitations, the field of arene C-H activation for the formation of carbon-boron bonds has received quite a bit of attention

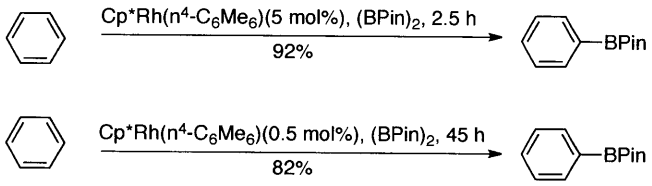
over the last two decades. In 1995, Hartwig and coworkers reported the first arene C-H activations using stoichiometric metal-boryl complexes.[10] Under photochemical conditions, manganese catecholboryl and rhenium catecholboryl complexes were found to afford monoborylated benzene in 45% and 50% yields respectively. Interestingly, the rhenium catecholboryl complex was also found to afford a 1.6:1 *meta*:*para* functionalized tolyl catecholboryl complex in a combined yield of 57%. Perhaps most interestingly, however, was the discovery that an iron catecholboryl complex afforded borylated benzene in 87% yield under photochemical irradiation (Scheme 9). This same complex also afforded borylated toluene derivatives in 70% combined yield in a 1.1:1 *meta*:*para* ratio under the same reaction conditions. While these findings required the use of stoichiometric metal-boryl complexes, it was the first example of metal mediated arene C-H activations to afford carbon-boron bonds.



Scheme 9: Stoichiometric metal-boryl arene borylations

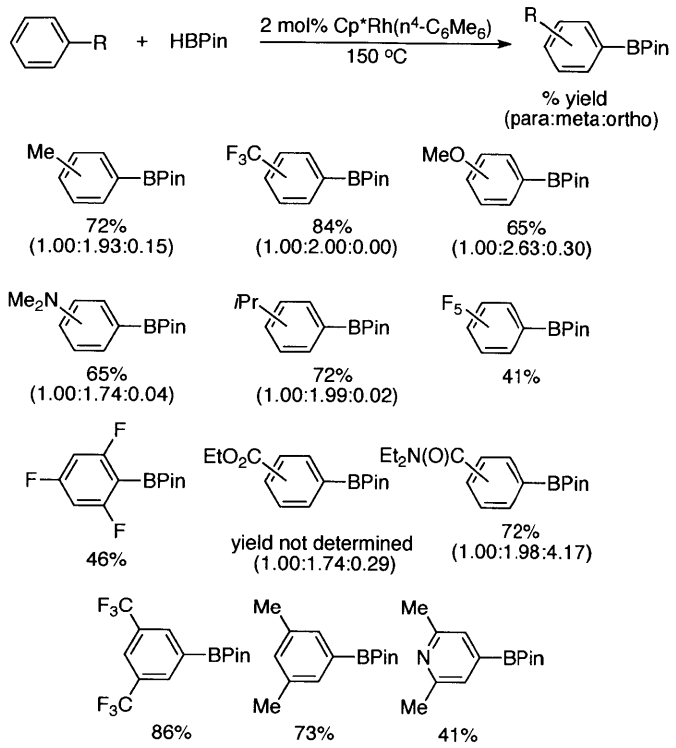
After this pioneering discovery in stoichiometric metal-boryl complex C-H activation, efforts were undertaken to develop catalytic metal-boryl systems that would effect C-H arene functionalizations. In addition to catalyzing the borylation of various alkane substrates, Hartwig and coworkers found that heating a solution of benzene to 150 °C in the presence of catalytic amounts of hexamethylbenzene pentamethylcyclopentadienyl rhodium with bis(pinacolato)diboron afforded between 82-

92% of the desired monoborylated benzene derivative (Scheme 10).[11] These transformations had an approximate catalyst turnover number of 328. While benzene was the only aryl substrate explored in this pioneering study, this result was the first example of a catalytic metal complex that could construct carbon-boron bonds *via* a C-H activation strategy.



Scheme 10: Pioneering catalytic metal arene borylations

Building on the work of Hartwig et. al., Smith and coworkers subsequently used Hartwig's catalyst system and pinacolborane to effect the catalytic borylation of various arenes (Scheme 11).[12,13] Interestingly, these results suggested that regioselectivity in arene borylations appeared to be governed predominately by steric rather than electronic properties; *meta* substitution patterns were the major products whether electron rich, electron poor, or electron neutral arenes were used as the substrate of interest. Interestingly, this same group also demonstrated that these same borylations could be conducted in inert solvents such as cyclohexane to generate similar yields and regiochemical distributions. This discovery was important because these borylations no longer needed to be performed neat with respect to the arene. While seemingly trivial at first glance, this result demonstrated that this methodology could potentially be used for the borylation of precious arene substrates in the future.

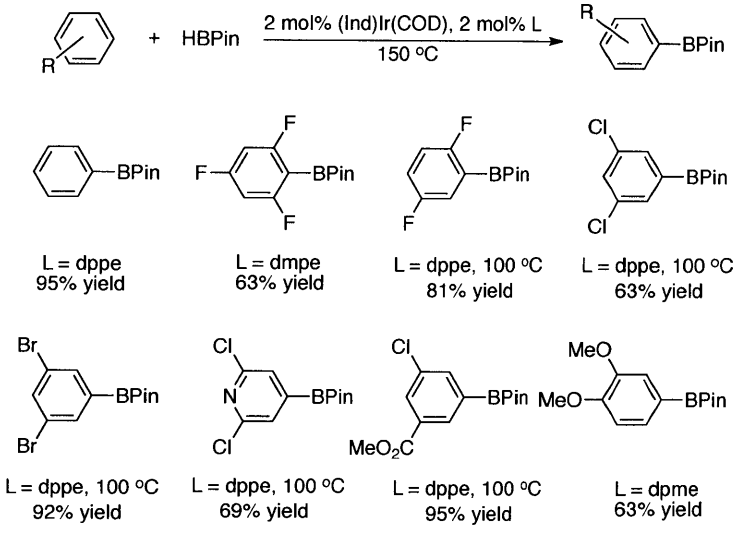


Scheme 11: Smith's rhodium complex borylations of arenes

At approximately the same time, Smith and coworkers also reported that Cp* iridium complexes could also catalyze the borylation of arenes.[14] However, unlike in the case of the Cp* rhodium complexes, these iridium systems suffered from low turnover numbers (approximately 3), resulting in the need for high catalyst loadings (17%). In their seminal study, perdeuterobenzene was reacted at 150 °C to afford the mono-boryl benzene derivative in 53% yield. The scope of this catalyst system with other arenes was later explored alongside their Cp* rhodium studies. While exploring electron rich, electron poor, and electron neutral arenes, they discovered that borylated arenes formed in 53-99% yield with a 20 mol% catalyst loading. It is important to note that the yields represent a combined mixture of regioisomers in the case of monosubstituted arene derivatives. In the case of monosubstituted arenes, the meta borylation was favored in all cases. In the case of 1,3 disubstituted arenes, 3,5-disubstituted arylboronate esters were isolated as the sole

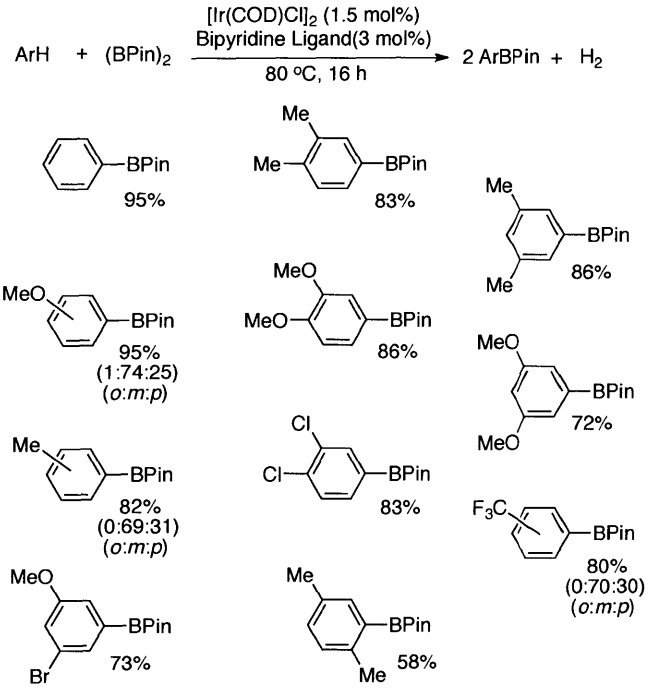
regioisomers, once again highlighting the importance of steric effects in these borylation reactions.

Shortly thereafter in 2002, Smith and coworkers further expanded the utility of this method by exploring iridium catalysts that contained phosphine ligands rather than Cp* ligands (Scheme 12).[15] Beginning from an indene iridium cyclooctadiene precursor, Smith and coworkers explored the effects of various phosphine ligands on the iridium catalyst. In the case of monodentate phosphine ligands such as trimethyl phosphine, they found a 2:1 ratio of ligand to catalyst resulted in the highest yields of arene borylation. With bidentate ligands such as dppe and dmpe, a 1:1 ligand:catalyst loading was found to be ideal. These new phosphine-ligated iridium complexes allowed for approximately a 10 fold drop in catalyst loading with respect to the Cp* iridium complexes from 20 to 2 mol%. A large substrate scope of arenes was also developed, representing compatibility of the catalyst system with aryl halides and aryl alkyl ethers. A pyridine derivative was also successfully borylated, and this was the first example of a heterocycle that was successfully employed in this borylation chemistry.



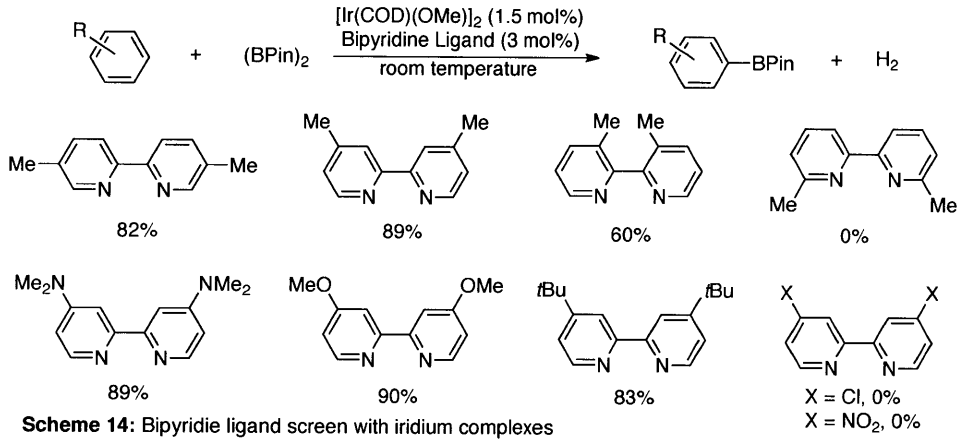
Scheme 12: Iridium phosphine catalyzed arene borylations

At the same time, Hartwig, Miyaura, and Ishiyama reported on the borylation of arenes using iridium complexes of bipyridine and di-*tert*-butyl-bipyridine derivatives (Scheme 13).[16] Interestingly, Hartwig and coworkers found that these catalyst systems were more active than their phosphine-ligated counterparts. In fact, while the work of Smith et. al. required temperatures between 100 to 150 °C depending on the electronic properties of the arene, Hartwig's report demonstrated that his bipyridine ligated complexes could catalyze the borylation of electron rich, electron neutral, and electron poor arenes in 16 h between room temperature and 80 °C. The catalyst loadings on these systems were also slightly better than in the case of Smith and coworkers - Hartwig et. al's systems required only 1.5 mol% of the $[Ir(COD)Cl]_2$ catalyst precursor as opposed to the 2 mol% for Smith's catalysts. Catalyst turnovers for these systems were impressive in the range of 500-1000.



Scheme 13: Hartwig's arene borylations with bipyridine ligands

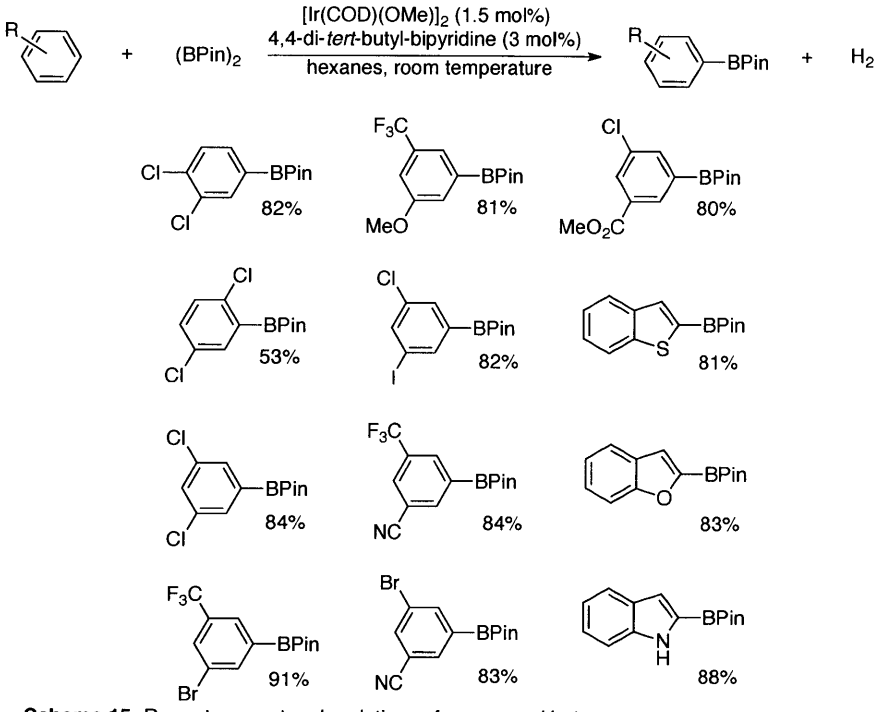
Upon discovering this result, Hartwig, Ishiyama and Miyaura and coworkers explored the effects of substitution patterns on the bipyridine ligands (Scheme 14).[17] In their work, Hartwig and coworkers explored various electron rich, electron poor, and sterically-unique ligands, ultimately finding their iridium cyclooctadiene methoxy dimer precatalyst with di-*tert*-butyl bipyridyl ligand to be ideal. Electron poor ligands did not result in the formation of the desired products, likely due to a lack of coordination to the iridium catalyst. Similarly, *ortho ortho* disubstituted methyl bipyridine could not successfully ligate the metal, ultimately preventing the formation of an activate catalyst. Hartwig and coworkers ultimately settled upon the di-*tert*-butyl ligand because it helped impart greater solubility of the catalyst in organic solvents and also because it would prevent undesired borylation of the ligand.



Scheme 14: Bipyridie ligand screen with iridium complexes

Upon discovering these bipyridine ligands, the borylation of various arene and heteroarene substrates was explored including benzofuran and indole. Perhaps the most important discovery in this report was that all of these borylations could be performed at room temperature (Scheme 15).[18] This was a drastic difference because all previous borylations had required heating of the system. However, it was noted that there were still issues with controlling the regioselectivity in these transformations. Perhaps more

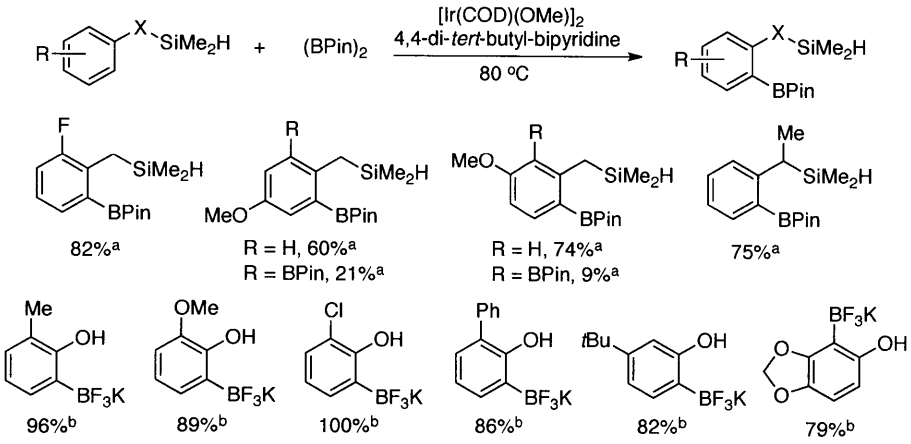
importantly, however, was the realization that it was seemingly going to be impossible to access selective *ortho* borylations on monosubstituted arenes using these standard arene substrate classes.



Scheme 15: Room temperature borylations of arenes and heteroarenes

In order to address the regiochemical issues with arene borylations, Hartwig and coworkers hypothesized that the presence of a dialkyl hydrosilyl group could afford *ortho* borylated arene derivatives. Benyzlic hydrosilanes and silylated phenols were used in this methodology, and Hartwig and coworkers hypothesized that the iridium catalyst would be able to add in to the silicon hydrogen bond. Thus, the system would be poised to perform an *ortho* C-H bond activation due to the fact that the *ortho* position would require the smallest ring size in the transition state. In fact, it would seemingly be the only geometrically feasible position for activation assuming that Si-H bond addition with the iridium complex would outcompete any intermolecular borylation pathways. Although commentary on complete mass balance in each of these reactions is not provided, their

high yields of isolated products suggests that the intramolecular borylation provides very ready access to this class of arene substrates (Scheme 16).[18] This study was the first example of *ortho* directed borylation, a feat which had thus far proven nearly impossible to achieve with standard C-H activation borylation conditions. It is also important to note that in certain cases the trifluoroborate salts were isolated to enhance the stability of the products.

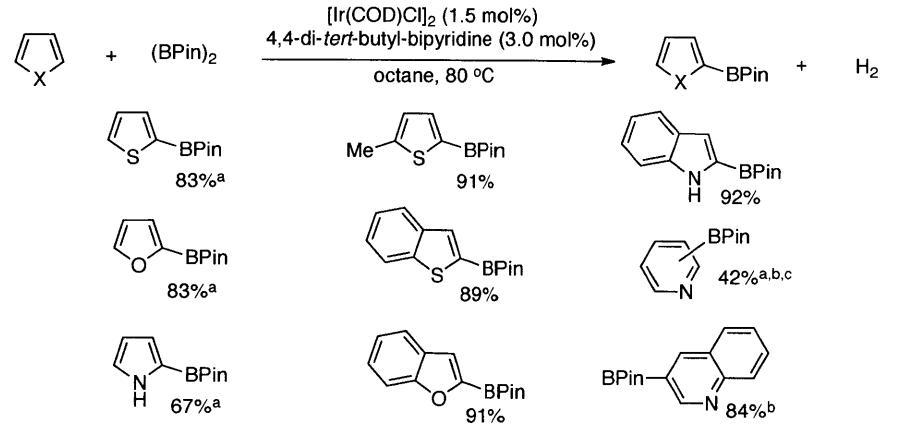


[a]Conditions: 0.25 mol% $[Ir(COD)Cl]_2$, 0.5 mol% dtbpy, 5 mol% HBPin, 1 equiv of $(BPin)_2$, THF. [b]Conditions: (1) 0.5 mol% $[Ir(COD)Cl]_2$, Et_2SiH in PhH. (2) 1.0 mol% $[Ir(COD)Cl]_2$, 2.0 mol% dtbpy, 1 equiv of $(BPin)_2$, THF. (3) 4 M KHF_2 (aq.) in THF

Scheme 16: *Ortho* borylations using dialkyl silane directing groups

Although previous studies had touched on the borylation of heteroarenes, the first studies that primarily focused on the borylation of these important substrates began around 2002 by Hartwig, Ishiyama, and Miyaura. In their pioneering work, they found that pyrrole, furan, and thiophene could be borylated using their iridium cyclooctadiene chloride dimer precatalyst with di-*tert*-butyl-bipyridine in octane at 80 °C to 100 °C (Scheme 17).[19] The yields on these substrates were good to excellent, ranging from 42% on pyridine (with low levels of regiocontrol) to excellent yields of 91% on 2-substituted thiophenes as well as benzofuran and indole. The discovery that iridium complexes

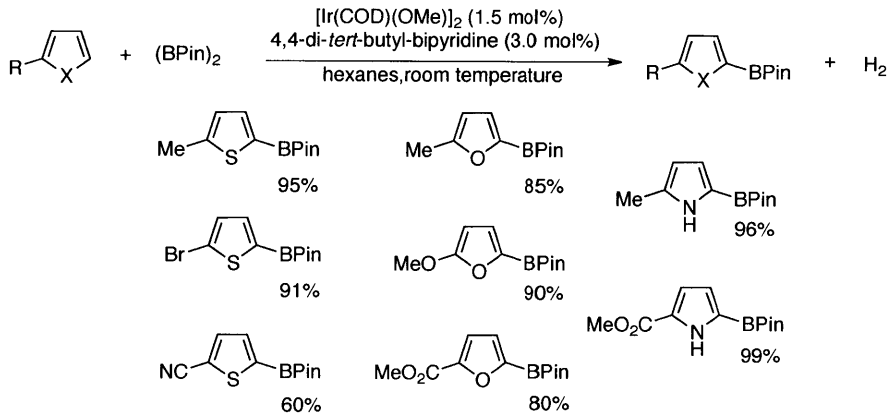
borylate indole at the C2 position was an important piece of data that allowed us to develop the reaction described herein.



[a]Diborylated products were produced in 12-17% yield. [b]Reaction conducted at 100 °C. [c]Ratio of 3- and 4-boryl pyridine was 67:33

Scheme 17: Heteroarene borylations with iridium complexes

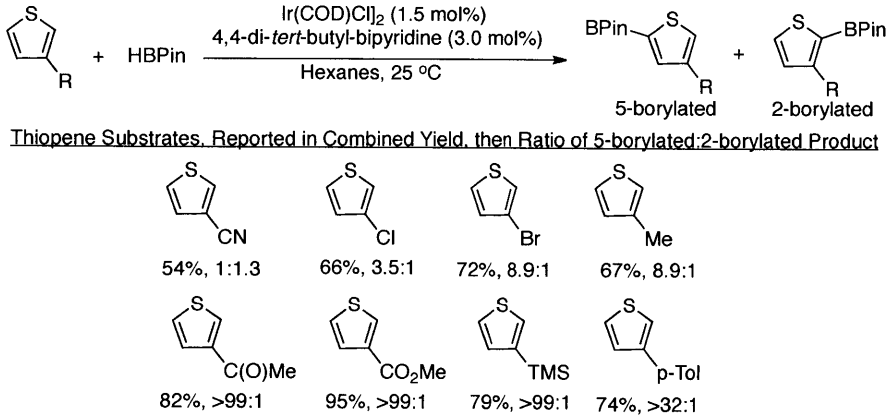
Hartwig and coworkers also demonstrated that the borylation on various 2-substituted heteroarenes would occur exclusively at the C2' position (Scheme 18).[20] These studies further expanded the scope of their heteroarene substitution work and demonstrated that their borylation conditions were compatible with alkyl groups, alkoxides, nitriles, and esters.



Scheme 18: Iridium catalyzed borylations on 2-substituted heteroarenes

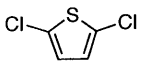
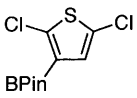
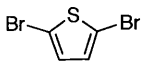
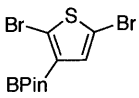
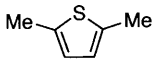
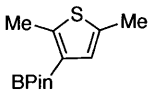
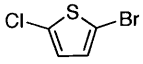
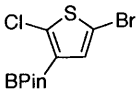
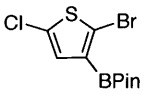
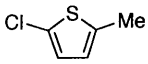
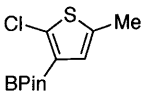
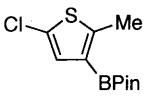
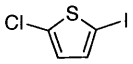
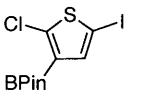
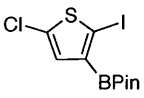
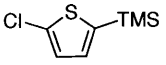
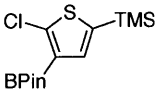
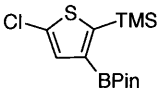
As a further study on the regioselectivity of heteroarene borylation, Smith and coworkers explored the iridium catalyzed borylations of 3-substituted thiophenes (Scheme 19).[21] Interestingly, it was found that the major products were the 3,5-disubstituted

thiophenes in all cases except for 3-cyanothiophene. From their data, it is apparent that the larger the size of the 3-substituent, the greater formation of the 3,5-disbustituted product rather than the 2,3-disubstituted product. This finding once again highlights the importance of steric factors in predicting the regiochemical outcome for these borylations.



Scheme 19: Iridium catalyzed borylations on 3-substituted thiophenes

Smith and coworkers also explored the borylations on 2,5-disubstituted thiophenes (Scheme 20).[21] While studying these substrates, regioisomeric mixtures of borylated heteroarylboronate esters were formed in high yields as combined mixtures. Once again, the ratio of these products favored substitution patterns adjacent to the smaller of the two thiophene substituents, suggesting once again that steric repulsion is perhaps the most significant factor in terms of predicting regioselection on heteroarene subunits.

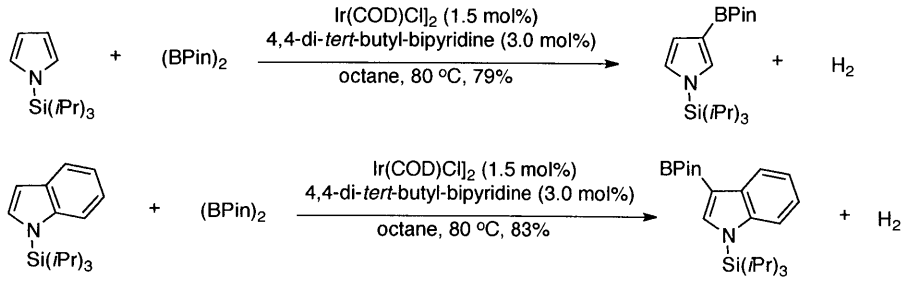
thiophene	conditions	3-borylated product	4-borylated product	ratio of 3-:4-borylated products[c]	% yield (combined)
	a		-----	n/a	86%
	a		-----	n/a	56%
	b		-----	n/a	97%
	a			2.0:1	87%
	a			2.3:1	86%
	a			5.7:1	89%
	a			>99:1	93%

[a]Reaction Conditions: 3-9 mol% [Ir]/dtbpy ([Ir] = [Ir(COD)(OMe)$_2$), 1.5-2.5 equiv HBPin, rt, 6-48 h. [b]Reaction Conditions: 2 mol% (Ind)Ir(COD), 2 mol% dmpe, 1.5 equiv HBPin, 150 °C, 16 h. [c]Isomer ratios determined by GC analysis and isomer identification based on NMR spectral data.

Scheme 20: Iridium catalyzed borylations on 2,5-disubstituted thiophenes

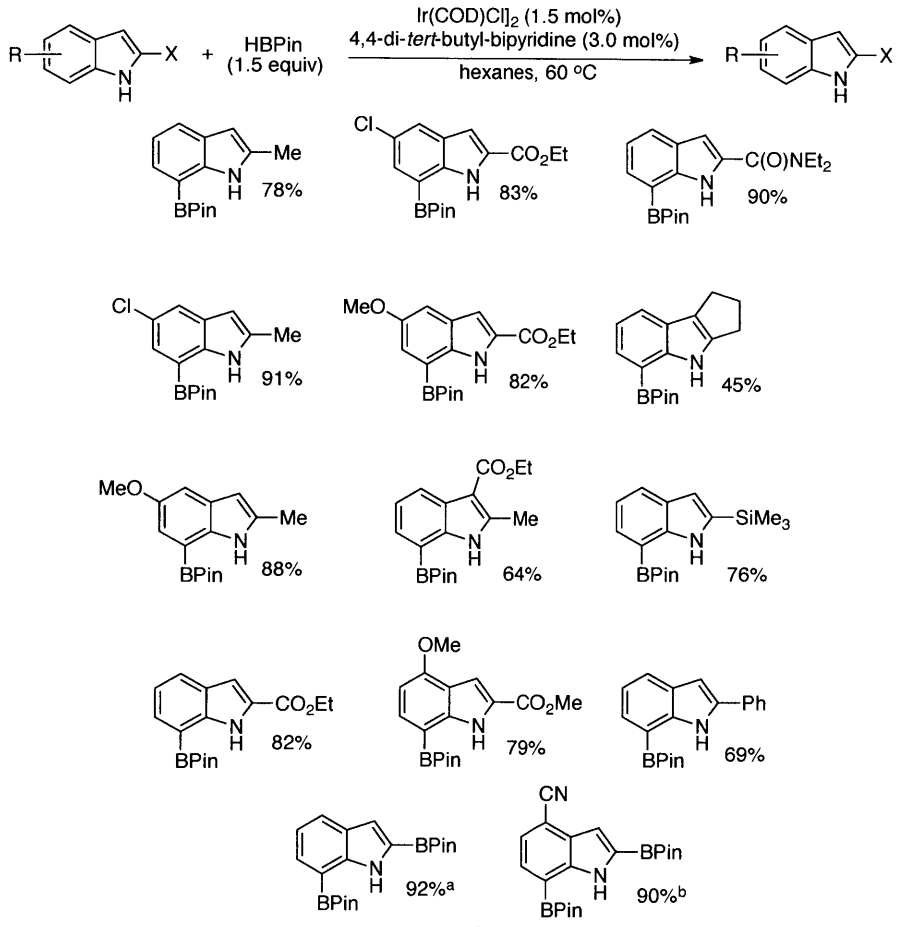
Interestingly, each heterocycle in Smith's work was borylated at the C2 position if it was unsubstituted with the only exception being pyridine which suffered from regiochemical issues. However, with the observation that *ortho* borylations are generally slow with respect to *meta* and *para* borylations on heteroarenes, Hartwig and coworkers demonstrated that N-*TIPS* pyrrole and N-*TIPS* indole are borylated selectively at the C3 position in 79% and 83% yields respectively (Scheme 21).[19] This finding demonstrated that the regiochemical outcome of heteroarene borylation could be altered - while the C2

position would normally be favored on both of these heteroarene substrates, increasing the steric bulk around the C2 position promotes C3 borylation.



Scheme 21: Regioselective C3 borylation on *N*-TIPS pyrrole and indole

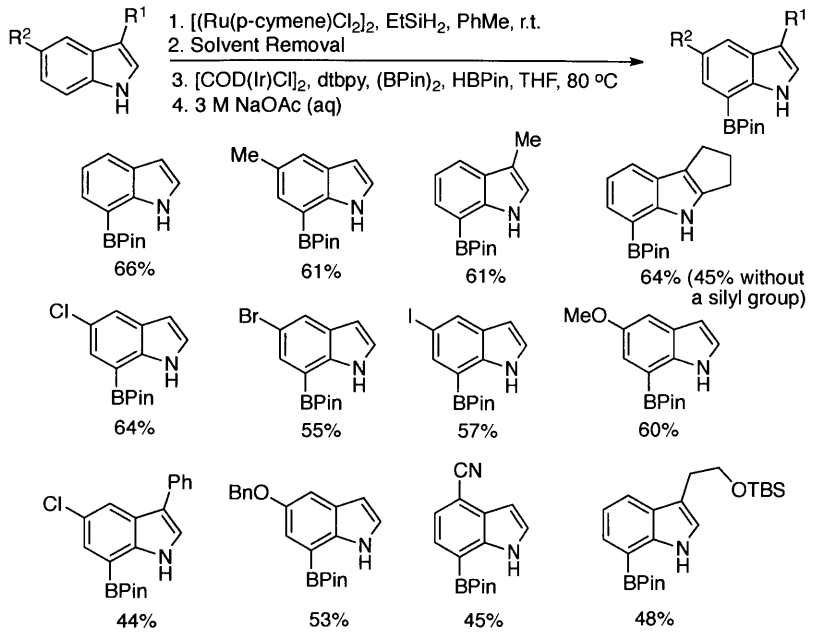
Interestingly, in 2006, Smith and coworkers further explored the iridium catalyzed borylation on indole derivatives. As previous work had already demonstrated that indole will react first at the C2 position under typical borylation conditions, Smith and coworkers wondered where C2-substituted indole derivatives would react with the iridium catalysts. While screening a wide-range of C2-substituted indole derivatives, Smith found that borylation occurred at the C7 position in good to excellent yields (Scheme 22).[22] Smith and coworkers proposed that this selectivity could be due to 1. indole ligation to the iridium center, 2. hydrogen bonding between a pinacolboron ligand on the iridium and the indole NH, or 3. indole NH activation by the iridium complex. Perhaps the most interesting substrate in their study was 2-trimethylsilyl indole. This substrate was borylated in 76% yield under these reaction conditions, and this product could subsequently be desilylated to afford 7-BPin indole in 88% yield. While this method is interesting, it requires the blocking of the C2 substituent with silicon for later removal.



Scheme 22: Iridium catalyzed borylations on 2-substituted indole derivatives

Finally, Hartwig and co-workers rationalized that it would perhaps be possible to use their dialkyl silane directed *ortho* borylation chemistry to directly access C7 borylated indole derivatives. This methodology would rely on the silylation of the indole nitrogen. This chemistry once again hinged upon the hypothesis that converting the borylation to an intramolecular process would promote the borylation of *ortho* positions due to a smaller sized ring in the transition state. Utilizing their dialkyl silane approach, Hartwig et. al. managed to access C7 borylated indole derivatives with excellent yields in a 3 step, 1 pot transformation. However, one limitation with their method is that they only explored indole derivatives; tryptophan and tryptamine substrates were not explored. Nevertheless,

their chemistry provides good yields and selective access to some C7 borylated indole derivatives. (Scheme 23)[23].



Scheme 23: Silyl directed C7 borylations on indole derivatves

With all of this beautiful work established, we wondered if we could utilize arene C-H activation to explore a new type of methodology to access C7 borylated indole derivatives. As has been shown in certain cross couplings, proteodeborylation (the exchange of a boron functionality for a proton) can occur under certain sets of reaction conditions. This transformation is usually regarded as a negative because it prevents subsequent cross coupling reactivity of the substrate. It is also problematic because it can require many steps to incorporate boron functionalities into molecules.

However, we wondered if we could use proteodeborylation to our advantage rather than to our detriment. To do this, we compiled 2 main observations from the literature. First, we knew that C3 substituted indoles are most nucleophilic/basic at their C2 positions. Second, we knew that diborylation would occur first at the C2 position and then at the C7 position if excess borylating reagent were present. Thus, we hypothesized that we

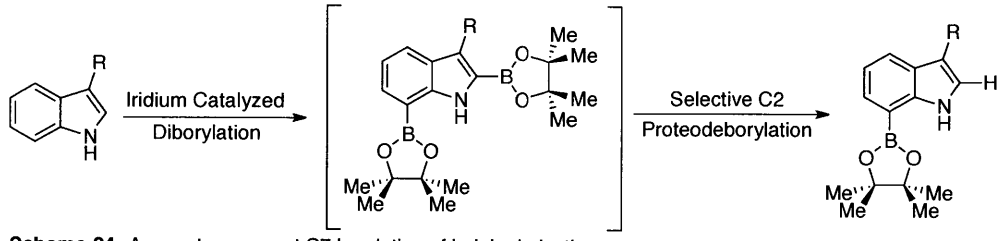
could potentially access high yields of C7 borylated indole derivatives by performing a C2/C7 diborylation followed by a C2 proteodeborylation. This transformation would provide us access to C7 borylated indole derivatives (especially tryptophan and tryptamine derivatives) in a one step, one pot fashion by adding acid at the end of a diborylation reaction. If this procedure were to work, it would allow an even more rapid and operationally facile access to C7 borylated indole derivatives than the current 1 pot, 3 step sequence for C7 borylation of indoles. The results we have found utilizing this methodology are discussed below.

Results and Discussion

As is mentioned above, our group is highly interested in rapid and high yielding access to C7 borylated tryptophan and tryptamine derivatives. The reason for this is two-fold. First, functionalizing the C7 position on these systems is often quite difficult and usually requires the use of an indole synthesis followed by a formylation/homologation/hydrogenation sequence which may or may not need to be asymmetric depending if optically active tryptophan is the substrate of interest. Secondly, we are interested in accessing this particular motif because we believe C7 organoborons could potentially be used in our directed ipso attack Friedel-Crafts strategy for the synthesis of complex alkaloids.

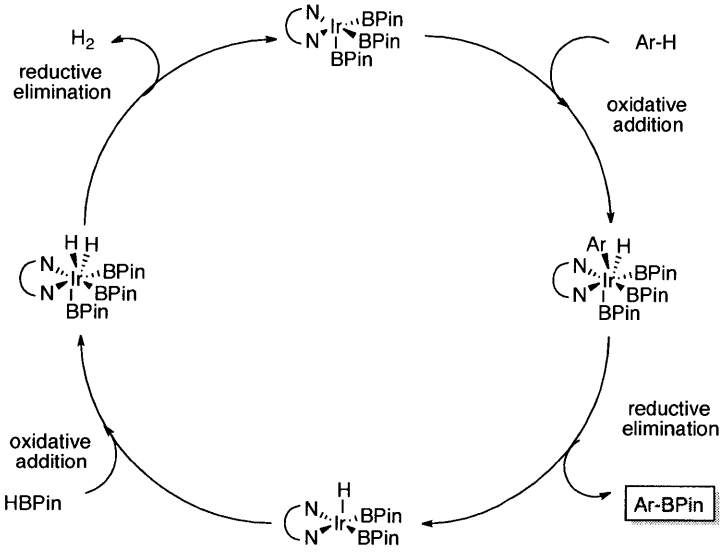
Although Hartwig's silyl directed borylation chemistry provides access to this interesting motif on indole derivatives, we believed that we could gain access to his substrates as well as valuable borylated tryptophans and tryptamines utilizing an alternative approach. To achieve this goal, we envisioned a synthetic sequence involving an iridium catalyzed diborylation at C2 and C7 followed by a selective C2 proteodeborylation (Scheme 24). This procedure would represent a complimentary approach to Hartwig's method that would require a single step instead of three. It would also share the advantage of requiring only a single chromatographic purification; two dimensional thin layer chromatography (TLC) of C7 indole-based boronic esters indicates that these substrates slowly decompose upon prolonged exposure to silica gel. Fortunately, the sensitivity of these compounds is low and it is still possible to attain good yields of the desired products even after chromatography. Nevertheless, we sought to make this a single chromatographic

transformation because it would ideally help improve the mass balance associated with these reactions



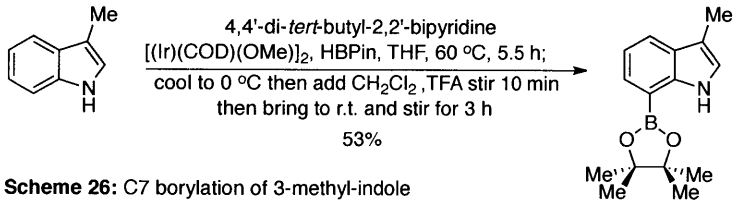
Scheme 24: A one step one pot C7 borylation of indole derivatives

In accord with the studies of Hartwig and coworkers, we believed that our diborylation would also mechanistically operate *via* an iridium(III)/iridium(V) redox catalytic cycle (Scheme 25). Oxidative addition of the active iridium(III) species into the relevant arene C-H bond would generate an iridium(V) species. Reductive elimination from this intermediate would afford the borylated product and an iridium(III) hydride species. Oxidative addition into the H-BPin bond followed by reductive elimination of hydrogen gas would regenerate the catalytically active species. We envisioned that this process would first occur at the C2 position followed by the C7 position as this would be in accord with all previous observations in the literature.



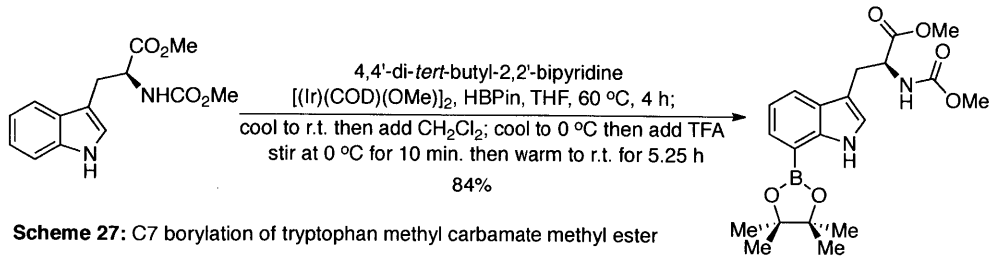
Scheme 25: Proposed catalytic cycle for iridium catalyzed borylations

In order to address these challenges, we first explored 3-methyl indole, a substrate that Hartwig and coworkers explored in their C7 directed borylation chemistry. As evidenced above (Scheme 23), Hartwig and coworkers were able to isolate 61% of the desired monoborylated product using their 3 step, 1 pot methodology. Excited by this result, we performed a bis-borylation on 3-methylindole in THF at 60 °C. We then cooled the reaction to 0 °C, added a 3 fold volume of dichloromethane followed by a dropwise addition of a 2 fold volume of trifluoroacetic acid. After stirring at 0 °C for 10 minutes, the reaction was allowed to warm to room temperature and stir for 3 h. At this time TLC of the reaction mixture indicated the full consumption of the bis borylated material, and the reaction was diluted with dichloromethane and quenched with saturated sodium bicarbonate. Silica gel chromatography afforded the product in 53% yield (Scheme 26). While this yield is slightly lower than Hartwig's, we envision that future advancements in our chemistry will improve the reaction mass balance even more in favor of the desired product.



Scheme 26: C7 borylation of 3-methyl-indole

With this metric in hand, we sought to explore substrates that were of greater interest to our group than simple indole derivatives. As such, we next focused our attention on L-tryptophan methyl ester methyl carbamate. Applying a very similar set of borylation conditions to tryptophan followed by an identical acidic quench, we were able to isolate the desired C7 monoborylated product in 84% yield (Scheme 27).

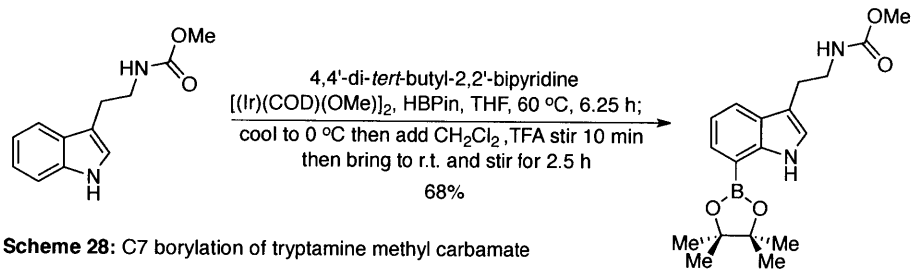


Scheme 27: C7 borylation of tryptophan methyl carbamate methyl ester

This result was in stark contrast to our initial conditions where attempts were made to directly add TFA to the cooled reaction flask with no dichloromethane. When TFA was added directly to the 0 °C THF reaction mixture and then allowed to stir at room temperature, significant amounts of tryptophan starting material was isolated. Crude NMR analysis of the bis borylated mixture indicated that the reaction had indeed proceeded to the desired bis borylated intermediate, and therefore this large amount of recovered starting material likely arose from the bis proteodeborylation of the diborylated material. While we do not yet have conclusive evidence as to why bis proteodeborylation occurs in THF and not in a mixture of THF and dichloromethane, we believe it is likely due to the higher dielectric constant of the media provided by use of THF as solvent with respect to dichloromethane. This increase could in theory assist in the stabilization of cationic intermediates formed during the proteodeborylation.

Interestingly, we were also able to synthesize more than 1 gram of the desired C7 monoborylated tryptophan product by conducting the reaction on a 1.4 gram scale. However, the yield for this transformation was slightly depressed with respect to its smaller scale counterpart (54% vs. 84%). While we are actively investigating the cause of this result, it is most likely due to chromatographic issues - as mentioned previously, this material will decompose on silica gel and it is not unlikely that this effect is magnified during a larger scale purification.

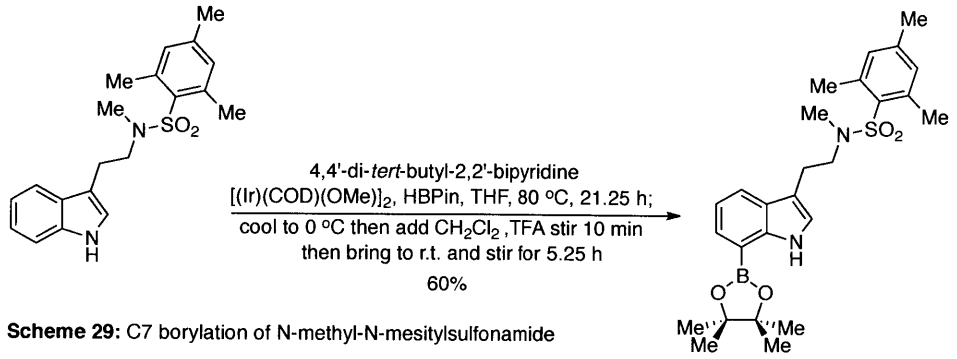
With the tryptophan series successfully explored, we developed conditions to access the C7 monoborylated derivative of tryptamine methyl carbamate. Preliminary attempts at proteodeborylating the bis borylated mixture by adding TFA to the 0 °C tryptamine reaction flask were met with similar issues as in the tryptophan case; significant amounts of starting material were isolated at the end of the reaction. However, crude NMR analysis of the borylated mixture once again indicated that the diborylated intermediate was forming in significant yield. Thus, we hypothesized that the higher dielectric constant of THF also promoted the bis proteodeborylation on tryptamine methyl carbamate. Attempts to only add a 1:5 volume:volume ratio of TFA to the 0 °C THF solution only resulted in slow conversion to the desired product. However, utilizing the same three fold dichloromethane to two fold TFA procedure employed for the tryptophan series afforded 68% of the desired product (Scheme 28).



Scheme 28: C7 borylation of tryptamine methyl carbamate

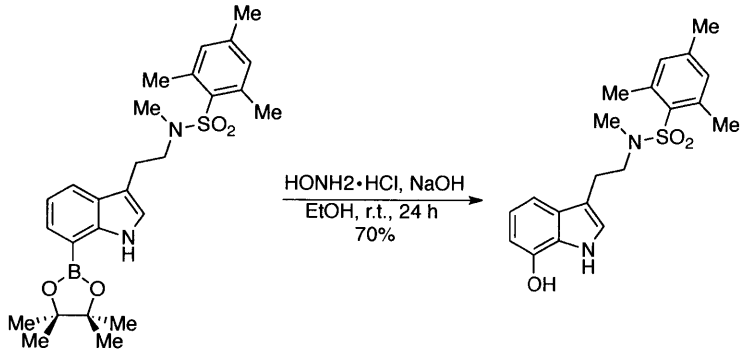
Finally, we were curious to examine the borylation on a substrate that was currently relevant to the chemistry proceeding in our group. As such, we explored the bis-borylation mono proteodeborylation sequence on N-methyl-mesitylsulfonamide. Utilizing a similar procedure as described for 3-methyl indole, tryptophan methyl carbamate methyl ester, and tryptamine methyl carbamate, we were able to isolate 60% of the desired product (Scheme 29). In addition to being relevant to our own group's chemistry, this result is also

interesting because it suggests that substrates with additional steric hindrance and a lack of the carbamate NH are also viable substrates for this transformation.



Scheme 29: C7 borylation of N-methyl-N-mesitylsulfonamide

As one means of demonstrating the utility of these substrates, we wanted to show that this C7 pinacolatoboron functionality could be converted into the phenol. We believed this would be an interesting substrate due to the enhanced electron density of the indole system and also its relevance to cross coupling chemistry; simple conversion to the aryl triflate allows access to a wide array of cross coupling reactions. Additionally, the corresponding halides can also be accessed through this C7 pinacolatoboron as demonstrated by Hartwig.[23] Treating a solution of the requisite boronic ester in absolute ethanol with hydroxylamine hydrochloride and powdered sodium hydroxide afforded the desired phenol in 70% yield (Scheme 30). In future studies, we will demonstrate further chemistry with these borylated tryptophan and tryptamine derivatives.



Scheme 30: C7 pinacolatoboron oxidation to phenol

Thus, in summary, our methodology provides complimentary access to C7 pinacolatoboronic esters on indole derivatives. This method boasts a one pot, one step access to these interesting substrates *via* a bis-borylation proteodeborylation sequence. We hope to further explore the limitations of this chemistry to afford a complimentary method to Hartwig's three step, one pot synthesis of these compounds. Additionally, we have expanded the substrate scope of these arene C-H borylations to include tryptophan and tryptamine derivatives, molecular subunits which are particularly relevant to natural product synthesis. A complete study on this interesting reaction will be reported in due course.

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Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using granular silica gel (60-Å pore size, 40–63 μm, 4–6% H_2O content, Zeochem).[1] Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and an aqueous solution of ceric ammonium molybdate (CAM) followed by heating on a hot plate (~ 250 ºC). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, methanol, pyridine, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs *et al.* under positive argon pressure.[2]

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker AVANCE-600 NMR spectrometer (with a Magnex Scientific superconducting actively-shielded magnet), are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ($CHCl_3$).[3] Data are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, sp = septet, m = multiplet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker AVANCE-600 NMR Spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.16). Data are reported as follows: chemical shift (assignment). Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). We are grateful to Dr. Li Li and Deborah Bass for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using an electrospray (ESI) ionization source.

^{13}C NMR Signals With Ipso Boron. Often the resonances for the carbon directly bonded to boron are not observed in the ^{13}C NMR due to quadrupolar relaxation, and this is indeed the case with the molecules presented herein; see Del Grosso, A.; Helm, M. D.; Solomon, S. A.;

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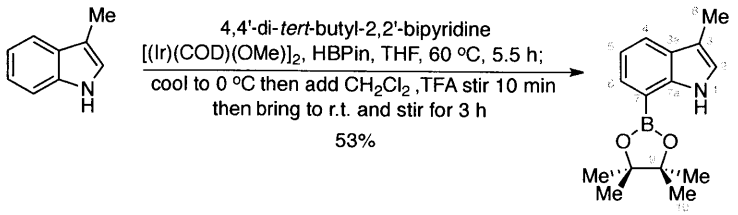
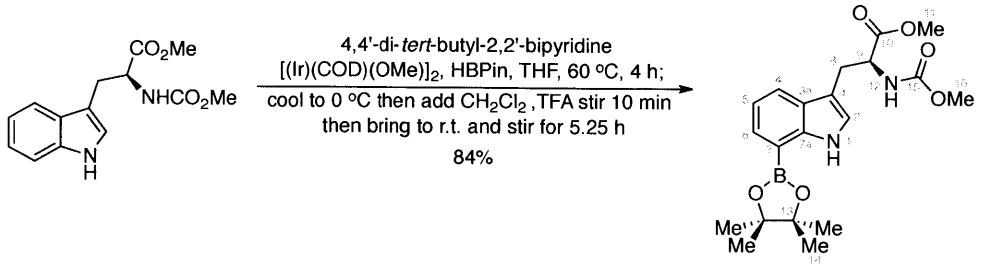


7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-3-methyl-indole

A pressure tube was charged with $[(Ir(COD)(OMe)]_2$ (0.005 g, 0.025 mmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.004 g, 0.050 mmol, 5 mol%) and 3-methyl-indole (0.039 g, 0.300 mmol, 1 equiv). The contents of the tube were subjected to three argon/vacuum cycles. Freshly distilled anhydrous THF (2 mL) was introduced to the flask via gas tight syringe to afford a clear dark brown solution. Pinacolborane (218 μL, 0.600 mmol, 5.00 equiv) was added in a single portion via gas tight syringe to afford a clear cherry red solution. The pressure tube was sealed and was allowed to stir at 60 °C for 5.5 h. The tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added via gas tight syringe. Trifluoroacetic acid (2 mL) was then added dropwise via gas tight syringe to afford a clear orange solution. The solution stirred at 0 °C for 10 minutes and was then warmed to room temperature and stirred for 3 h. The solution was diluted with dichloromethane (50 mL) and was washed with saturated sodium bicarbonate (50 mL) until excess trifluroacetic acid was quenched. The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (isochratic: 1.5% acetone in hexanes) to provide the boronic ester (0.041 g, 0.160 mmol, 53%) as an off white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (600 MHz, $CDCl_3$, 20 ºC):	δ 8.94 (br-s, 1H, N_1**H**), 7.69 (d, *J* = 7.9, 1H, C_4**H**), 7.63 (d, J = 7.0, 1H, C_6**H**), 7.11 (t, J = 7.2, 1H, C_5**H**), 7.00 (d, J = 0.6, 1H, C_2**H**), 2.33 (s, 3H, C_8**H**), 1.37 (s, 1H, C_{10}**H**).
^{13}C NMR (150 MHz, $CDCl_3$, 20 ºC):	δ 141.5 (**C**$_{7a}$), 129.2 (**C**$_6$), 127.3 (**C**$_{3a}$), 122.5 (**C**$_4$), 121.6 (**C**$_2$), 118.7 (**C**$_5$), 111.2 (**C**$_3$), 83.9 (**C**$_9$), 25.1 (**C**$_{10}$), 9.8 (**C**$_8$).
FTIR (thin film) cm^{-1}:	3462 (s), 2977 (s), 2923 (m), 1607 (m), 1592 (m), 1437 (m), 1371 (s), 1136 (s), 848 (m).
HRMS (ESI) (*m/z*):	calc'd for $C_{15}H_{20}BNO_2$ $[M+H]^+$: 258.1587, found:
TLC (5% Diethyl Ether in Hexanes), R*f*:	0.26 (UV, CAM).

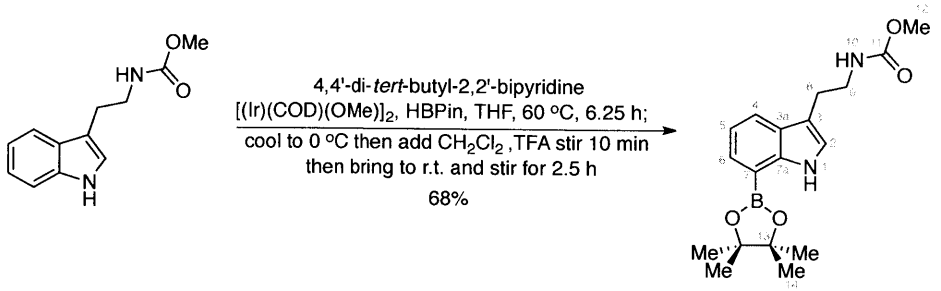


7-(4,4,5,5-tetramethyl-1,3,2-Dioxaborolan-2-yl)-1*H*-indol-3-methylester-*N*-methylcarbamate

A pressure tube was charged with $[(Ir(COD)(OMe)]_2$ (0.005 g, 0.025 mmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.004 g, 0.050 mmol, 5 mol%) and methyl carbamate-tryptophan-methyl ester (0.083 g, 0.300 mmol, 1 equiv). The contents of the tube were subjected to three argon/vacuum cycles. Freshly distilled anhydrous THF (2 mL) was introduced to the flask via gas tight syringe to afford a clear dark brown solution. Pinacolborane (218 μL, 0.600 mmol, 5.00 equiv) was added in a single portion via gas tight syringe to afford a clear cherry red solution. The pressure tube was sealed and was allowed to stir at 60 °C for 4 h. The tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added via gas tight syringe. Trifluoroacetic acid (2 mL) was then added dropwise via gas tight syringe to afford a clear orange solution. The solution stirred at 0 °C for 10 minutes and was then warmed to room temperature and stirred for 5.25 h. The solution was diluted with dichloromethane (50 mL) and was washed with saturated sodium bicarbonate (50 mL) until excess trifluroacetic acid was quenched. The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (isochratic: 8% acetone, 30% dichloromethane, 62% hexanes) to provide the boronic ester (0.1012 g, 0.252 mmol, 84%) as an off white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (600 MHz, $CDCl_3$, 20 ºC):	δ 9.16 (br-s, 1H, N_1**H**), 7.65 (d, *J* = 8.4, 1H, C_4**H**), 7.62 (d, *J* = 7.2, 1H, C_6**H**), 7.13 (app-t, J = 7.3, 1H, C_5**H**), 7.05 (d, *J* = 1.7, 1H, C_2**H**), 5.28 (d, *J* = 8.1, 1H, N_{12}**H**), 4.68 (q, *J* = 2.8, 1H, C_9**H**), 3.66 (s, 3H, C_{11}**H**), 3.64 (s, 3H, C_{16}**H**), 3.30 (d, *J* = 4.7, 2H, C_8**H**), 1.37 (s, 12H, C_{14}**H**).
^{13}C NMR (150 MHz, $CDCl_3$, 20 ºC):	δ 172.6 (**C**$_{10}$), 156.5 (**C**$_{15}$), 141.3 (**C**$_{7a}$), 129.5 (**C**$_6$), 126.5 (**C**$_{3a}$), 122.9 (**C**$_2$), 122.2 (**C**$_4$), 119.2 (**C**$_5$), 109.3 (**C**$_3$), 83.9 (**C**$_{13}$), 54.5 (**C**$_9$), 52.4 (**C**$_{11}$), 52.3 (**C**$_{16}$), 28.0 (**C**$_8$), 25.0 (**C**$_{14}$).
FTIR (thin film) cm^{-1}:	3448 (s), 2979 (s), 2953 (m), 1722 (s), 1591 (m), 1516 (s), 1374 (m), 1329 (m), 1134 (s), 684 (w).

HRMS (ESI) (*m/z*):	calc'd for $C_{20}H_{27}BN_2O_6$ $[M+H]^+$: 403.2050, found: 403.2030.
TLC (10% Acetone, 20% DCM, 70% Hex), R*f*:	0.19 (UV, CAM).

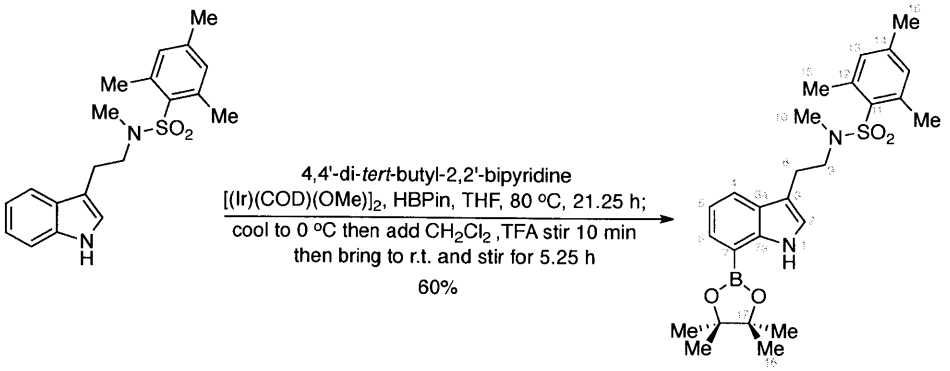


7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-*N*-methylcarbamate

A pressure tube was charged with $[(Ir(COD)(OMe)]_2$ (0.005 g, 0.025 mmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.004 g, 0.050 mmol, 5 mol%) and tryptamine methyl carbamate (0.067 g g, 0.300 mmol, 1 equiv). The contents of the tube were subjected to three argon/vacuum cycles. Freshly distilled anhydrous THF (2 mL) was introduced to the flask via gas tight syringe to afford a clear dark brown solution. Pinacolborane (218 μL, 0.600 mmol, 5.00 equiv) was added in a single portion via gas tight syringe to afford a clear cherry red solution. The pressure tube was sealed and was allowed to stir at 60 °C for 6.25 h. The tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added via gas tight syringe. Trifluoroacetic acid (2 mL) was then added dropwise via gas tight syringe to afford a clear orange solution. The solution stirred at 0 °C for 10 minutes and was then warmed to room temperature and stirred for 2.5 h. The solution was diluted with dichloromethane (50 mL) and was washed with saturated sodium bicarbonate (50 mL) until excess trifluroacetic acid was quenched. The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (isochratic: 10% acetone, 20% dichloromethane, 70% hexanes) to provide the boronic ester (0.0699 g, 0.203 mmol, 68%) as an off white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (600 MHz, $CDCl_3$, 20 ºC):	δ 9.07 (br-s, 1H, N_1**H**), 7.71 (d, *J* = 7.8, 1H, C_4**H**), 7.64 (d, *J* = 6.9, 1H, C_6**H**), 7.13 (app-t, J = 7.3, 1H, C_5**H**), 7.09 (br-s, 1H, C_2**H**), 4.71 (br-s, 1H, N_{10}**H**), 3.63 (s, 3H, C_{12}**H**), 3.49 (app-q, 2H, C_9**H**), 2.97 (app-t, 2H, C_8**H**), 1.37 (s, 12H, C_{14}**H**).
^{13}C NMR (150 MHz, $CDCl_3$, 20 ºC):	δ 157.2 (**C**$_{11}$), 141.7 (**C**$_{7a}$), 129.6 (**C**$_6$), 126.3 (**C**$_{3a}$), 122.4 (**C**$_4$), 122.2 (**C**$_2$), 119.1 (**C**$_5$), 112.4 (**C**$_3$), 84.0 (**C**$_{13}$), 52.2 (**C**$_{12}$), 41.4 (**C**$_9$), 25.9 (**C**$_8$), 25.1 (**C**$_{14}$).
FTIR (thin film) cm^{-1}:	3451 (s), 2978 (s), 2939 (s), 1713 (s), 1522 (m), 1373 (m), 1135 (s), 966 (w), 684 (m).
HRMS (ESI) (*m/z*):	calc'd for $C_{18}H_{25}BN_2O_4$ $[M+H]^+$: 345.1994, found: 345.1996.

TLC (10% Acetone, 20% DCM, 70% Hex), R*f*: 0.21 (UV, CAM).



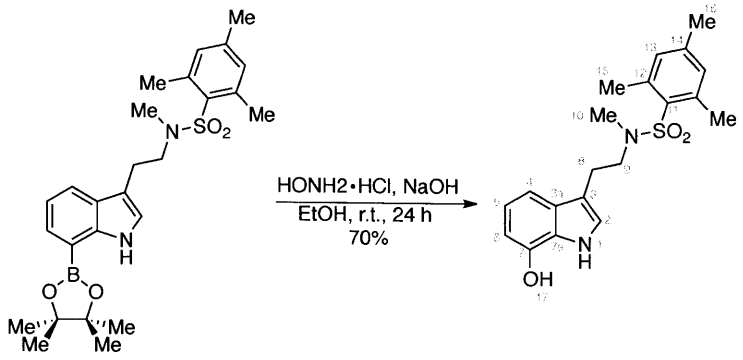
2,4,6-Tetramethyl-N-(2-(7(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-(methyl)benzenesulfonamide

A pressure tube was charged with $[(Ir(COD)(OMe)]_2$ (0.005 g, 0.025 mmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.004 g, 0.050 mmol, 5 mol%) and N-methyl-N-mesitylsulfamide tryptamine (0.107 g, 0.300 mmol, 1 equiv). The contents of the tube were subjected to three argon/vacuum cycles. Freshly distilled anhydrous THF (2 mL) was introduced to the flask via gas tight syringe to afford a clear dark brown solution. Pinacolborane (218 μL, 0.600 mmol, 5.00 equiv) was added in a single portion via gas tight syringe to afford a clear cherry red solution. The pressure tube was sealed and was allowed to stir at 80 °C for 21.25 h. The tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added via gas tight syringe. Trifluoroacetic acid (2 mL) was then added dropwise via gas tight syringe to afford a clear orange solution. The solution stirred at 0 °C for 10 minutes and was then warmed to room temperature and stirred for 5.25 h. The solution was diluted with dichloromethane (50 mL) and was washed with saturated sodium bicarbonate (50 mL) until excess trifluroacetic acid was quenched. The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (isochratic: 5% acetone, 15% dichloromethane, 80% hexanes) to provide the boronic ester (0.086 g, 0.179 mmol, 60%) as an off white solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (600 MHz, $CDCl_3$, 20 ºC): δ 9.03 (br-s, 1H, N_1**H**), 7.62 (d, *J* = 7.0, 1H, C_6**H**), 7.47 (d, *J* = 7.8, 1H, C_4**H**), 7.05 (app-t, J = 7.3, 1H, C_5**H**), 7.01 (d, *J* = 1.7, 1H, C_2**H**), 6.86 (s, 2H, C_{13}**H**), 3.39 (t, *J* = 7.7, 2H, C_9**H**), 3.00 (t, *J* = 8.0, 2H, C_8**H**), 2.85 (s, 3H, C_{10}**H**), 2.55 (s, 6H, C_{15}**H**), 2.27 (s, 3H, C_{16}**H**), 1.38 (s, 12H, C_{18}**H**).

^{13}C NMR (150 MHz, $CDCl_3$, 20 ºC): δ 142.4 (**C**$_{14}$), 141.5 (**C**$_{7a}$), 140.3 (**C**$_{12}$), 132.4 (**C**$_{11}$), 131.9 (**C**$_{13}$), 129.3 (**C**$_6$), 126.0 (**C**$_{3a}$), 122.1 (**C**$_4$), 122.0 (**C**$_2$), 118.9 (**C**$_5$), 112.0 (**C**$_3$), 83.9 (**C**$_{17}$), 49.7 (**C**$_9$), 33.0 (**C**$_{10}$), 25.1 (**C**$_{18}$), 23.8 (**C**$_8$), 22.9 (**C**$_{15}$), 21.1 (**C**$_{16}$).

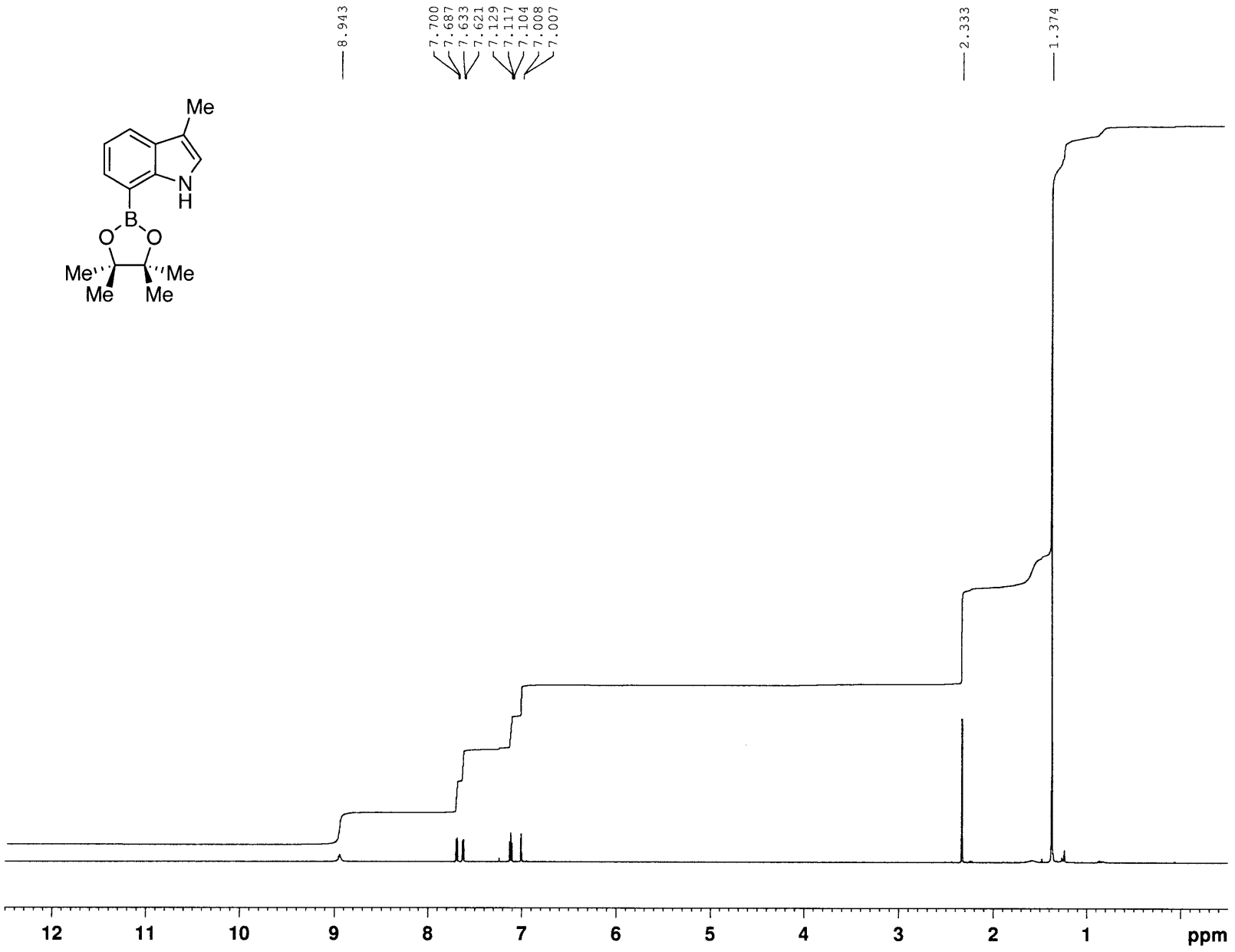
FTIR (thin film) cm^{-1}:	3457 (s), 2978 (s), 2936 (s), 1605 (m), 1592 (m), 1372 (s), 1328 (s), 1151 (s), 729 (w).
HRMS (ESI) (m/z):	calc'd for $C_{26}H_{25}BN_2O_4S$ $[M+H]^+$: 483.25, found: 483.24.
TLC (5% Acetone, 15% DCM, 80% Hex), R*f*:	0.11 (UV, CAM).



2,4,6-Tetramethyl-(2-(7-Hydroxy-1*H*-indol-3-yl)ethyl)-*N*,2,4,6-tetramethylbenzenesulfonamide

To a solution of *N*-methyl-mesitylsulfonamide tryptamine boronic ester (51 mg, 0.106 mmol, 1 equiv) in absolute ethanol (2.1 mL) were sequentially added hydroxylamine hydrochloride (22 mg, 0.318 mmol, 3.00 equiv) and freshly pulverized sodium hydroxide (13.0 mg, 0.318 mmol, 3.00 equiv). The reaction stirred at room temperature for 20 h. Hydroxylamine hydrochloride (44.0 mg, 0.636 mmol, 6.00 equiv) and sodium hydroxide (26.0 mg, 0.636 mmol, 6.00 equiv) were then added. The reaction stirred for 3 h. Hydroxylamine hydrochloride (110 mg, 1.59 mmol, 15 equiv) and sodium hydroxide (65 mg, 1.59 mmol, 15 equiv) were then added a third time. The reaction was stirred for 1.3 h and was concentrated under reduced pressure. The resulting orange residue was purified by column chromatography on silica gel (eluent: isochratic, 27.5% acetone in hexanes) to afford the phenol (27.8 mg, 0.075 mmol, 70.0%) as a film. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (600 MHz, $CDCl_3$, 20 ºC):	δ 8.16 (br-s, 1H, N_1**H**), 6.95 (d, *J* = 7.9, 1H, C_4**H**), 6.92 (br-s, 1H, C_2**H**), 6.85 (t, J = 6.4, 1H, C_5**H**), 6.85 (s, 2H, C_{13}**H**), 6.55 (d, J = 7.4, 1H, C_6**H**), 5.10 (br-s, 1H, O_{17}**H**), 3.39 (t, *J* = 7.4, 2H, C_9**H**), 2.96 (t, 2H, C_8**H**), 2.82 (s, 3H, C_{10}**H**), 2.53 (s, 6H, C_{15}**H**), 2.26 (s, 3H, C_{16}**H**).
^{13}C NMR (150 MHz, $CDCl_3$, 20 ºC):	δ 142.5 (**C**$_{14}$), 141.7 (**C**$_7$), 140.4 (**C**$_{12}$), 132.4 (**C**$_{11}$), 131.9 (**C**$_{13}$), 129.4 (**C**$_{3a}$), 126.1 (**C**$_{7a}$), 122.1 (**C**$_2$), 119.9 (**C**$_5$), 113.1 (**C**$_3$), 111.5 (**C**$_4$), 106.6 (**C**$_6$), 49.6 (**C**$_9$), 33.1 (**C**$_{10}$), 24.0 (**C**$_8$), 22.9 (**C**$_{15}$), 21.1 (**C**$_{16}$).
FTIR (thin film) cm^{-1}:	3405 (s), 1583 (m), 1455 (m), 1374 (w), 1304 (m), 1143 (s), 1054 (w), 948 (w), 729 (m).
HRMS (ESI) (*m/z*):	calc'd for $C_{20}H_{24}N_2O_3S$ $[M+H]^+$: 373.16, found: 373.16.
TLC (30% acetone in hexanes), R*f*:	0.19 (UV, CAM)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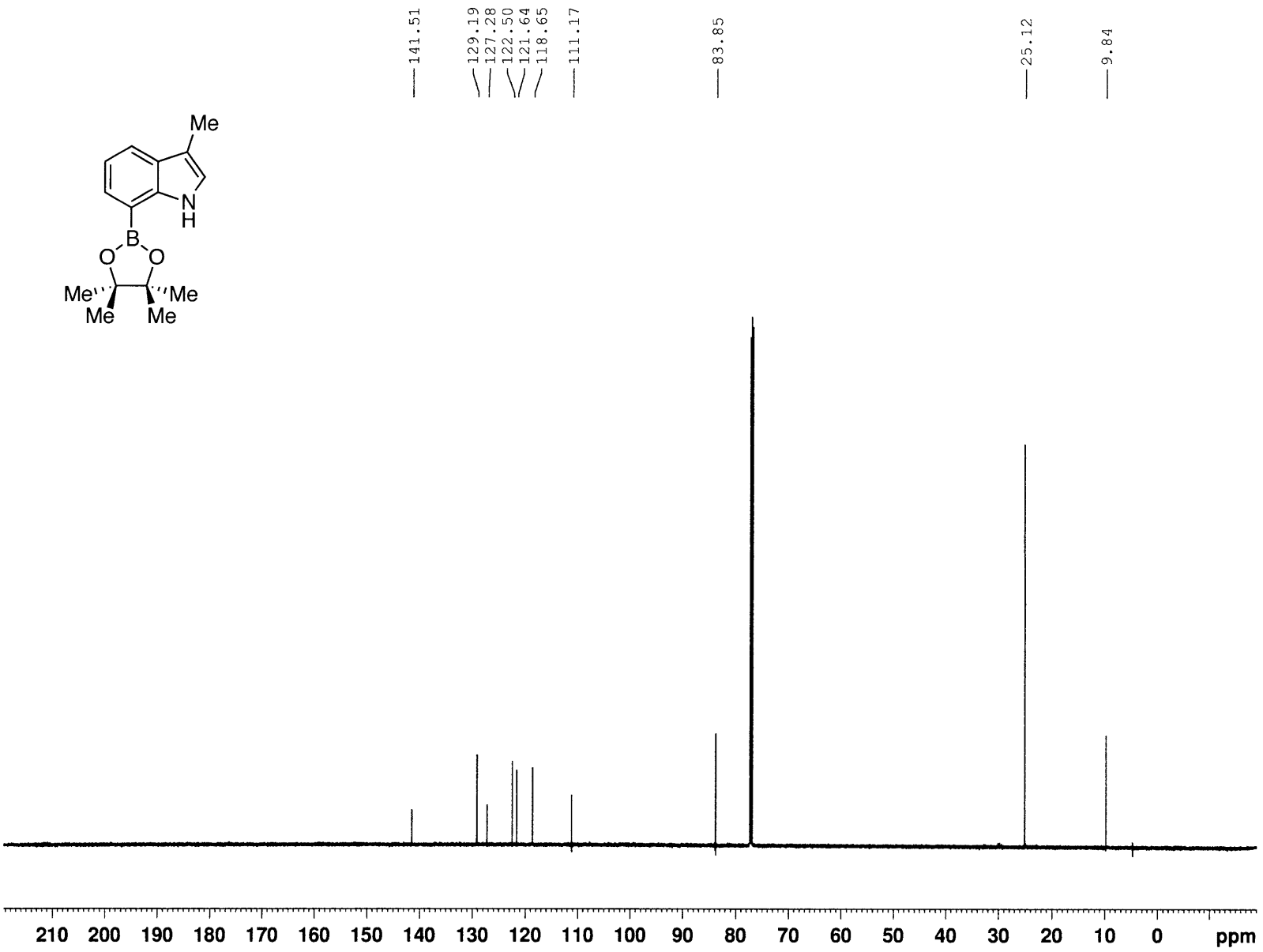
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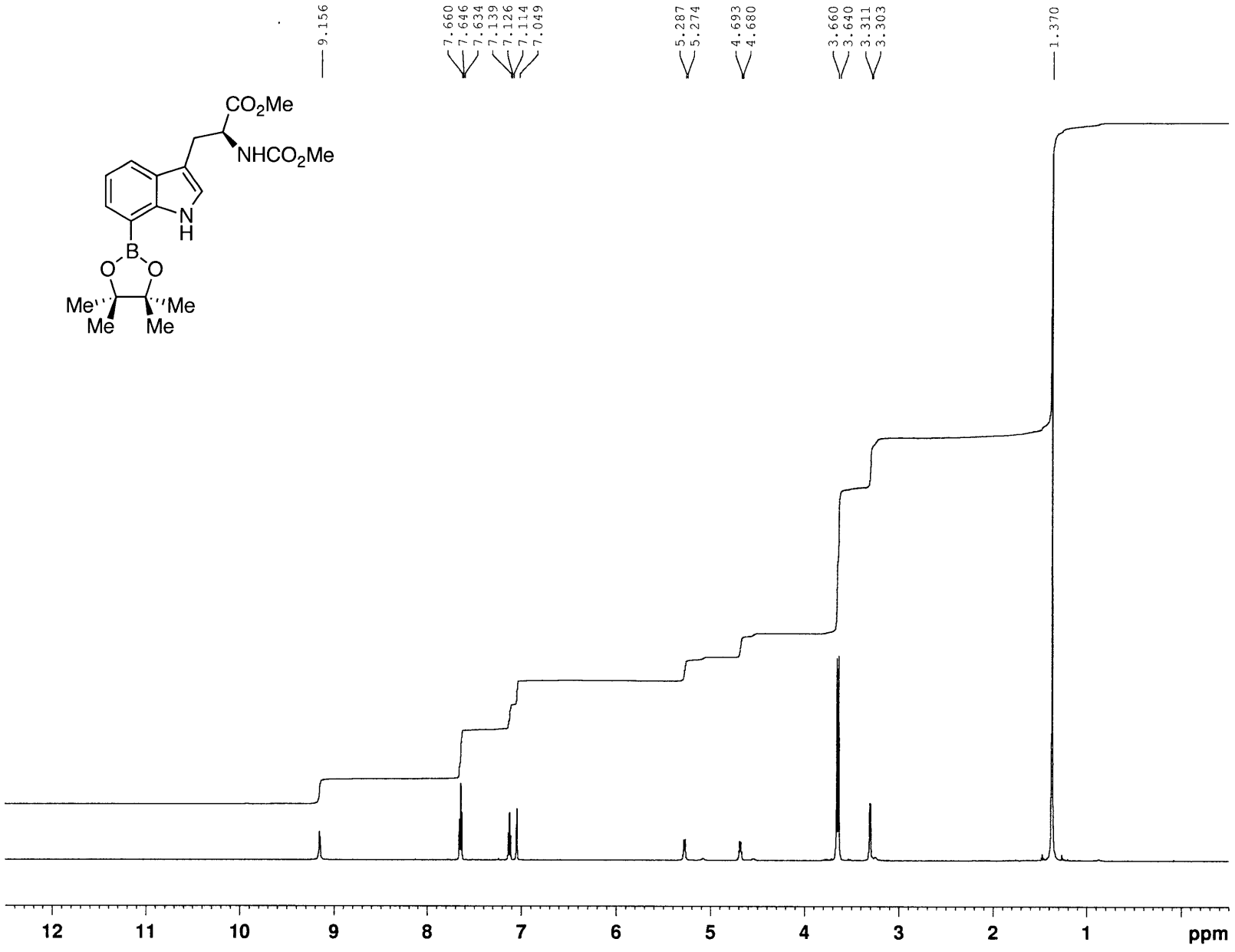
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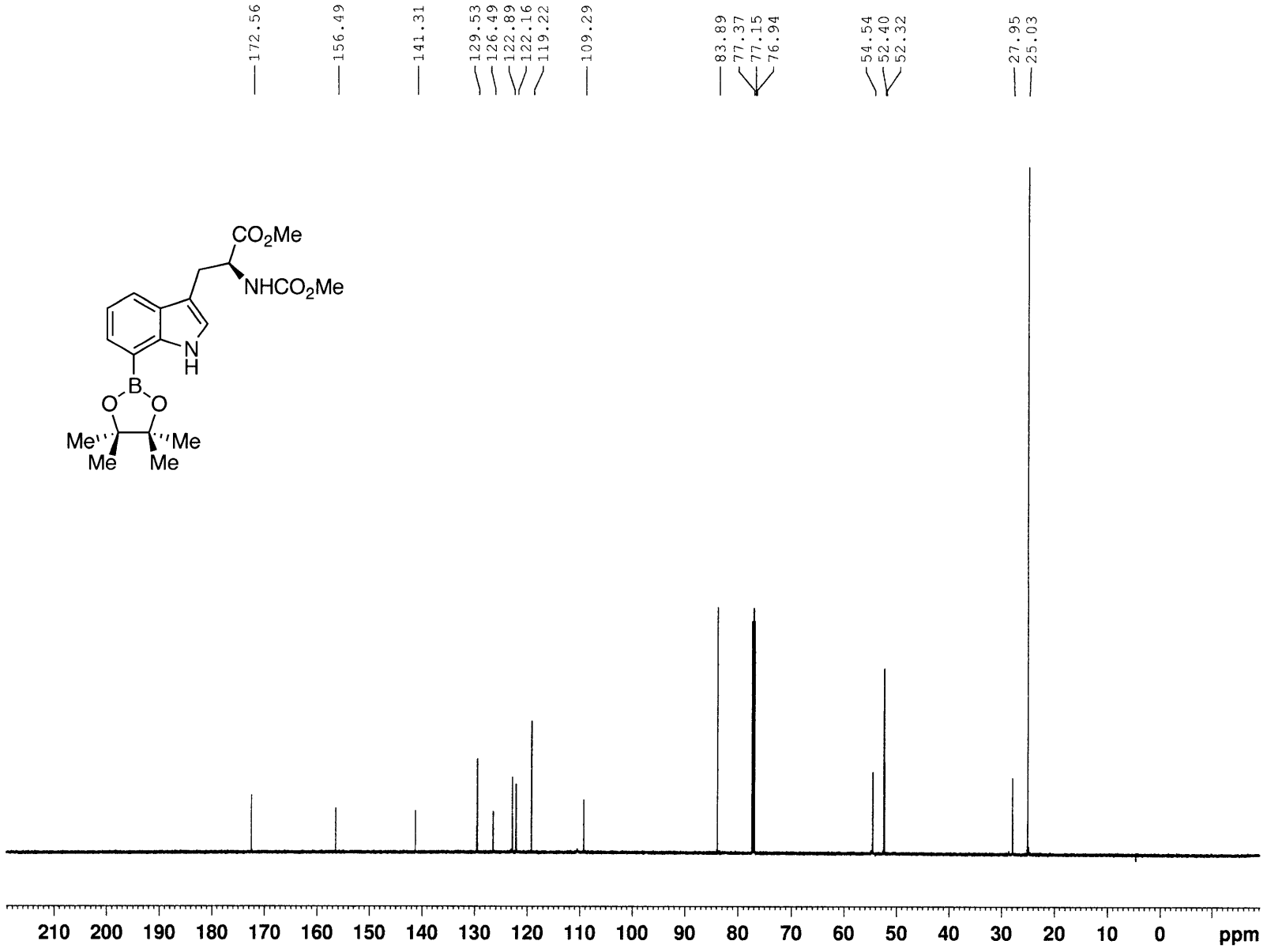
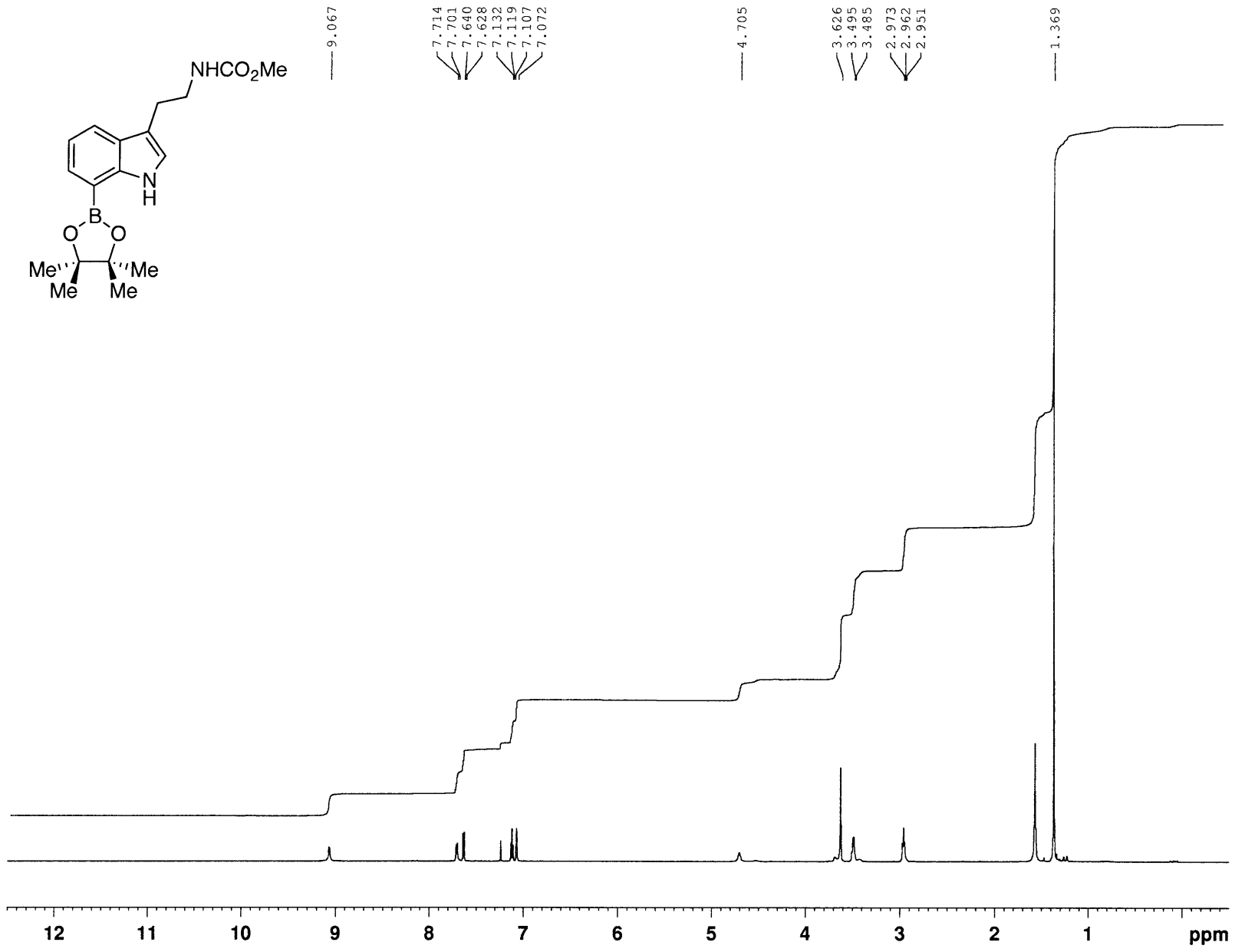
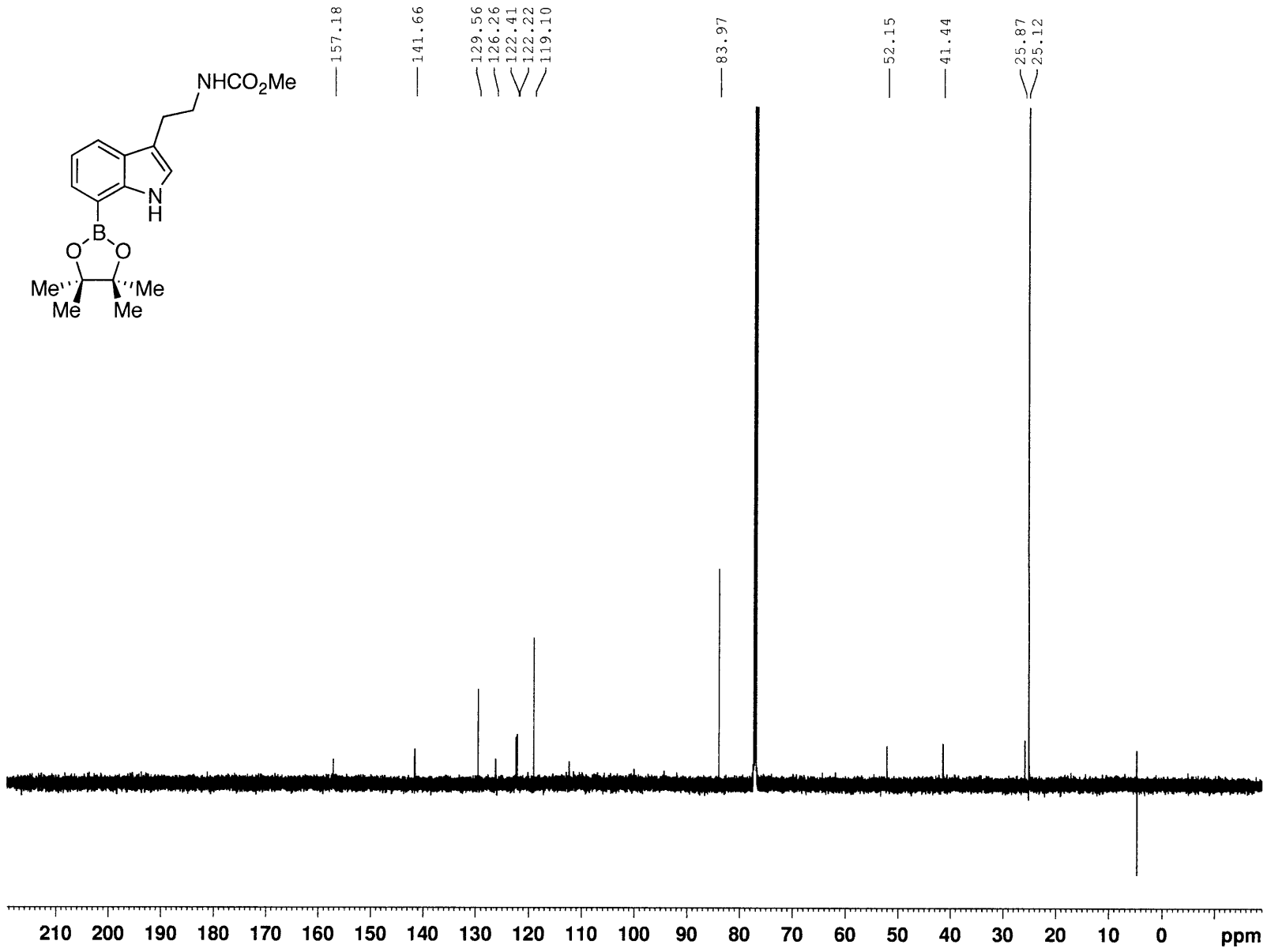
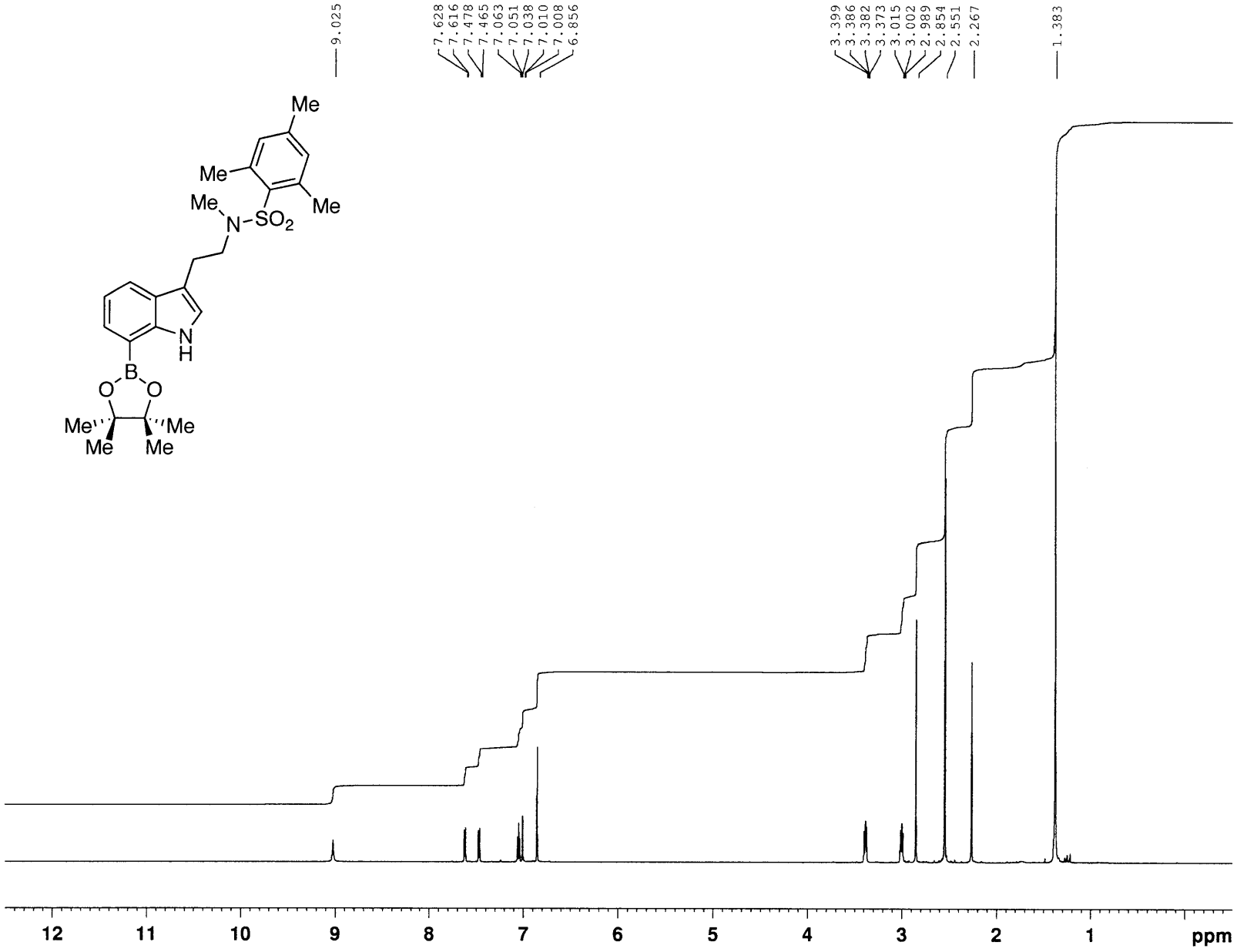
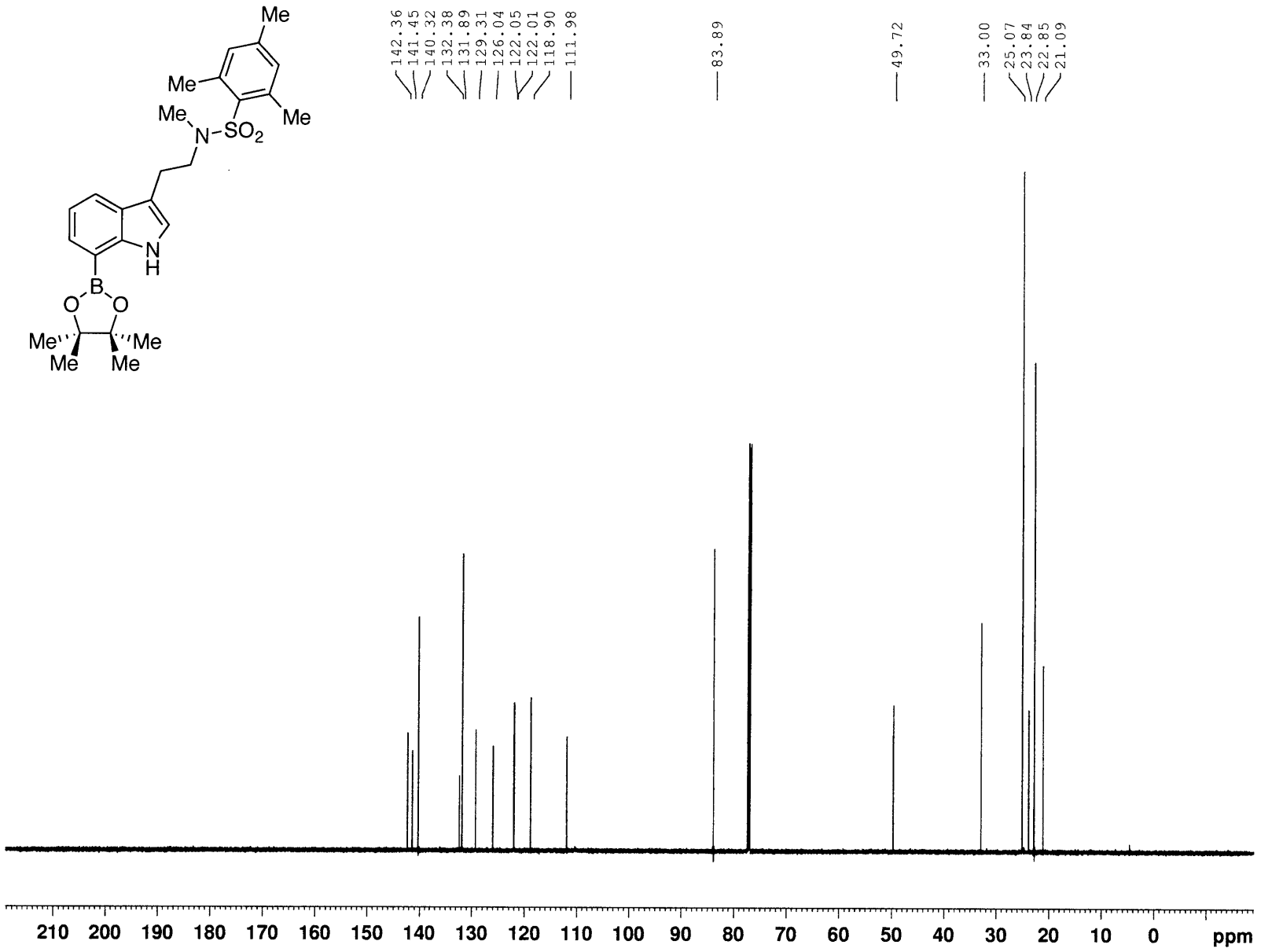
ppm

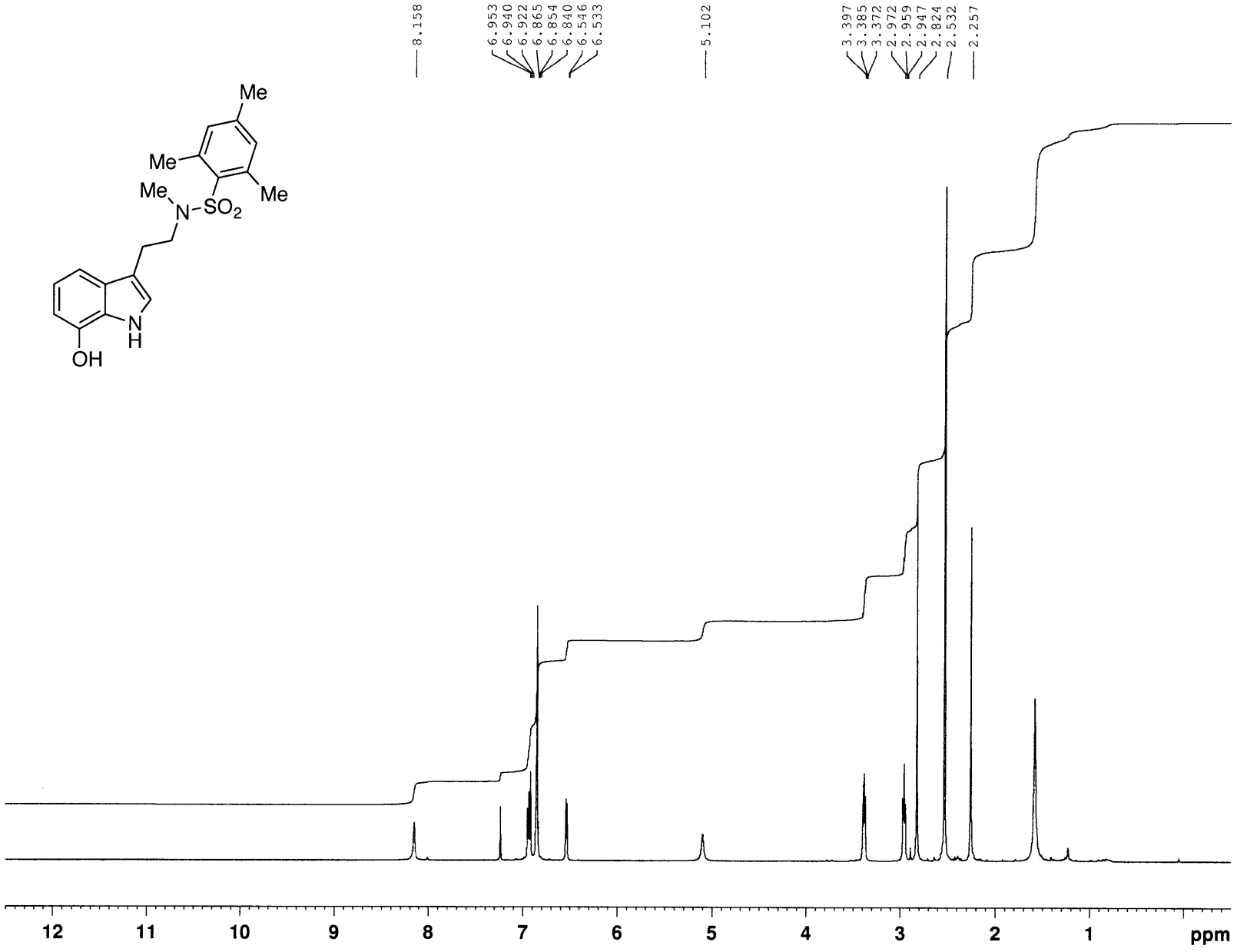

172.56
156.49
141.31
129.53
126.49
122.89
122.16
119.22
109.29
83.89
77.37
77.15
76.94
54.54
52.40
52.32
27.95
25.03
CO2Me
NHCO2Me
N
H
B
O
O
Me
Me
Me
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

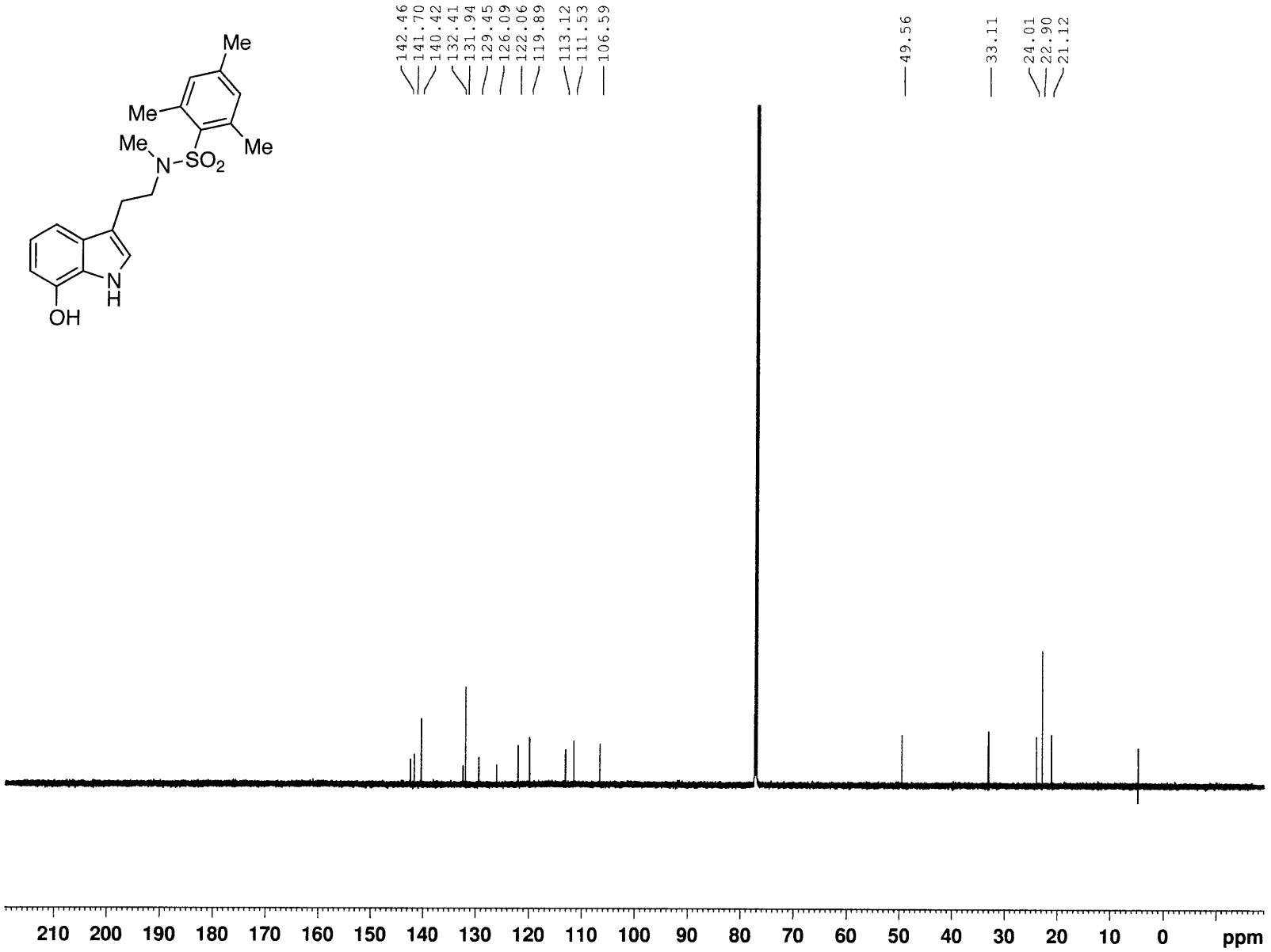

NHCO2Me
N
H
B
O
O
Me
Me
Me
Me
9.067
7.714
7.701
7.640
7.628
7.132
7.119
7.107
7.072
4.705
3.626
3.495
3.485
2.973
2.962
2.951
1.369
12
11
10
9
8
7
6
5
4
3
2
1
ppm


NHCO2Me
N
H
B
O
O
Me
Me
Me
Me
157.18
141.66
129.56
126.26
122.41
122.22
119.10
83.97
52.15
41.44
25.87
25.12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.025
7.628
7.616
7.478
7.465
7.063
7.051
7.038
7.010
7.008
6.856
3.399
3.386
3.382
3.373
3.015
3.002
2.989
2.854
2.551
2.267
1.383
Me
Me
Me
Me
N
SO2
N
H
B
O
O
Me
Me
Me
Me
12
11
10
9
8
7
6
5
4
3
2
1
ppm


Me
Me
Me
Me
N
SO2
N
H
B
O
O
Me
Me
Me
Me
142.36
141.45
140.32
132.38
131.89
129.31
126.04
122.05
122.01
118.90
111.98
83.89
49.72
33.00
25.07
23.84
22.85
21.09
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.158
6.953
6.940
6.922
6.865
6.854
6.840
6.546
6.533
5.102
3.397
3.385
3.372
2.972
2.959
2.947
2.824
2.532
2.257
Me
Me
Me
Me
N
SO2
N
H
OH
12
11
10
9
8
7
6
5
4
3
2
1
ppm


142.46
141.70
140.42
132.41
131.94
129.45
126.09
122.06
119.89
113.12
111.53
106.59
49.56
33.11
24.01
22.90
21.12
Me
Me
Me
Me
N
SO2
N
H
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Curriculum Vitae
Owen S. Fenton

Massachusetts Institute of Technology
Department of Chemistry
77 Massachusetts Avenue, 18-106
Cambridge, MA 02139

Phone: (413) 454-2731
Email: osfenton@mit.edu

Current Position: Graduate Student, Movassaghi Laboratories

Education:

2010 - Present: Ph.D. Organic Chemistry, Massachusetts Institute of Technology
May 2012 - Full Ph.D. Candidate - Complete Pass of Oral Qualifying Exams

2006 - 2010: B.A., Summa Cum Laude, Chemistry, College of the Holy Cross
Class Rank: 1 of 715
GPA: 3.98/4.00

2002 - 2006: High School Diploma, Top 1% of Class of 2006, Longmeadow High School

Research Experience:

November 2010 - Present: Graduate Research (Massachusetts Institute of Technology)
Total Synthesis of Complex Alkaloid Natural Products
Principal Investigator: Professor Mohammad Movassaghi

June 2009 – August 2009: Undergraduate Research (University of California, Berkeley)
Asymmetric Gold-Catalyzed [4+2] Cycloadditions of Allene-Dienes
Principal Investigator: Professor F. Dean Toste

May 2008 – May 2010: Undergraduate Research (College of the Holy Cross)
Development of Catalytic P(III) and P(V) Reactions for the Phosphorylation of Alcohols
Principal Investigator: Professor Bianca R. Sculimbrene

January 2007 – May 2008: Undergraduate Research (College of the Holy Cross)
Quantitative Analysis of Illicit Drugs Using Raman Spectroscopy and Chemometrics
Principal Investigator: Professor Kimberley A. Frederick

Awards and Honors:

2012: National Science Foundation Graduate Student Research Fellowship Recipient

2009: Goldwater Scholarship Recipient

2009: Dana Scholar

2009: Amgen Scholar (University of California, Berkeley)

2009: Fenwick Scholarship Recipient

2009: Dean's List 6X out of 6 Semesters

2008: Honorable Mention for the Goldwater Scholarship

2008: Mrs. Kate C. Power Medal Recipient
- Award presented to the highest-ranking student (1 of) in the second year class at Holy Cross

2008: Jean Dreyfus Boissevain Undergraduate Scholarship

2008: PolyEd Achievement in Organic Chemistry Award

2008: Undergraduate Research Award

2007: Annual CRC Press Freshman Chemistry Award

2006: AP Scholar with Distinction
- Chemistry: 5, BC Calculus: 5, AB Calculus Subscore: 5, Physics B: 5, Spanish: 5, English Literature and Composition: 4

Publications:

Research Articles

1. P.B. Brady, E.M. Morris, **O.S. Fenton**, and B.R. Sculimbrene. "Efficient Catalyst Turnover in the Phosphitylation of Alcohols with Phosphoramidites", *Tetrahedron Lett.* **2009**, 50, 975-978

2. K.Y. Noonan, L.A. Tonge, **O.S. Fenton**, D. Damiano and K.A. Frederick. "Rapid Classification of Simulated Street Drug Mixtures using Raman Spectroscopy and Principal Components Analysis", *Appl. Spectrosc.* **2009**, 63, 742-747

3. **O.S. Fenton**, L.A. Tonge, T.H. Moot and K.A. Frederick. "Quantitative Analysis of Simulated Illicit Street-Drug Samples Using Raman Spectroscopy and Partial Least Squares Regression", *Spectroscopy Letters*, **2011**, *44*, 229-234

4. **O.S. Fenton**, and B.R. Sculimbrene. "A Wet-Lab Approach to Stereochemistry Using ^{31}P NMR Spectroscopy", *J. Chem. Ed.*, **2011**, *88*, 662-664

5. **O.S. Fenton**, E.E. Allen, K.P. Pedretty, S.D. Till, J.E. Todaro, and B.R. Sculimbrene. "Catalytic Lewis Acid Phosphorylation with Pyrophosphates", Accepted, *Tetrahedron.*

Presentations:

O.S. Fenton, B.R. Sculimbrene
Development of Catalytic Phosphorylation Reactions
ACS Meeting, March 2010
O.S. Fenton, B.R. Sculimbrene
"A Wet-Lab Approach to Stereochemistry Using ^{31}P NMR Spectroscopy"
ACS Meeting, March 2010

O.S. Fenton, Ana Z. Gonzalez, F. Dean Toste
Asymmetric Gold-Catalyzed [4+2] Cycloadditions of Allene-Dienes
Amgen Scholars Summer Research Symposium, August 2009

O.S. Fenton, E.M. Morris, B.R. Sculimbrene
Development of a Catalytic Reaction for the Phosphorylation of Alcohols
ACS Meeting, March 2009

O.S. Fenton, K.A. Frederick, D.B. Damiano
Quantitative Measurements of Illicit Drugs Using Raman Spectroscopy and Chemometrics
ACS Meeting, August 2007

GRE Scores:

General Test
- Math: 790 (92nd percentile)
- Verbal: 650 (93rd percentile)
- Analytical Writing: 6.0/6.0 (98th percentile)

Chemistry Subject Test
- Chemistry: 840 (86th percentile)

Coursework:

Massachusetts Institute of Technology
- Tutorial in Organic Chemistry
- Synthetic Organic Chemistry I
- Molecular Structure and Reactivity
- Organometallic Reaction Mechanisms
- Special Problems in Chemistry
- Organic Chemistry Seminar
- Crystal Structure Analysis
- NMR & Organic Structure Determination
- Synthetic Orgnaic Chemsitry II

- Chemistry in Industry
- Crystal Structure Refinement

Science and Mathematics (College of the Holy Cross)

- Fenwick Scholarship (Full Time Research Project)
- General Chemistry I & II (Lab Included)
- Organic Chemistry I & II (Lab Included)
- Classical Physical Chemistry
- Physical Chemistry Lab I
- Modern Physical Chemistry
- Modern Physical Chemistry/Inorganic Chemistry Lab I
- Synthetic Organic Chemistry
- Instrumental Chemistry/Analytical Methods I (Lab Included)
- Independent Research I (Analytical)
- General Research I & II (Organic)
- General Physics I & II (Lab included)
- Multivariable Calculus
- Directed Project I: Using Differential Equations to Model Biological Systems