DISCOVERY AND THE DEVELOPMENT OF BISMUTH SALT MEDIATED CATALYTIC DEBORYLATION AND ALLIED STUDIES

By

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Chemistry−Master of Science

2015

ABSTRACT

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Arylboronate esters are versatile synthetic building blocks. Iridium catalyzed C–H activation/borylation reactions are a green way of making such building blocks as these reactions often obviate the need for prior functionalization (e.g. halogenation), the use of pyrophoric reagents, cryogenic conditions, etc. Installation of multiple boron substituents about the starting arene and then Ir catalyzed selective deborylation of the individual borons can allow for the formation of an even greater diversity of borylated building blocks.

The regioselectivity of Ir-catalyzed borylation is usually driven by sterics, however heterocycles are known to borylated at positions that exhibit heightened C-H acidity through the influence of the heteroatom. The regioselective borylation attained with a tryptophan derivative has been utilized in the development of a novel convergent route to the TMC-95 core. While pursuing a model synthesis of this natural product, the ability of bismuth salts to catalyze deborylations was discovered. These bismuth salts mediated methods can be highly selective in the in the deborylation of di and triborylated indoles. Furthermore, bismuths compounds are safe and less expensive as compared to the Ir-catalysts that facilitated deborylation. Numerous screening experiments on both substrates and other metal salts afforded a better understanding of how these novel deborylations can be applied in various synthetic settings and provided insight into possible mechanisms.

To Yue and Mei

ACKNOWLEDGEMENTS

Dr. Robert E. Maleczka Jr

Dr. Milton R. Smith, III

Dr. Babak Boham

Dr. Kevin Walker

Dr. William D. Wulff

Dr. Luis Sanchez

Steve Polious

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Chapter 1. Introduction of Ir catalyzed borylation /deborylation

1.1. Significance

According to Roughley and Jordan in 2011,[1] "The Suzuki cross-coupling reaction is the single most numerous reaction within the C–C bond forming group, accounting for 40% of all such reactions". Thus for cross-couplings (Figure 1) and other organoboron transformations, the synthesis of aryl and heteroarylboronic esters is an important operation for pharmaceutical chemists.[2]

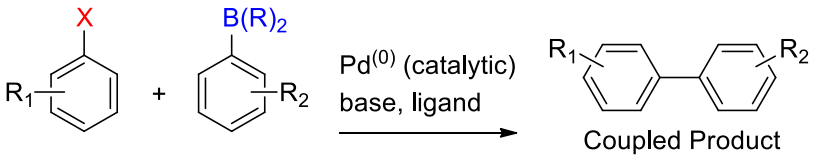


Figure 1. Suzuki cross-coupling reaction

Often, the synthesis of these compounds is carried out from Grignard or lithium species generated via metal-halogen exchange or from halide-containing precursors via Miyaura coupling (Figure 2). These and related methods suffer from the need for halogenated starting materials, pyrophoric bases and/or cryogenic temperatures.[3]

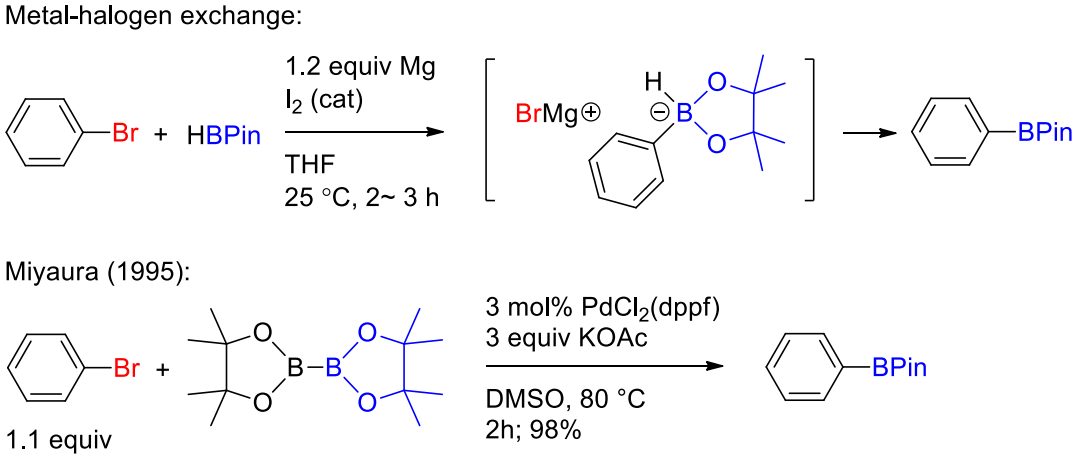


Figure 2. Preparing the aryl boronic ester

Chemists have recently developed ways to avoid these unfavorable conditions when preparing aryl and heteroarylboronic esters. In 1999, the Smith group demonstrated an Ir-catalyzed arene C-H activation/borylation process that operates thermally and proceeds without the need for stoichiometric bases or additives (Figure 3).[4]

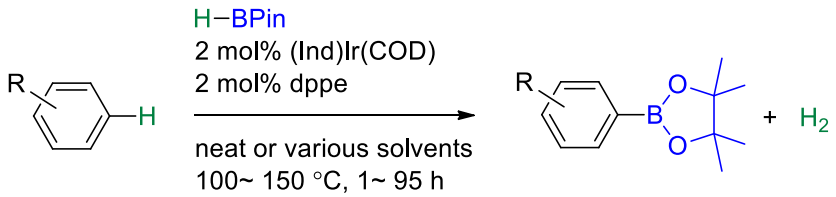


Figure 3. Example of a C–H activation/borylation

1.2. Highlights of Ir-catalyzed aromatic C-H activation/borylation

Iridium catalyzed C–H activation/borylations not only allow for the direct replacement of an aromatic hydrogen with a boronic ester, but also tolerate numourous functional groups. The products can be readily employed in other transformations, such as cyanations, Suzuki couplings, oxidations, halogenations, etc. (Figure 4).[5]

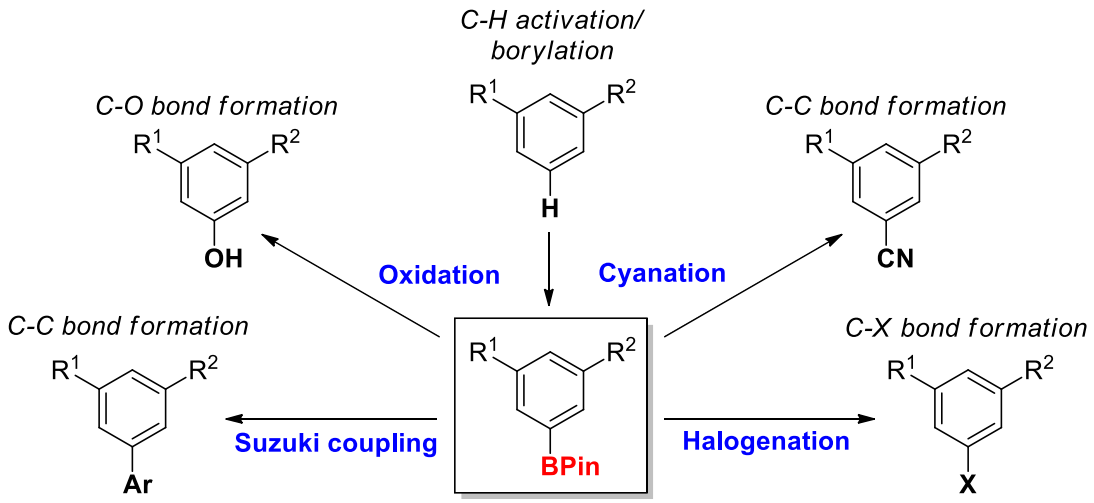


Figure 4. Synthetic utility of borylated arenes

It is notable that the iridium catalyzed C–H activation/borylation regioselectivity is directed by sterics, as opposed to electronics, complementing electrophilic aromatic substitution and

functional group-directed metalation. Synthetic utilization of this characteristic allows access to structures that are often inaccessible via traditional routes. 3-Bromo-5-chlorophenol highlights the challenges of using classical chemistry to prepare a contra electronically substituted benzene (Figure 5). For over 75 years the most "efficient" synthesis of this phenol was by Hodgson and Wignall who used ten steps and started with TNT![6]

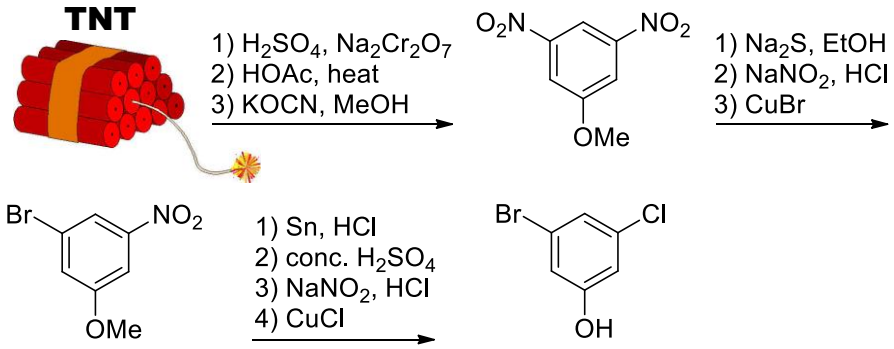


Figure 5. Synthesis 3-Bromo-5-chlorophenol via traditional route

By utilizing the key features of C-H activation/borylation method, namely the ability to select for specific hydrogens and to follow the borylation with other reactions (e.g. oxidations) in a one-pot fashion, 3-bromo-5-chlorophenol was obtained in two steps and in 79% yield from commercially available 1,3-bromo chlorobenzene (Figure 6).[7]

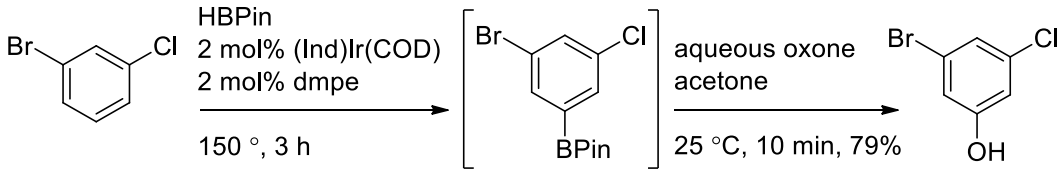


Figure 6. Synthesis 3-Bromo-5-chlorophenol via our method.

Given the selectivity and atom economy (H_2 is the only stoichiometric byproduct) of these reactions, iridium catalyzed C–H activation/borylations also represent an example of green chemistry. Another green aspect of the method is that it can eliminate the need for halogenated

starting materials, which can lower the expense of preparation or avoid its potential harmful to biological organisms.

1.3. Iridium catalyzed deborylation

One pot transformation we wanted to explore is boron-deuterium exchange. As shown in Figure 7[8], 1,2,3-trichlorobenzne had been subjected to a one-pot Ir-catalyzed C–H borylation/deuteration. The deuterium coorpration in the product was low owing to that incomplete borylation in step 1. To obtain high deuterium incoorpnation the borylated material was purified. Interestingly, when isolated 1,2,3-trichlorobenzene-5-BPin was subjected to the same deuteration condition as step 2 protiodeborylation was not observed. However, by adding fresh Ir catalyst to this reaction with pure boronic ester, 1,2,3-trichlorobenzene was regenerated. This indicated that the observed deborylations were Ir-catalyzed.

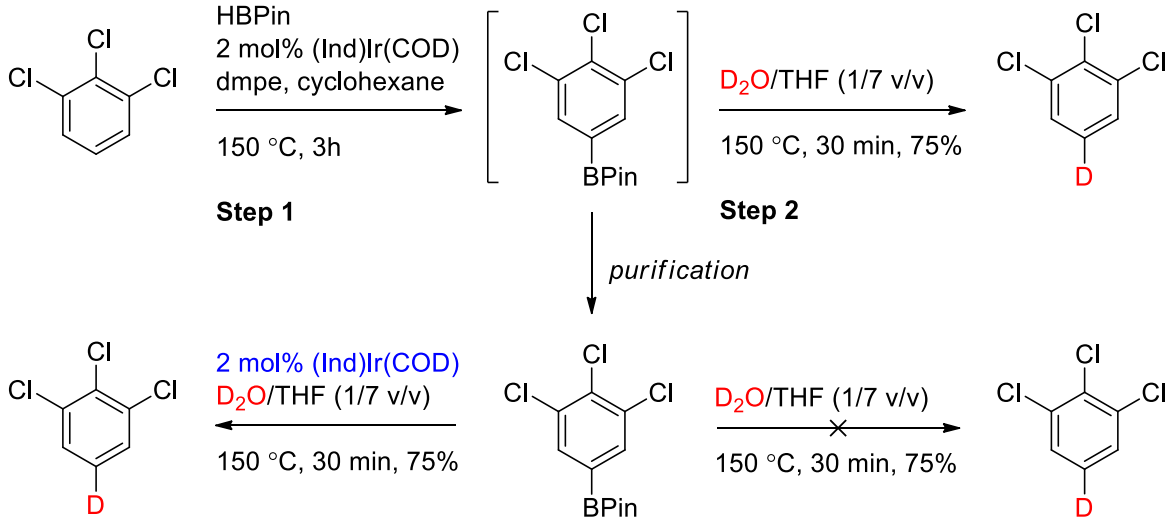


Figure 7. Discovery of Ir catalyzed deborylation during the borylation of trichlorobenzene

A full mechnistic study on these deborylation have not yet been conducted. However, Smith and his co-workers suggested the possible mechanism for this process, which is illustrated in Figure 8.[8]

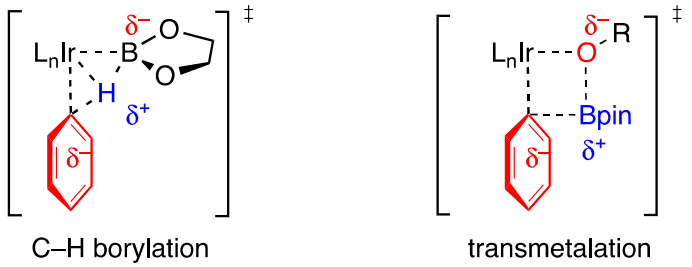
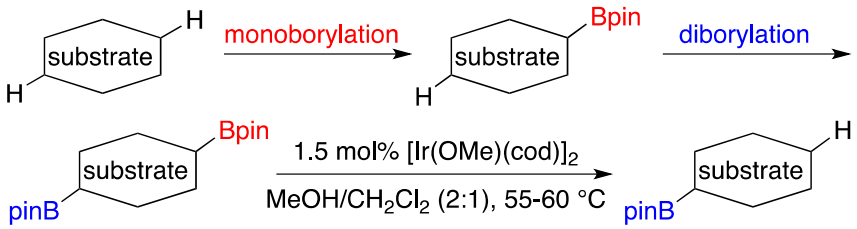
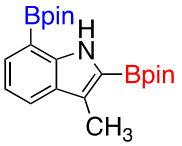
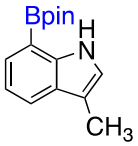
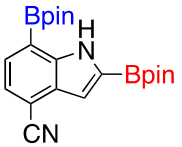
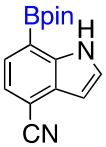
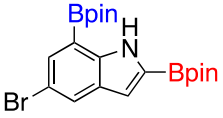
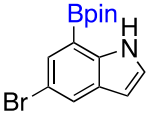


Figure 8. Putative mechanism of Ir-catalyzed borylation/deborylation

It is possible to install more than one BPin into a substrate. For example, when exposed to excess B_2Pin_2 indole substrates borylate at the 2-position quickly, afterwards a second BPin is then installed at the 7-position. Investigation into the Ir-catalyzed deborylation of such diborylated species revealed an interesting and useful trend. The first boron "on" during the Ir-catalyzed borylation was the first boron "off" in the Ir-catalyzed deborylation.[8]

Table 1**.** Synthesis of monoborylated compounds via diborylation/deborylation



entry	diborylated compound	product	time,[b] yield
1			0.75 h, 68%
2			1 h, 85%
3			1.75h, 83%

Thus, the diborylation/deborylation sequence shown in Figure 8 can afford 7-borylated protected tryptophan, which complements the regioselectivity of mono-borylating the tryptophan starting material.[8] A tryptophan-based building block prepared in this manner has been utilized in model studies toward the development of a novel convergent route to the TMC-95 core. A discussion of these efforts is described in next chapter.

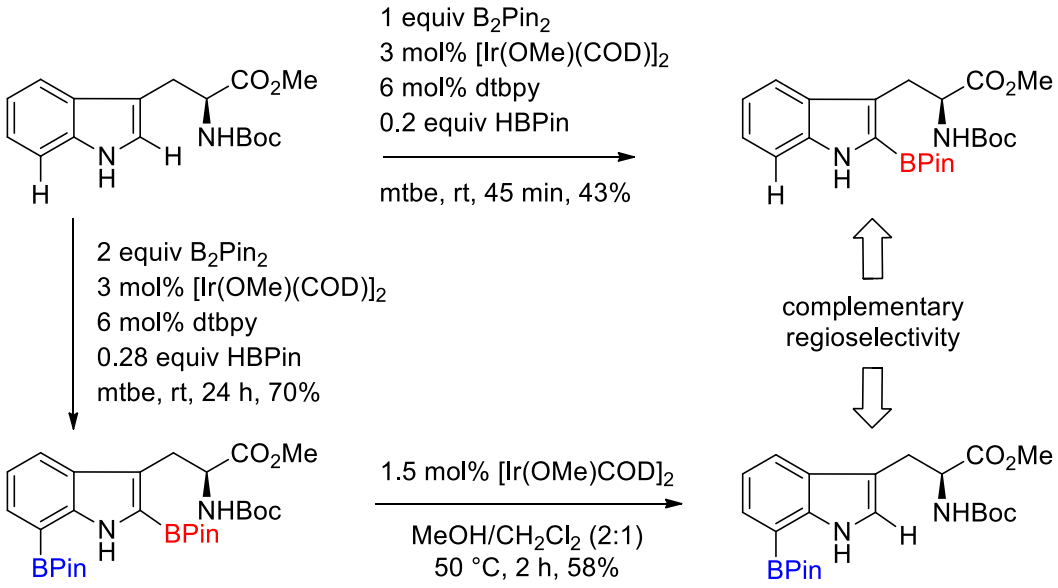


Figure 9. Ir-catalyzed borylations and deborylation on protected tryptophan

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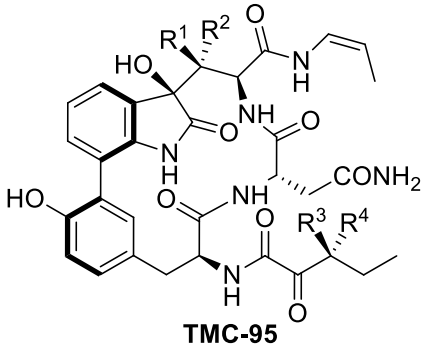
Chapter 2. Model studies for the synthesis of the TMC-95 core

2.1. Target choice and significance

The isolation of TMC-95A–D (Figure 10), a novel family of fungal metabolites with a distinctive cyclic peptide structure, from a fermentation broth was reported in 2000.[1] Their intriguing structure was accompanied by remarkable activity and selectivity as proteasome inhibitors.[2] Such bioactivity makes them promising agents for the treatment of immune and other diseases.[3]



	R^1	R^2	R^3	R^4	
A	H	OH	CH_3	H	Most active proteasome inhibitor
B	H	OH	H	CH_3	
C	OH	H	CH_3	H	
D	OH	H	H	CH_3	

Figure 10. TMC-95 nature products

Owing to such properties, a number of groups embarked on efforts to synthesize TMC-95 A and its analogs. Such synthetic efforts were aimed at furthering the understanding of these molecules biological activity, but also used TMC 95 as a vehicle to advance new chemical methods. Similarly, we viewed TMC-95 as an excellent opportunity to demonstrate the power of our group's Ir-catalyzed C-H activation/borylation/deborylation chemistry through its use as a tool to access these compounds in a highly efficient and environmentally or "green" friendly way.

2.2. General analysis of the reported synthesis of TMC-95 compounds

The distinctive cyclic peptide structure of TMC 95A is composed of a highly oxidized L-tryptophan, (Z)-1-propenylamine, L-tyrosine, L-asparagine and 3-methyl-2-oxopentanoic moiety. Two major retro synthetic disconnections were evident for this macrocycle (Figure 11). One of the disconnections is at the aryl-aryl linkage, which in the forward synthetic sense could be formed by

a Suzuki cross-coupling. The other disconnection is through one of the two cyclic amide bonds. In practice, disconnection of the Trp-Asp amide bond leads to a more convergent synthesis. Either formation of the biaryl bond or the Trp-Asp bond could be used to join the major fragments *or* close the ring. Thus, one could imagine a Suzuki ring closure of compound **A** or macrolactamization of compound **B**.

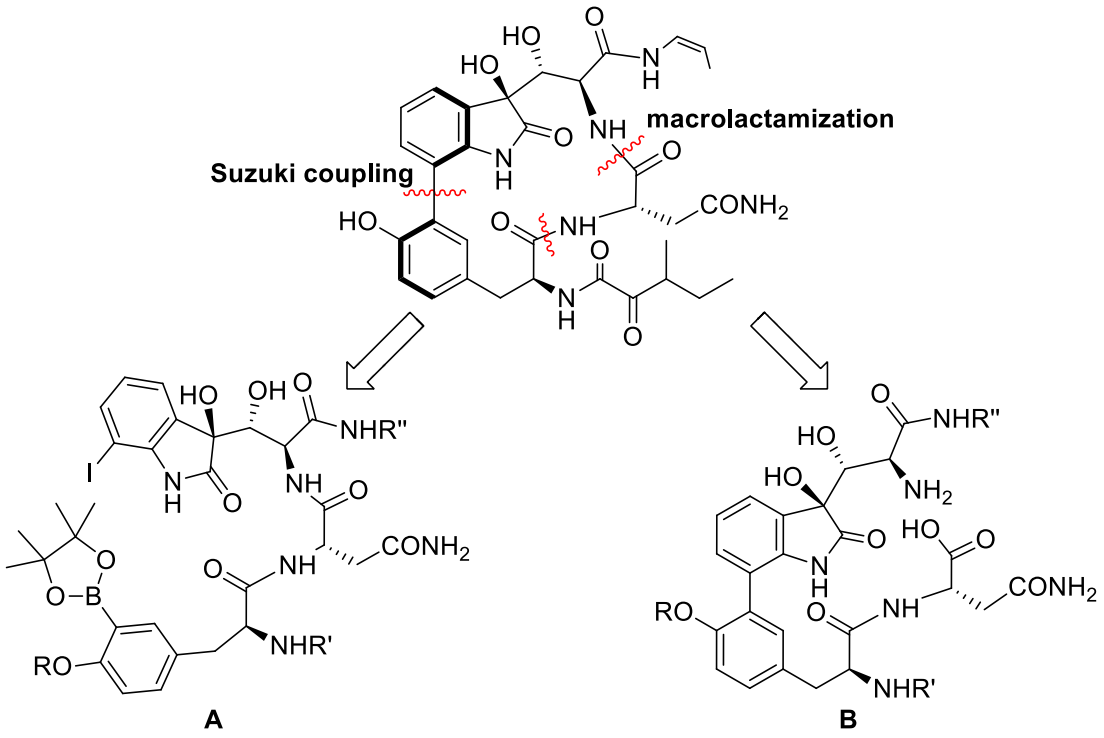


Figure 11. Retro synthetic pattern

To date, Danishefsky's group,[4] Inoue and Hirama's group[5] and the Williams' group[6] have successfully synthesized TMC-95. In all three cases they built a dipeptide chain similar to compound **B** first (Figure 12) and then closed the ring by macrolactamization.

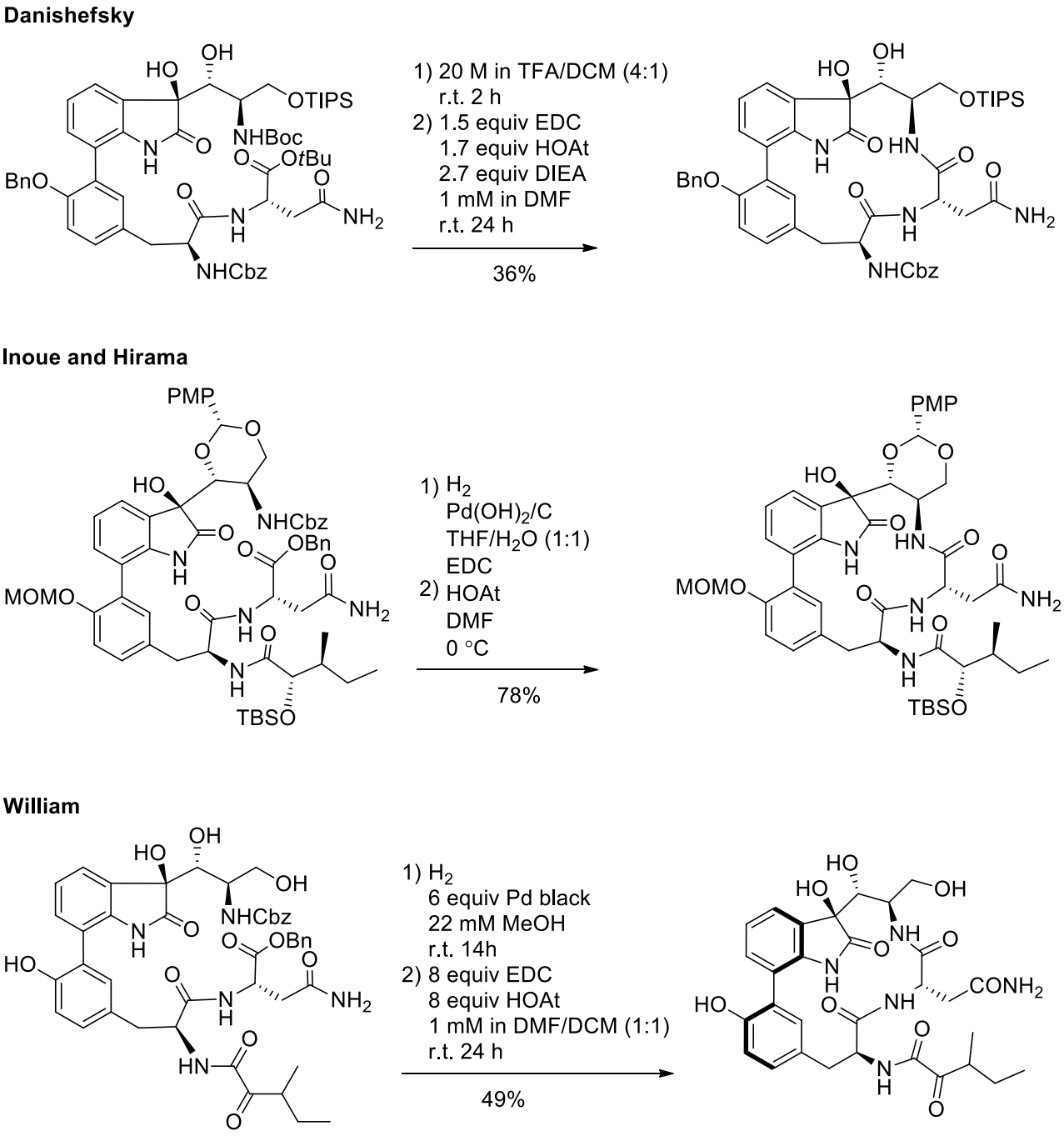


Figure 12. Ring Closure by macrolactamization

For the ring closure, Danishefsky's group used EDC/HOAt-mediated amidation that afforded a 36% yield of the macrocycle. This cycloamidation pathway has been used by most of the research groups in their subsequent TMC-95 syntheses (Figure 12).

Besides the total syntheses, there have been a considerable number of reports on the preparation of TMC-95 analogs, particularly coming from the Moroder[7] and Vidal groups[8]. In Moroder's analog, he noticed even with a racemic mixture at the C3 chiral center of the oxidole, which resulted from the oxidation of the indole moiety, only the exact 3*S* cyclic stereoisomer was formed (Figure 2-2).

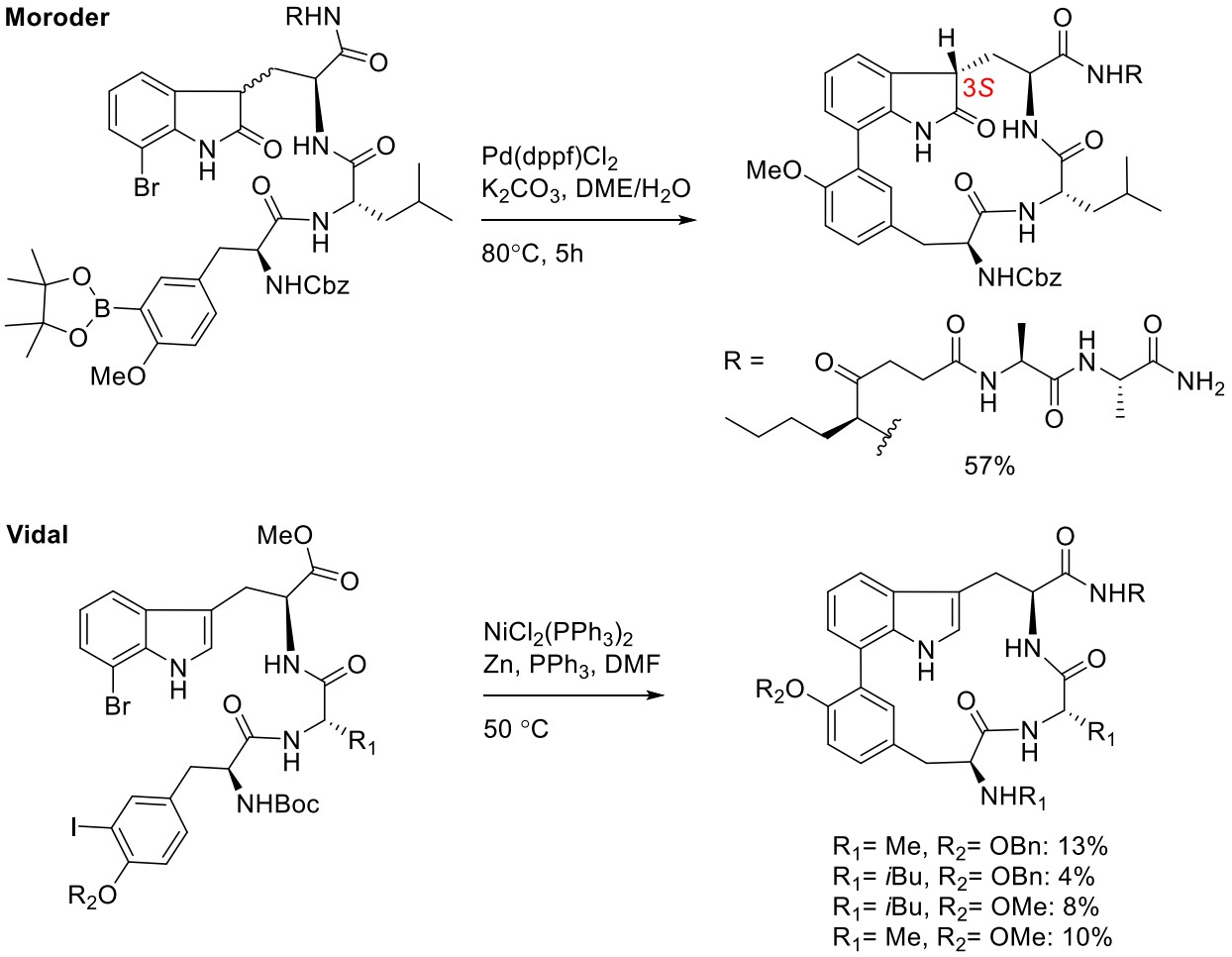


Figure 13. Ring closure by cross coupling reactions

Vidal also replaced the highly oxidized tryptophan, but this action led to rather disappointingly fact low yields during nickel catalyzed intramolecular Negishi cross-couplings (Figure 13). This finding is consistent with what Moroder inferred, that a sp^3 center is needed at the indole 3-position to ensure a successful ring closure.

2.3. Our synthetic approach to the TMC-95 core

Our TMC-95 core synthesis also substitutes the highly oxidized tryptophan with a tryptophan. In other words, the "required" sp^3 hybridized C3 oxidole structure is lacking in our synthesis (Figure 14). However, we thought to test if switching the reactant partners in the Suzuki-cross coupling partners would offer different results. Specially, we wanted to examine the cross coupling of a 7-BPin-Trp and a halide bearing tyrosine. An efficient route to intermediate **2-2**, which contains an L-tryptophan-based structure with a reactive pinacolboryl functional group at the 7-position would provide access to a cyclic tripeptide **2-1** through Suzuki coupling.

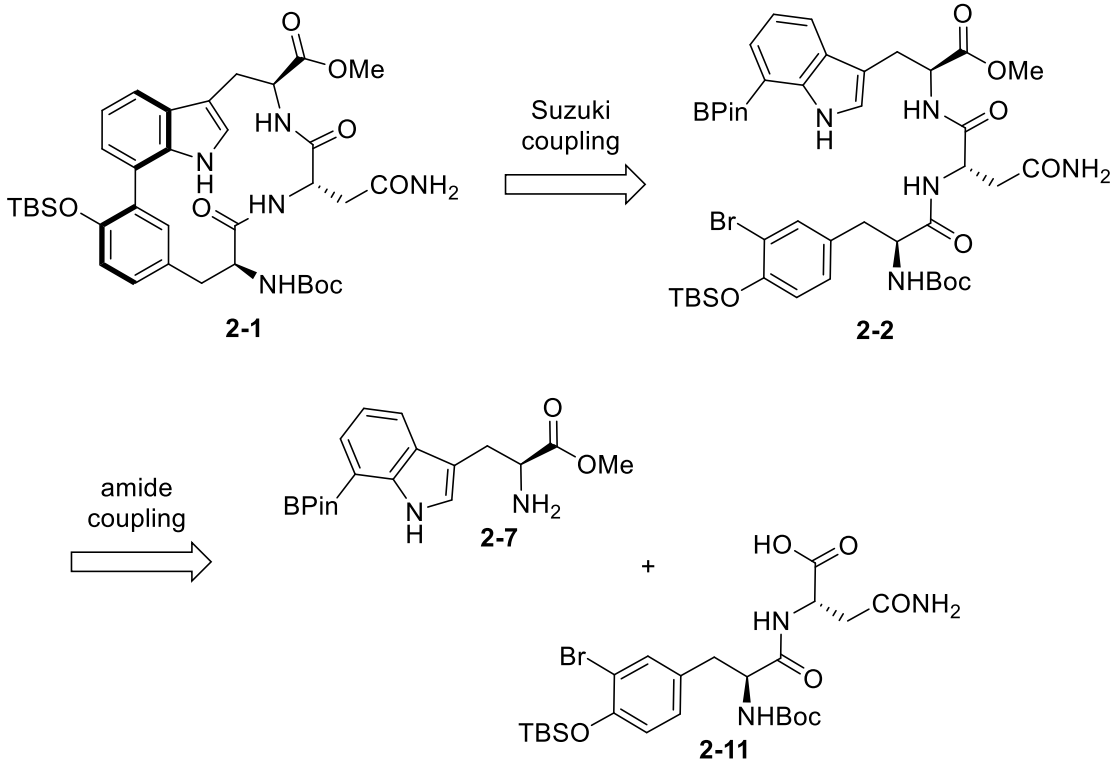
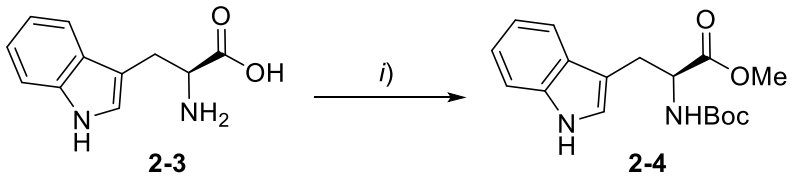


Figure 14. Retro synthetic design of our approach

2.4. Results and discussion

Synthesis of 7-pinacolboryl-L-tryptophan methyl ester (***2-7***). One of the building blocks for **2-2** was the N-Boc methyl ester of tryptophan **2-4**, which was converted to its 7-BPin derivative **2-7**

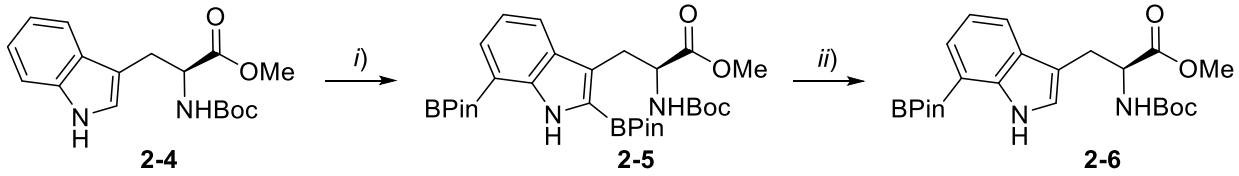
for a subsequent peptide coupling step. To start the synthesis of **2-7** both the amine and carboxylic acid groups were protected as a Boc carbamate and methyl ester, respectively (Figure 15).



i) a) 2.5 equiv $SOCl_2$, MeOH, 94%;[9] b) $NaCO_3$, Boc_2O, 80%.[10]

Figure 15 Protection of L-tryptophan

Now with compound **2-4** fully protected we were ready to apply our key borylation/deborylation sequence (Figure 16). First diborylation of **2-4** gave BPins at the 2 and 7 positions, then 7-borylated protected tryptophan **2-6** was obtained by deborylation which followed the rule of the first boron on during the Ir-catalyzed borylation being the first boron off in the Ir-catalyzed deborylation. The overall yield in these was 55%[11], which gave the functionalized building block for TMC-95 biaryl formation.

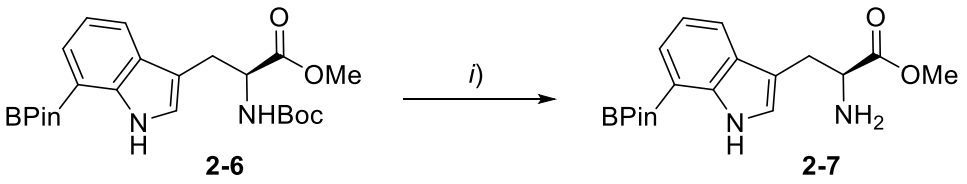


i) 2 equiv B_2Pin_2, 3 mol% $[Ir(OMe)(COD)]_2$, 6 mol% d^{t}bpy, 0.28 equiv HBPin, THF, r.t. 24 h, 70%; *ii*) 1.5 mol% $[Ir(OMe)COD]_2$, MeOH/CH_2Cl_2 (2:1), 50 °C, 2 h, 55% of **6** and 28 % of **5**

Figure 16. Preparation of a 7-pinacolboryl-L-tryptophan derivative

A key step in the reaction sequence to **2-1** required N-Boc deprotection of an early-stage precursor **2-6**. While TFA is the most commonly used reagent for Boc deprotection in peptide chemistry.[12] Attempts at converting **2-6** into **2-7** by treatment with TFA resulted in non-specific cleavage of the methyl ester and release of the BPin group. Efforts to control the rate of TFA addition and

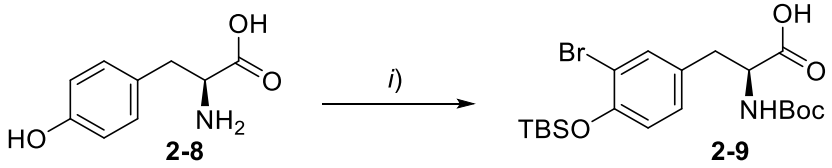
keeping the reaction temperature low did not alleniate this problem. Thus, Lewis acid $BiCl_3$, a milder Boc deprotection reagent, was tested at various concentrations in reactions containing **2-6**. Stoichiometric amounts of $BiCl_3$ gave the best conversion to **2-7**, in contrast to the catalytic quantities employed in the original report.[13] Under these conditions Boc deprotection of **2-6** with $BiCl_3$ provided **2-7** in 133% crude yield (Figure 17). The preparation of building block **2-7**, containing a BPin group at C-7 and a free amine, encouraged the development of a route to dipeptide **2-11**.



i) 1.2 equiv $BiCl_3$, CH_3CN/H_2O (50:1), 60 ºC, 2 h, quantitative (used crude in following step)

Figure 17. $BiCl_3$-mediated deprotection of a 7-pinacolboryl-L-tryptophan derivative

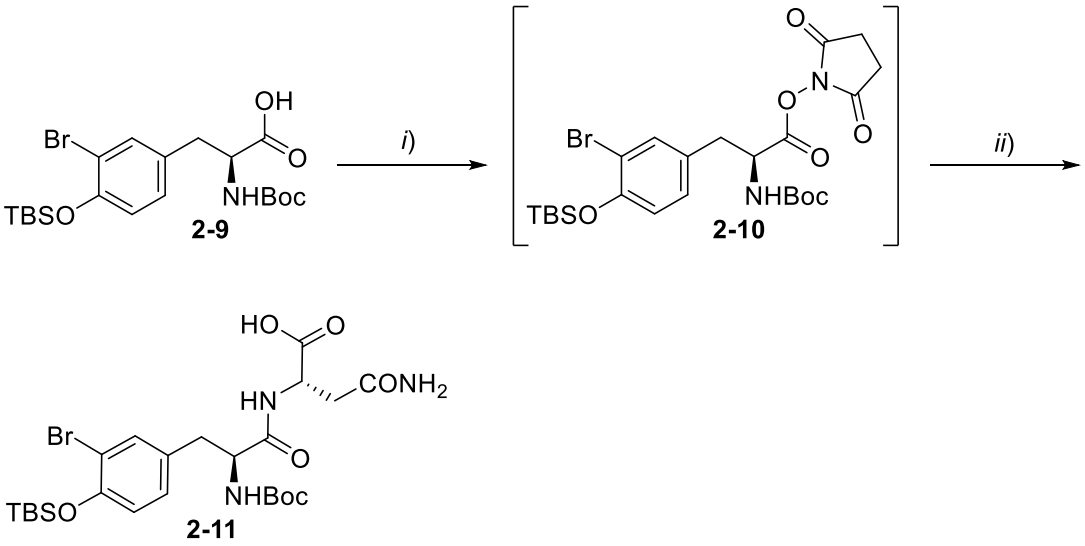
Synthesis of Dipeptide (***2-11***). To acquire dipeptide **2-11**, L-tyrosine **2-8** was converted to its arylbromo derivative by acetic acid-catalyzed bromination.[14] The resulting compound was *N*-Boc protected and then the phenol hydroxyl group was protected as a TBS ether to afford **2-9** in 70% yield (Figure 18).[15]



i) a) Br_2, HBr/AcOH, r.t. 89%; b) Boc_2O, *t*BuOH/H2O, pH 9, r.t. 89%; c) TBSCl, imidazole, then K_2CO_3, H_2O,r.t. 70% of **9**

Figure 18 Preparation of the tyrosine unit for the synthesis of the TMC-95 core

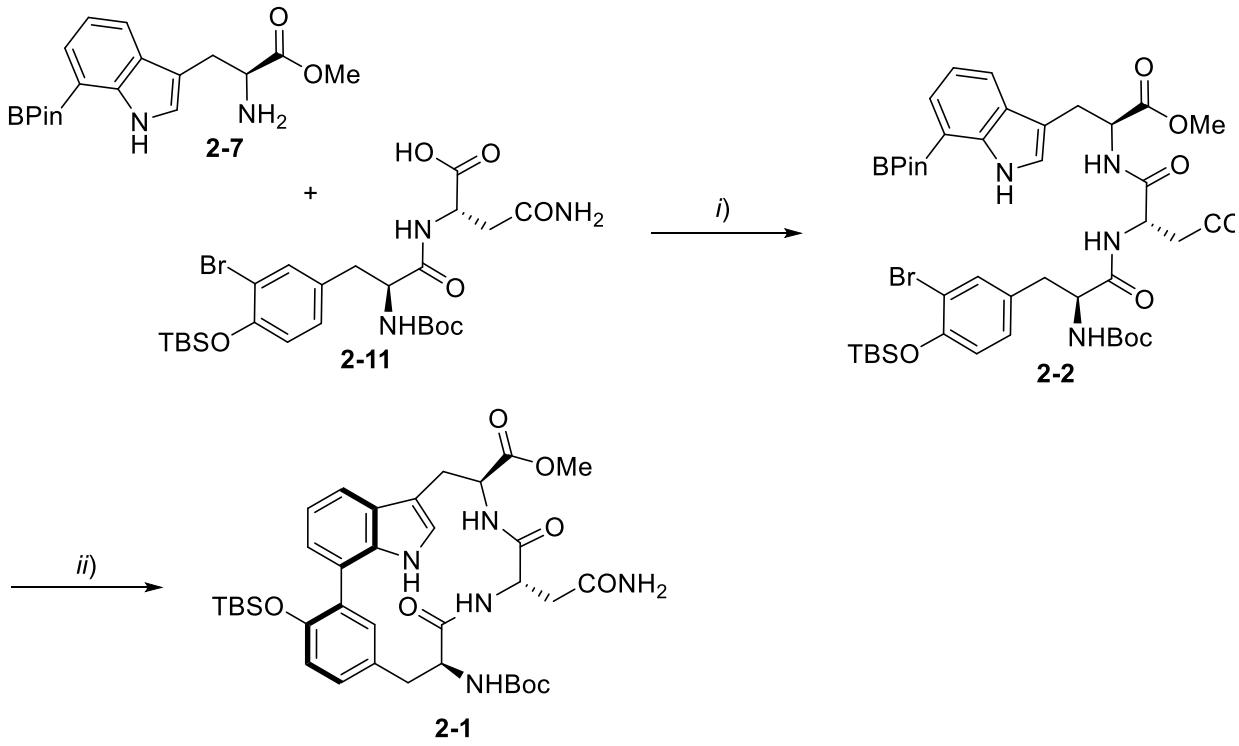
Compound **2-9** was activated to its hydroxysuccinimide ester **2-10** and coupled to L-asparagine monohydrate in one step. This method precluded the need to protect and subsequently deprotect L-asparagine as an ester. This convenient "one-step" reaction afforded dipeptide **2-11** in 79% yield (Figure 19).[16] Thus, the resulting dipeptide **2-11**, with its free carboxylic acid group, was already poised for the formation of the tripeptide **2-2**.



i) *N*-hydroxysuccinimide, DCC, DCM, r.t. 4 h; *ii*) L-asparagine, $NaHCO_3$, dioxane, water, 79% **2-11**

Figure 19. Preparation of a tyrosine-asparagine dipeptide

*Synthesis of Tripeptide (**2-2**) and Its Ring-Closure*. Dipeptide **2-11** was further coupled with **2-7** (Figure 2-8) to afford the first model tripeptide **2-2** in 68% yield (Figure 20)**.**



i) a) EDC, HOBT, NEt_3, THF, 0 °C to r.t. 68%; b) cataXium A, Pd_2dba_3, CuCl, K_2CO_3, dioxane/H_2O, at 60 °C

Figure 20. Preparation of a tripeptide and followed with the Suzuki coupling reaction

With an ample supply of **2-1**, high throughput screening of coupling conditions were explored to find an operative catalyst and reaction conditions. After 268 experiments stoichiometric CuCl, catalytic Pd_2dba_3, and cataXium ligand emerged as the first successful coupling conditions for the formation of **2-2**.[17] The coupling occurred in 30% yield and was accompanied by an undesired isomer. Optimization of these conditions for the selective formation of **2-6** and its oxidation to afford the TMC-95 core are currently underway.

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REFERENCES

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Chapter 3. Bismuth acetate as a green (and sometimes pink) catalyst for the selective protonation of substituted indoles

3.1. Prior art

Arylboronates are versatile synthetic building blocks.[1,2] Iridium catalyzed C–H activation/borylation reactions are a green way of making such compounds as such reactions can obviate the need for prior functionalization (e.g. halogenation), pyrophoric reagents, cryogenic conditions, etc.[3] While the regioselectivity of aromatic C–H borylations is mainly driven by steric effects, C–H acidity is a secondary driver.[4] For example, Ir-catalyzed borylation of unprotected indoles first installs a Bpin group at C2 and then upon further reaction at C7.[5]

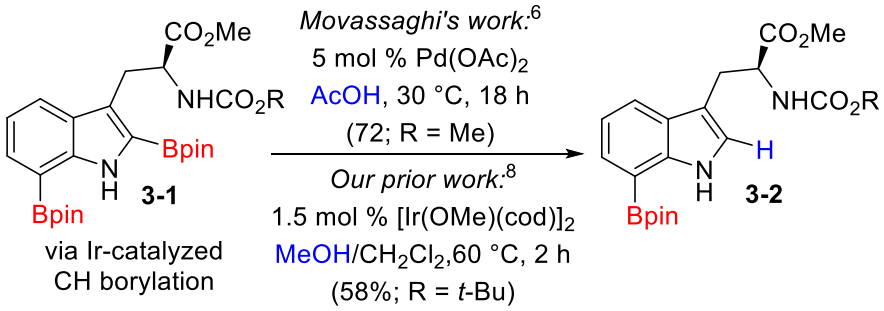


Figure 21. Prior art

Recently, Movassaghi and co-workers[6] showed that the 2,7-diborylation of tryptophans, tryptamines, and 3-alkylindoles could be followed by in situ palladium-catalyzed C2-protodeboronation to selectively afford the C7-products (Figure 21). While at first glance this tactic may not seem "green" owing to the loss of atom economy, from a strategic perspective such a borylation/protodeboronation sequence enables a streamlined approach to 7-borylated indoles that are otherwise difficult to access without additional steps and/or prefunctionalization.[7] We too had observed selective deborylations of a number of diborylated heterocycles, including several 2,7-diborylated indoles (Figure 21).[8] Our protodeboronations were Ir-catalyzed, and for some systems could be performed by simply exposing the crude borylation mixture to protic material.

Perhaps most usefully, we noted that for diborylated indoles, azaindoles, thiophenes, and benzthiophenes the first Bpin "on" during the Ir-catalyzed borylation was the first Bpin "off" in the Ir-catalyzed protodeboronation.

3.2. Discovery and development of bismuth mediated deborylation

Unanticipated synthetic problems that arise during a total synthesis can inspire the invention of new synthetic methods that solve the problem at hand as well as benefit future syntheses. This proved true during our synthetic work. During the preparation the 7-borylated product **3-2** as shown in Figure 3-1, the next step in the synthesis called for $BiCl_3$ promoted for the removal of the Boc group[9] (Figure 22). Close examination of this deprotection revealed that **3-3** formed along with trace amounts of byproduct **3-4** where the C7-BPin was missing.

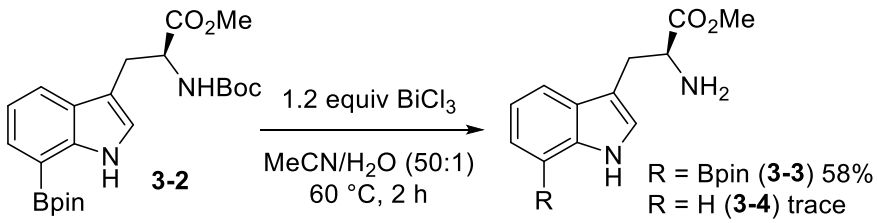
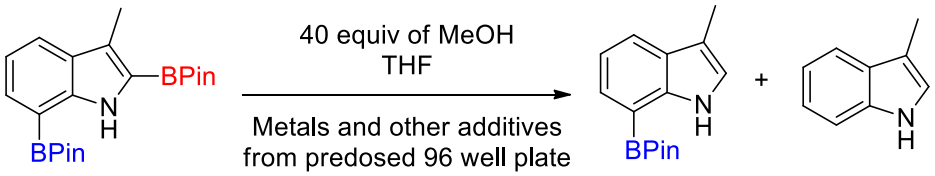


Figure 22 Discovery of Bi catalyzed protodeboronations

This small amount of deborylated byproduct led us to consider whether bismuth salts could facilitate selective protodeboronation in a way similar to the previously described Ir- and Pd-catalyzed protodeboronations. Such a method would be quite attractive since bismuth salts are earth abundant, harmless, and orders of magnitude less inexpensive than the corresponding precious metal salts.[10] We also recognized that bismuth may not be the only additive capable of facilitating deborylation. Thus, this initial bismuth mediated deborylation motivated us to screen a wide range of metal salts and other additives for their potential deborylating ability.[11] Numerous chemicals were screened for the ability to deborylate 3-methyl 2,7-bisborylatedindole (Table 2).

Chemicals screened included bases, free radical initiators, metal salts in different oxidation states, main group elements, lanthanide metals, transition metals, oxidants, reductants, etc.

Table 2. High throughput experiments on 3-methyl 2,7-bisborylatedindole deborylation



	1	2	3	4	5	6	7	8	9	10	11	12
A	control	LiCl	NaF	NaBr	NaI	NaCN	Na TFA	Na TCA	NaBF4	NaOTs	Na2SO3	Na2S2O3
B	Na2SO4	KCl	CsF	CsCl	V(acac)2	CrCl2	MnCl2	FeCl2	FeCl3	Fe (II) acac	Fe (III) acac	Co (acac)2
C	Co(acac)3	NiF2	NiBr2 /DME	Ni (II) acac	(PPh3) NiCl2	CuCl	CuCl2	CuBr	CuI	Cu (II) (acac)	(1,10-phenan)Br2 Cu II	Cp_2ZrCl_2
D	Mo(acac)	Pd(OAc)2	Pd (Cl)2dppf DCM	Pd2(dba)3	Ag2O	AgOTf	AuCl	AuCl3	Mg 325 mesh	Al 200 mesh	Cu <75 micron	Zn 100 mesh
E	Pd black	Mg(OTf)2	Ca(OTf)2	Sc(OTf)3	Zn(OTf)2	Ga(OTf)3	Y(OTf)3	In(OTf)3	Sn (II) OTf2	La(OTf)3	Sm(OTf)3	Yb(OTf)3
F	Hf(OTf)3	BiOTf3	Boron oxide	Al(OiPr)3	Ti(OMe)4	CeCl3	ZnCl2	K2CO3	KHCO3	KOAc	K3PO4	2,2-diphenyl ethylamine
G	proton sponge	4-phenylpy	oxalic acid	BSA	citric acid	3-phenyl propanoic acid	Bu4NBr	NaBH4	PhI(OAc)2	CAN	oxone	AIBN
H	BHT	18-Crown-6	4A, MS	diamine	aminoalcohol	TPP	dppf	CataXCium A	X phos	salen	phenantroline	phenantroline

Conditions: 10 μmol substrate, 100 uL solvent, 40 equiv of each MeOH
Standard : 0.1 equiv of 1,3,5-tri-tertbutylbenzene
Reaction was monitiored at **3 time points**. 1: 4 h at 25 °C 2: 12h/ 40°C and 3: 10 h at 80 °C (Data showing here are at 25 °C for 4h)

Feedback of the high throughput screening showed that only few metal salts responded positively, including as $Bi(OTf)_3$, $Bi(OAc)_3$, CuCl and AgO_2. Notably, not all Ag, Cu, Bi and Ir salts worked, for example even $BiCl_3$ proved to be a fairly poor deborylating reagent and only gave trace amounts of product. Ag_2O and CuCl gave fast deborylations, but removed both the BPins from substrates.

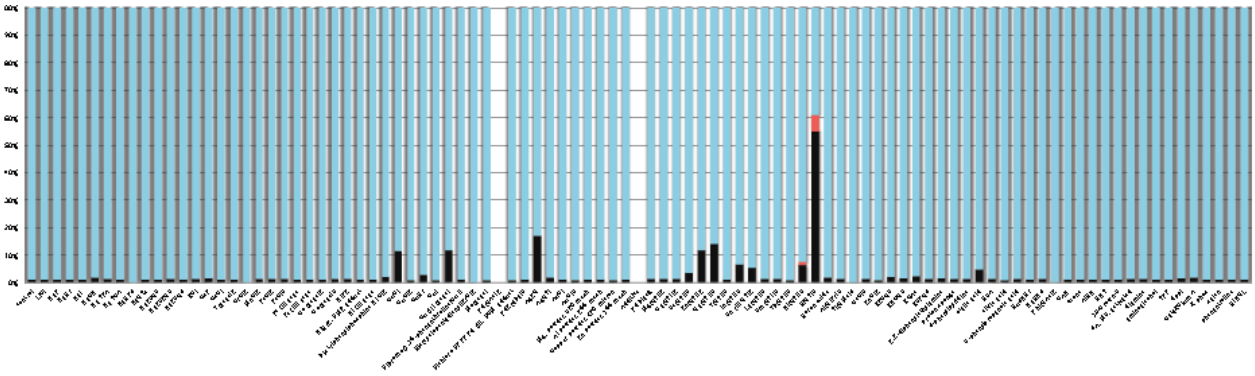


Figure 23. Deborylation feedback from high throughput screening

Having screened a series of metal salts against one substrate, we next screened a series of substrates against the Cu, Ag, Bi and Ir salts that emerged from the first screening (Figure 24). $Bi(OAc)_3$ showed selectivity, only efficiently deborylating heterocycles when the BPin was α to the heteroatom. In contrast, arenes or heterocycles where the boron was remote to the heteroatom, required Ir or Ag salts for facile deborylation. Finally, when boron was on the aryl moiety of the substrates explored, deborylation was the quickest with Ag, deborylation did not occur with Bi, and was slow with Ir.

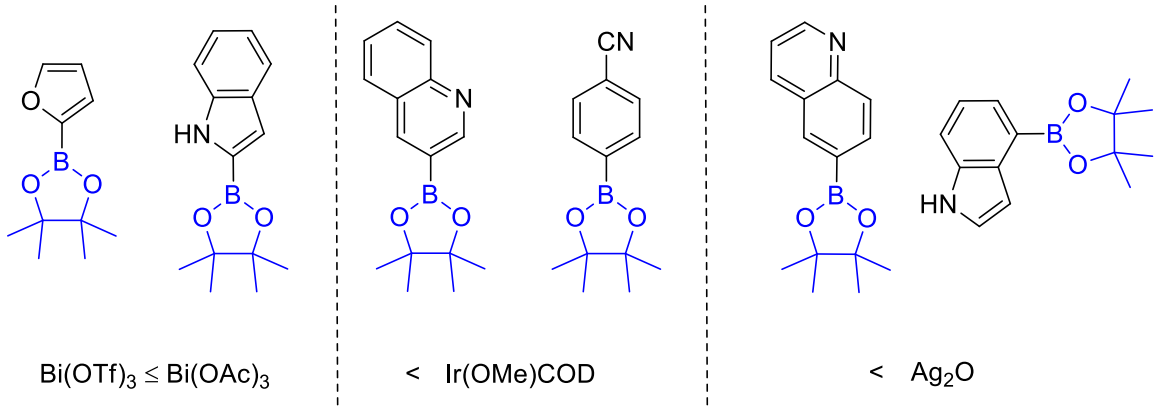


Figure 24. Study on the relative rate of deborylations

3.3. Results and discussion

These data gave us some sense what catergory of substrate responds best to different deborylation conditions. We thought to use the obsevered differential reactivity to selectively deborylate di- or triborylate indoles with the aim of generating indoles with BPins at different positions (Figure 25).

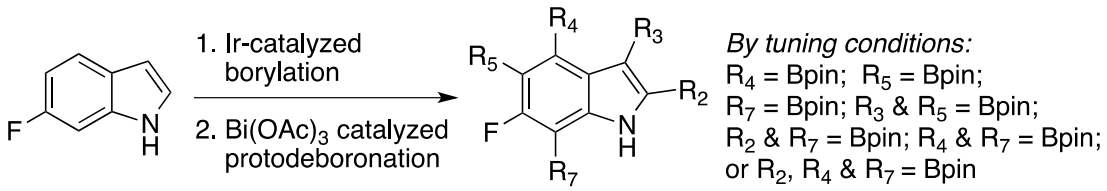


Figure 25. Aiming to borylated all position on the substrates has indole moiety

After screening several bismuth salts,[11] $Bi(OAc)_3$ emerged as the Bi-catalyst of choice. Subjecting purified **3-1** to 20 mol % $Bi(OAc)_3$ in MeOH (127 equiv) and THF at 80 °C (sealed tube) for 7 h afforded 7-borylated **3-2** in 90% yield (Figure 26).

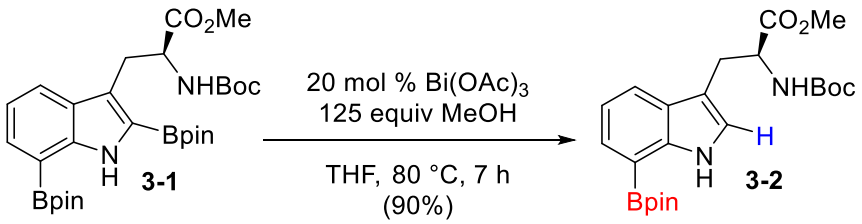
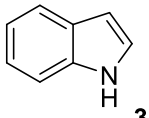
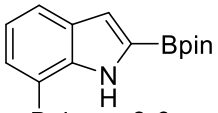
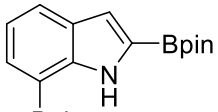
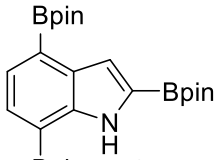
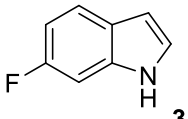
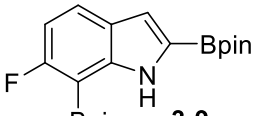
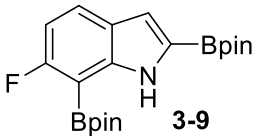
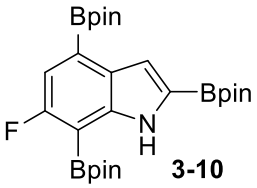
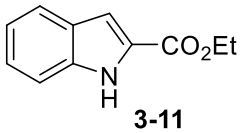
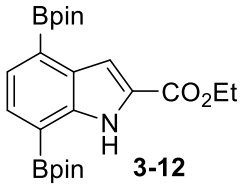
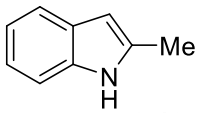
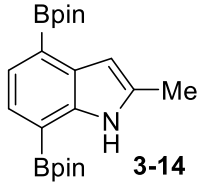
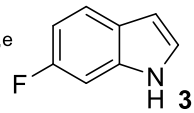
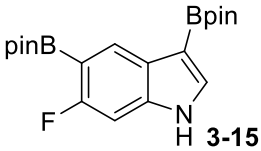
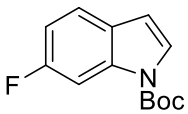
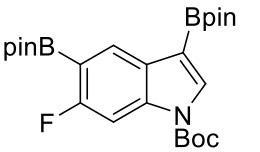


Figure 26. $Bi(OAc)_3$ catalyzed protodeboronation of 3-1

Table 3. Ir-catalyzed borylation of indoles

Entry	Starting Indole	Product	Time	Yield[a]
1[b]	 **3-5**	 **3-6**	48 h	77%
2[c]	 **3-6**	 **3-7**	12 h	96%
3[b]	 **3-8**	 **3-9**	24 h	82%
4[c]	 **3-9**	 **3-10**	12 h	92%
5[b]	 **3-11**	 **3-12**	12 h	84%
6[b]	 **3-13**	 **3-14**	24 h	71%
7[d,e]	 **3-8**	 **3-15**	5 h	90%
8[e]	 **3-16**	 **3-17**	3 h	80%

[a]Isolated yields. [b]Borylations ran with 2.0 equiv B_2pin_2, 0.5 mol % $[Ir(OMe)COD]_2$, 1 mol % d^{t}bpy, at 80 °C. [b]Borylations ran as described above, but with 1.0 equiv B_2pin_2. [d]Substrate stirred in neat HBpin (4 equiv) at rt for 1 h before being subjected to the borylation conditions. [e]Borylation ran with 2.0 equiv B_2pin_2, 3 mol % $[Ir(OMe)COD]_2$, 6 mol % d^{t}bpy, at 80 °C.

Given this favorable result, a series of indoles were subjected to multiple borylations (Table 3). Several of these Ir-catalyzed borylations are worthy of comment. Following C7 borylation the next site for C–H borylation proved to be C4. In this way, 2,4,7-triborylated indoles **3-7** and **3-10** (entries 2 & 4) and 4,7-diborylated **3-12** and **3-14** (entries 5 & 6) were generated.[12] We previously showed that placing a Boc[13] or Bpin[14] on the indole nitrogen directs borylation to the C3-position. Provided the C6 position is blocked, borylation of in situ N-borylated (entry 7) or N-Boc protected (entry 8) indoles occurs at the C3 and then the C5-positions, affording **3-15** and **3-17** respectively.[15,16,17]

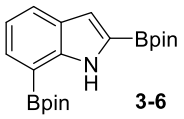
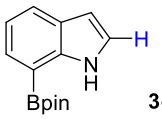
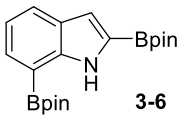
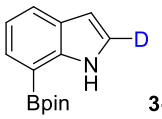
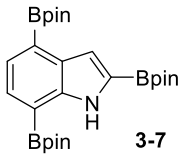
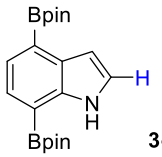
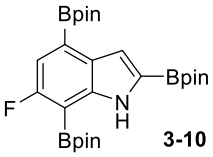
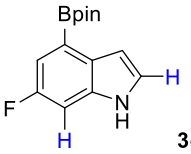
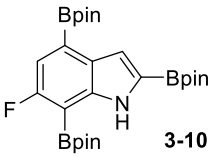
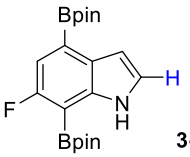
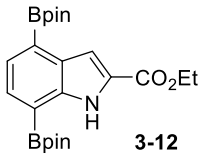
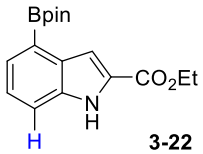
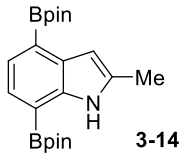
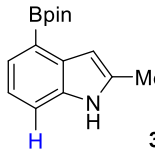
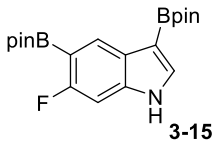
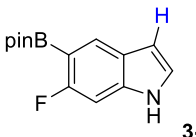
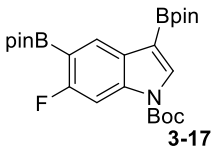
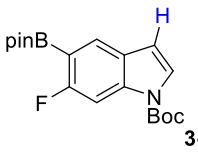
With the borylated indoles in hand, we explored their $Bi(OAc)_3$ mediated protodeboronations (Table 4). Examining first 2,7-diborylated indole (**3-6**), we found that heating this compound with 20 mol % $Bi(OAc)_3$ and 125 equiv of ACS grade MeOH in THF, afforded the 7-borylated indole (**3-17**) in 82% yield after 17 h (entry 1). Curiously, when we looked to deuterate **3-6**, the reaction was complete (79% isolated yield 84% deuterium incorporation[18,19]) after stirring with 60 equiv of 99.8% CD_3OD for 12 h at room temperature (entry 2). A closer look into these differences revealed that the grade of MeOH could significantly impact the reaction rate. For example, protodeboronation of **3-6** with sure sealed anhydrous MeOH was complete in less than three hours. Although not quantified, we suspect that common MeOH impurities such as formaldehyde, N,N-dimethyl acetamide, and dimethyl acetals of simple alkanones and/or alkanals[20] or materials that leach from the plastic bottle slow the reaction. Notably, reactions with either grade of methanol were reproducible. To highlight the method's relative robustness and economy we chose to continue our study with the lower grade methanol (reactions with either grade of methanol were reproducible, and the study of the influence by different grade of MeOH will be shown in section 3.4.).

Within these parameters, 2,4,7-triborylated indole (**3-7**) was monoprotodeboronated to afford 4,7-diborylated indole (**3-19**) in 75% yield under similar conditions (entry 3). Attempts at the selective C2/C7 diprotodeboronation of **3-7** were disappointing. While 4-borylated indole was formed as the major product, NMR analysis of the crude reaction mixture revealed a 50/45/5 mixture of 4-borylated indole/**3-19**/indole.[21] In contrast, with the aid of an increase in the amount of methanol employed 2,4,7-triborylated-6-fluoroindole (**3-10**) underwent clean diprotodeboronation to afford **3-20** in 80% yield (entry 4) when the amount of MeOH was increased. A qualitative feature of deborylating **3-10** is that upon completion the reaction mixture takes on a slight pink color. Monoprotodeboronation of **3-10** (entry 5) provided further indication that these reactions are in part substrate dependent, as relative to **3-7**, trisboylated **3-10** required less time and equivalents of methanol to achieve the selective deborylation of the Bpin at C2 in similar yields.

The protodeboronation of 4,7-diborylated-2-carboethoxy-indole **3-12** (entry 6) was instructive, if not synthetically satisfying. After 24 h at 80 °C, compound **3-12** and 40 mol % $Bi(OAc)_3$ in MeOH/THF gave monoprotodeboronated **3-22** as the major product, but this compound was formed along with fully protodeboronated **3-11** and unreacted **3-12** in a 54/9/41 ratio per NMR analysis of the crude reaction product. Despite giving a mixture, the bismuth mediated protocol offered better access to **3-22** than our recently published Ir-mediated conditions of 1.5 mol % $[Ir(OMe)COD]_2$ in 2:1 MeOH/CH_2Cl_2 at 60 °C, which when applied to **3-12** gave a ratio of 67% of the fully protodeboronated **3-11** to 33% **3-22** after 2 h. 4,7-Diborylated-2-methyindole **3-14** behaved similarly under the $Bi(OAc)_3$ conditions affording a 52/5/43 mixture of monoprotodeboronated **3-23** to **3-13** to **3-14** respectively. In practice, compound **3-14** was a substrate where Ir-mediated protodeboronation proved superior, giving a 91/9 mixture of **3-23** and starting material **3-14** with **3-23** being isolated in 74% yield (entry 7).

The 3,5-diborylated indoles (**3-15** and **3-17**) were also instructive substrates in their own right. Compound **3-15** was exclusively monoprotodeboronated at C3 by 20 mol % $Bi(OAc)_3$, in MeOH/THF after 3 h at 80 °C, affording **3-24** in 88% yield (entry 8). Deborylation of **3-15** under our published Ir-catalyzed protodeboronation conditions proved less selective. Under the Ir-conditions, the crude reaction product contained 13% of fully deboronated 6-fluoroindole (**3-8**) and **3-24** was isolated in 66% yield. Although not extensive in our efforts, attempts to optimize Ir-protodeboronation of **3-15** never met with the selectivity observed with $Bi(OAc)_3$ unless the reaction was stopped prior to complete consumption of starting material.[21]

Table 4. $Bi(OAc)_3$ catalyzed protodeboronations

Entry	Starting Indole	Product	Conditions and Yield
1	 **3-6**	 **3-18**	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 82%[a]
2	 **3-6**	 **3-18-*d*$_1$**	20 mol % $Bi(OAc)_3$, 40 equiv CD_3OD, THF, 80 °C, 2.5 h, 83%[a]
3	 **3-7**	 **3-19**	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 75%[a]
4	 **3-10**	 **3-20**	20 mol % $Bi(OAc)_3$, 250 equiv MeOH, THF, 80 °C, 15 h, 80%[a]
5	 **3-10**	 **3-21**	20 mol % $Bi(OAc)_3$, 60 equiv MeOH, THF, 80 °C, 5 h, 67%[a]
6	 **3-12**	 **3-22**	40 mol % $Bi(OAc)_3$, 375 equiv MeOH, THF, 80 °C, 16 h, (54:9:41 **3-22**:**3-11**:**3-12**)[b] Ref 8 Ir-catalysis[c] (33:67 **3-22**:**3-11**)[b]
7	 **3-14**	 **3-23**	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (52:5:43 **3-23**:**3-13**:**3-14**)[b] Ref 8 Ir-catalysis[c] 74%[a] (91:9 **3-23**:**3-14**)[b]
8	 **3-15**	 **3-24**	20 mol % $Bi(OAc)_3$, 50 equiv MeOH, THF, 80 °C, 3 h, 88%[a] Ref 8 Ir-catalysis[c] 66%[a] (87:13 **3-24**:**3-8**)[b]
9	 **3-17**	 **3-25**	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (no reaction)[b] Ref 8 Ir-catalysis[c] 47%[a] (60:40 **3-25**:**3-16**)[b]

[a]Isolated yields. [b]Ratio determined by ^{1}H-NMR of the crude reaction mixture. [c]See Supporting Information for details.

In contrast to **3-15**, Boc-protected **3-17** failed to undergo any protodeboronation by the action of $Bi(OAc)_3$ (entry 9). This substrate was susceptible to Ir-catalyzed protodeboronation, but again our previously published conditions proved too harsh, giving the N-Boc protected 6-fluoroindole as the major product (21/79 **3-25**/**3-16** in the crude reaction mixture). The ratio of **3-25**/**3-16** improved to 60/40 (47% isolated yield of **3-25**) when the protodeboronation was run with 3 mol % Ir in MeOH/THF at room temperature for 10 h.

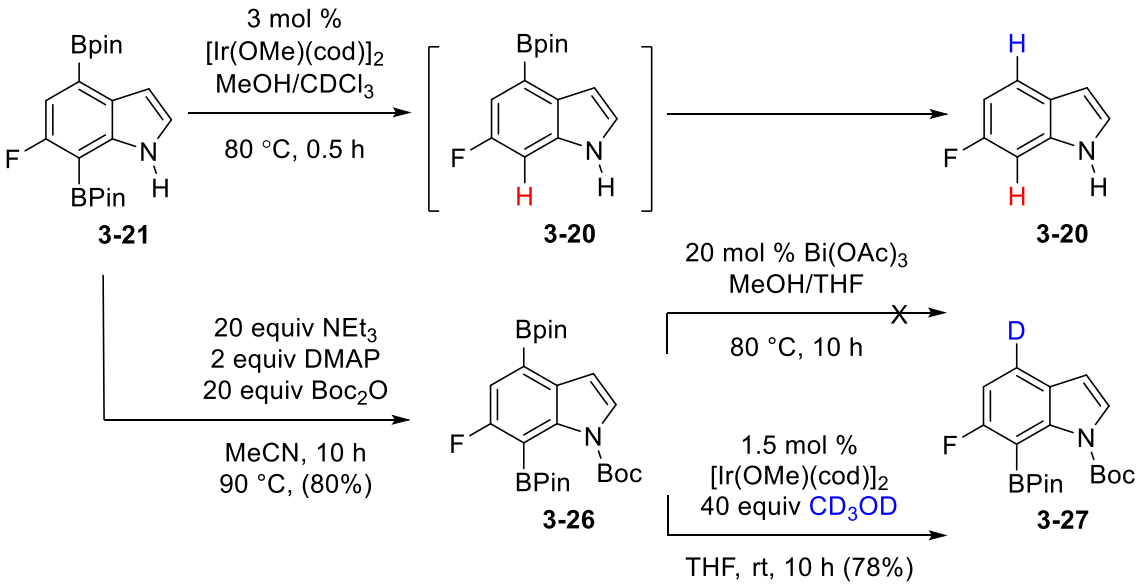


Figure 27. Changing the sequence of protodeboronation

The reactivity difference between unprotected and N-Boc-protected indoles was probed further. 4,7-Diborylated-6-fluoroindole **3-21** was converted to its Boc derivative (**3-26**) and then subjected to both the Bi and Ir deboronation conditions (Figure 27). Again, there was no reaction by $Bi(OAc)_3$. However, under the Ir-catalyzed protodeboronation conditions, using CD_3OD as the protic material, afforded the C4 deuterated product **3-27** in 78% yield. This result demonstrates that the general order of the first boron "on" being the first born "off" in Ir-catalyzed deboronations can be altered by post borylation by introducing nearby functionality that is sterically demanding.

Our conclusions on the order of deborylation obviously rests on the strength of our structural assignments of the various indoles illustrated in Figure 28. The regio-chemical assignments of compounds **3-20**, **3-21**, **3-26** and **3-27** were made as follows. For compound **3-21**, H_2 and H_3 couple with the NH and each other and therefore afford the two doublet of doublets observed at 7.27 ppm and 6.98 ppm. The NMR signal for the remaining proton H_5 would only be split by the C-6 fluorine. The doublet observed at 7.33 ppm is consistent with such a proton. Thus we have assigned compound **3-21** as having its two BPins at carbons 4 and 7. Subjecting compound **3-21** to the deborylation conditions result in the protiodeborylation of one of its BPins. The proton NMR of this compound (**3-20**) showed a new doublet of doublets at 7.14 ppm with the signal for H_7 also as a double of doublets. These coupling patterns for H_5 and H_7 are consistent with both being ortho to fluorine and meta to each other. Therefore we have assigned compound **3-20** as having a BPin at C-4. Were the BPin at C-7 the coupling pattern would be different with larger J values expected for the H_5 doublet of doublets. In fact such a doublet of doublets is observed at 7.46 ppm (dd, J = 10.3, 2.5 Hz) in the NMR of compound **3-20**. The proton NMR of **3-26** is comprised of three doublets. The doublet at 7.41 ppm and 7.01 ppm are clearly coupled to each other and were therefore assigned as protons H_2 and H_3. Again H_5 appears as a doublet with J coupling that is consistent with a proton ortho to fluorine. When compound **3-26** is mono debory-deuterated to afford compound **3-27** H_3 shifts upfield to 6.50 ppm, a chemical shift that is similar to that which is observed for Boc protected 6-fluoroindole. Furthermore, two doublets are observed, the doublet at 7.42 ppm has J values of 3.4 Hz, and while the doublet of doublets at 6.95 ppm has J values of 9.3 Hz which this coupling pattern is consistent with one proton that ortho coupled to fluorine (H_5). Hence, we are confident in the structures of compounds **3-20**, **3-21**, **3-26** and **3-27** and the conclusion that the corresponding deborylations proceeds following the first on first off rule.

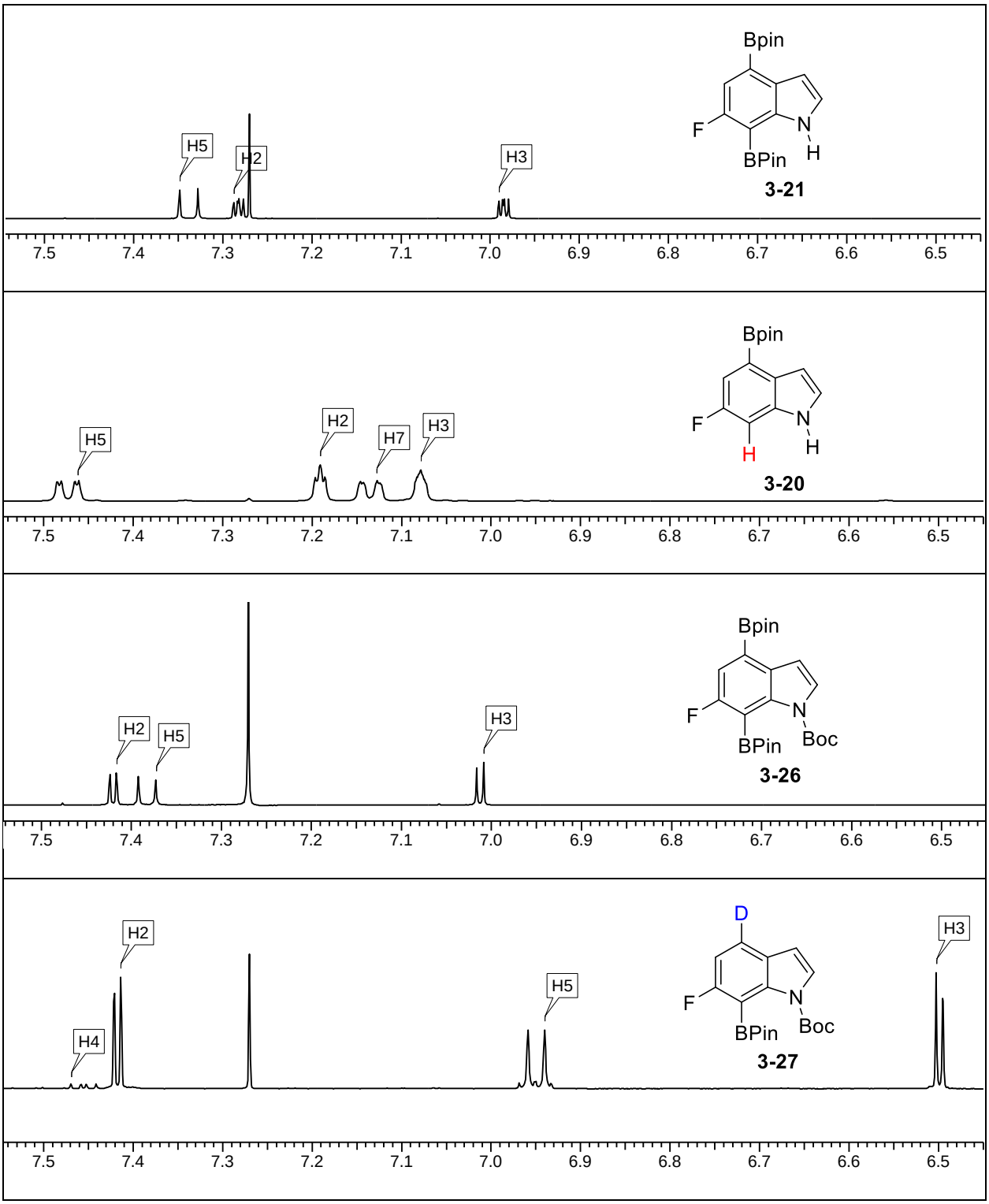


Figure 28 The protecting Boc group changed the sequence of deborylation

Having observed bismuth's ability to deborylate BPins at C-2 and C-7 of indoles, and it not being very effective at deborylating a C-4 BPin, we proposed a mechanistic explanation based on these observations. Literature examples of "Atrane"-type heterocyclic bismuth triamide are known and are prepared by the ligand exchange reaction of $Bi(NMe_2)_3$ with tris(aminoethyl)amines (Figure 29).[22]

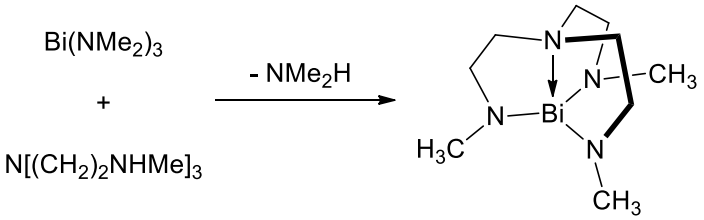


Figure 29. Figure of preparing the heterocyclic bismuth triamide

The structure of this product was characterized by X-ray crystallography, and the distance of Bi and the central coordinating N (3.021 Å) was found to be much shorter than the calculated van der Waals radii of Bi and N atoms (3.94 Å), but longer than a covalent Bi-N bond (2.180 to 2.189 Å in $Bi(NMe_2)_3$).[23] This infers that Bi-N coordination may be possible during the Bi-mediated deborylation. Hence we propose the transition states illustrated in Figure 30.

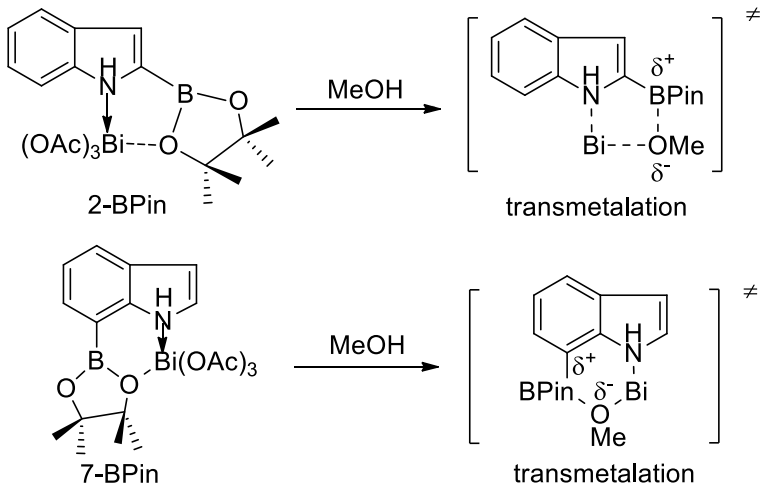
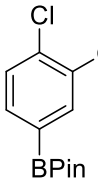
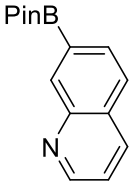
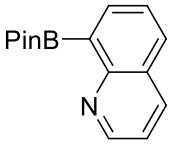
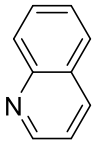
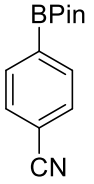
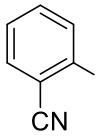
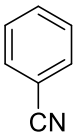
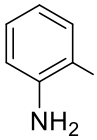
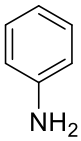
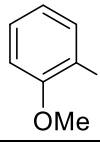
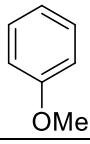


Figure 30. Putative transition states of Bi-catalyzed deborylation

To test this mechanism, more substrates were subjected to Bi-mediated deborylation. As shown in Table 5, Bi failed to deborylate halide containing arene **3-28** where neither of those two boron containing materials bare nearby heteroatoms.

Table 5. Deborylation on arenes

Arene substrates	20 mol% $Bi(OAc)_3$, MeOH, 80 °C, THF			
Entry	Substrate	Product	Time	NMR conv.
1	 **3-28**	/	48 h	0%
2	 **3-29-a**	/	48 h	0%
3	 **3-29-b**		7h	100%
4	 **3-30-a**	/	48 h	0%
5	 **3-30-b**		21 h	30%
6	 **3-31**		5 h	100%
7	 **3-32**		24 h	50%

Comparing compounds **3-29-a** and **3-29-b**, bismuth cannot deborylate the remote BPin in **3-29-a**, but can deborylate the BPin in compound **3-29-b**. This is consistence with hypothesis that deborylation is facilitated by an adjacent N atom. We also examined nitriles, which have a nitrogen

atom but where the sp hybridization would make coordination of the type illustrated in Figure 29 difficult to achive. However, 2-BPin benzonitrile **3-30-b** gave the deborylated product in 30% yield after 21 h. Meanwhile, 4-BPin benzonitrile **3-30-a** was unreactive. Thus, our hypothesis of nearby heteroatoms being a requirement of fast deborylation was only pointly supported by experiments. The exact mechnism still remains as open question.

We also wanted to explore if the presence of other heteroatom containing substituents would facilitate deborylation. Subjecting compound **3-32** to deborylation conditions resulted in 50% yield of the deborylated product. Thus, oxygen can facilitate deborylation; however, its ability to do so appears diminished as evidence by the need for the 24 h reaction time needed to deborylate **3-32** vs. 5 h for **3-31**.

In Table 4, indole substrates **3-7**, **3-12** and **3-14** were subjected to bimuth catalyzed deborylation reactions in order to selectvely remove the C-2 and C-7 BPins and keep the 4-BPin. The quantity of the catalysis load and the amount of MeOH were tuned many times; however, no good conditions were found. These additional experiments indicated that a nearby heteroatom is not an absolute requirement for Bi-mediate deborylation since some deborylation at C-4 position was aways observed.

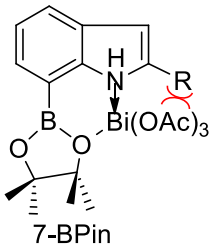


Figure 31. Proposed transition structure of 2-substituted indole during the deborylation

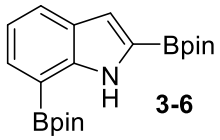
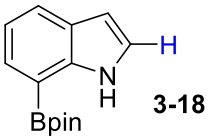
Hence through these observations we proposed the the transition structure of 2-substituted indole during the deborylation in Figure 31. The substitution group on the 2 position hindered the

coordination between NH and Bi makes an efficient and a clean Bi-mediated deborylation hard to achive.

3.4. The source of MeOH is another significant factor in Bi-catalyzed deborylation

During the course of our work we determined that the grade of MeOH used in the deborylation can significantly impact the reaction rate. This issue emerged when we explored the deborylation of **3-6** to **3-18**. Experiments initially conducted at MSU required 17 h at 80 ℃ to complete the monodeborylation of the BPin at C-2. In contrast the same deborylation conducted at Merck was complete in 2 h 45 min at r.t (Table 6). Multiple attampts by multiple individuals at MSU failed to reproduce the Merck results although the reaction was reproducble at Merck. The Merck results were initially obtained by reactions run in well plates. Hypothesizing that the different reaction vessels used by MSU and Merck might be impacting the speed of the reaction the Merck researcher performed the deborylation in the traditional glassware following MSU protocols. Even under these "MSU" conditions deborylation occurred much faster than 17 h.

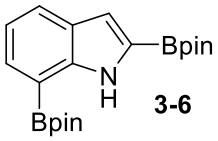
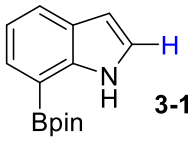
Table 6. Condition established from MSU and Merck

Entry	Starting Indole	Product	Conditions and Yield
1	 **3-6**	 **3-18**	MSU: 20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 82%[a] Merck: 20 mol % $Bi(OAc)_3$, 40 equiv MeOH, THF, rt, 2 h 45 min

Our next thought was the quality of the starting material, $Bi(OAc)_3$, MeOH or THF being used by Merck must be different than that of the reagents being used at MSU. To test this we secured all of these materials from Merck and set up a series of deborylations illstrated in Table 7. All MSU

reagents were used in entry 1 and all Merck reagents were used in row 5. We exchanged MSU, $Bi(OAc)_3$, MeOH and THF with Merck material in rows 2, 3, and 4 respectively. Running these reactions under Merck conditions of 2 h 45 min at r.t. with 20 mol% $Bi(OAc)_3$ in MeOH and THF revealed that the batch of $Bi(OAc)_3$ has little effect on the reaction as entries 1 and 2 gave similar levels of deborylation (about 10 to 12%). In contrast when the ACS grade MeOH typically used at MSU (no certificate of analysis can be found, which means the recommended use by date had passed was exchanged for sure sealed anhydrous 99.8% MeOH used at Merck the rate of deboryation showed a marked increase with 37% starting material deborylated. Replacing freshly distilled THF (MSU) with sure sealed THF (Merck) also resulted in an increase in the amount of deborylation.

Table 7. Parameters controlling experiments

Entry	Starting Indole	Product	Conditions
1	 **3-6**	 **3-18**	20 mol % $Bi(OAc)_3$, 40 equiv MeOH, THF, rt, 2 h 45 min

Row 1	Row 2	Row 3	Row 4	Row 5
$Bi(OAc)_3$ MeOH THF	$Bi(OAc)_3$* MeOH THF	$Bi(OAc)_3$ MeOH* THF	$Bi(OAc)_3$ MeOH THF*	$Bi(OAc)_3$* MeOH* THF*
Results (ratios were determined by NMR):				
3-6 : 3-18 90 : 10	**3-6 : 3-18** 88 : 12	**3-6 : 3-18** 37 : 63	**3-6 : 3-18** 57 : 43	**3-6 : 3-18** 0 : 100

*Reagents sourced from Merck

Although not quantified we suspect that common impurities in ACS grade MeOH such as formaldehyde and/ or material that may have leached from the plastic container can slow the reaction. In the case of the THF the difference between the distilled and sure sealed THF is less obvious, but the freshly distilled THF should be the most anhydrous. Thus it is possible that trace

moisture in the "Merck" THF may be facilitating deborylation. Again these results point to $Bi(OAc)_3$ mediated deborylations as being highly dependent upon the quality of the MeOH and somewhat THF dependant.

3.5. Possible impact of the trace amount HOAC in bismuth mediated deborylation

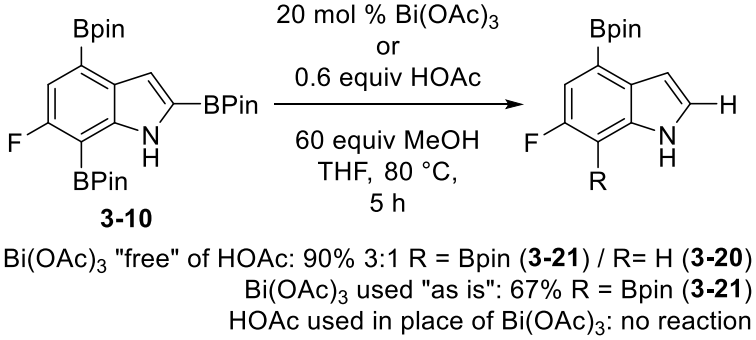


Figure 32 Exploring the potential role of HOAc

Although the mechanism of these $Bi(OAc)_3$ mediated deboronations remains to be established, the above examples point to an interaction with the indole nitrogen as being important to achieving selectivity and gaining reactivity. Given Movassaghi and co-workers' Pd-catalyzed C2 protodeboronation of indoles with HOAc as the proton source,[6] we questioned if HOAc, either residual in the $Bi(OAc)_3$ or in situ generated, was playing a part in our bismuth-catalyzed protodeboronations. Towards this end, we examined the reactivity of diborylated **3-10** with 0.6 equiv of HOAc, which would correspond to the theoretical amount of acetic acid available from 20 mol % of $Bi(OAc)_3$ (Figure 32). Under these conditions no protodebornation was observed. Increasing the amount of HOAc to 40 equiv had no effect as again only starting **3-10** was observed after 5 h at 80 °C. The next set of experiments was performed with free $Bi(OAc)_3$ that had been washed CCl_4 until the washings showed no HOAc by NMR. Somewhat surprisingly, the HOAc free $Bi(OAc)_3$ exhibited enhanced reactivity, with washed $Bi(OAc)_3$ affording a 3:1 mixture of **3-21** and **3-20** whereas the same reaction with unwashed $Bi(OAc)_3$ afforded no **3-20**. We suspect

adventitious HOAc interferes with the putative interaction of the bismuth salts the indole nitrogen thereby lowering the relative reactivity of the unwashed $Bi(OAc)_3$.

3.6. Summary

Our efforts toward the total synthesis of TMC-95A reviewed that $Bi(OAc)_3$ is capable of facilitating deborylations. This inspired the screening (Table 2 and Figure 24) of numourous bases, free radical initiators, metal salts in different oxidation states, transition metals, etc. For their ability to selectively deborylate a series of substrates. These screening indentified silver and copper salts as valueble deborylating agents.

Several trends were indentified iridium and bismuth mediated deborylation follow the same boron "on" the first boron "off" rule. However for bismuth to efficiently effect deborylation the presence of a nearby heteroatom is optimal. A mechnistic hypothesis for the observed bismuth mediated deborylations was proposed. This mechanistic model is consistent with literature presented and most of our expermentl results. However the reactivity of 2-substituted indole suggest that this mechanistic piture may need refinenent. In addition these studies demonstrated that solvent grade is very influencial in reaction times. Lastly a general reactivity pattern of Ag> Ir> Bi in deborylating strength was observed. The different reactivities of Ir and bismuth have been shown to enable the selective generation of 2-, 3-, 4-, 7-, 2,7-, 7,4- and 2,7,4-borylated indoles via a unified borylation/ deborylation stratergy.

In conclusion, bismuth acetate is a safe, shelf stable, inexpensive, and operationally simple alternative to Ir and Pd for the catalytic protodeboronations of indoles. Whereas the conditions for deboronations with Ir[8] and Pd[6] call for an inert atmosphere, Bi-catalyzed deboronations can be run under air. Furthermore, while reaction times are dependent on the grade of methanol employed, solvents need not be distilled or degassed. In general, sequential deboronations with $Bi(OAc)_3$

occur in the same order in which the Bpin groups are installed via Ir-catalyzed borylation. Relative to related methods, $Bi(OAc)_3$ tends to offer greater selectivity in protodeboronations of di- and triborylated indoles. Thus, by tuning the C–H borylation and deboronation conditions one can access a variety of boron substitution patterns from a single starting indole. Furthermore, it is also easy to consider using deuterated protic materials in the deborylation so as to afford noval deuterated product. A description of such a process is presented in the next chapter.

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11. The details of these and other screening experiments will be presented elsewhere.

12. Indole and 6-fluoroindol could be converted to their triborylated analogues in a single step, but the overall yields and combined catalyst loads required were better if diborylated **6** and **9** were isolated and then converted to **7** and **10**. See the Supporting Information for additional details.
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15. For the 3,5-diborylation of 7-azaindole see reference 8.

16. Ir-catlayzed borylation of 3-borylated-*N*-Boc-indole afforded an ~1:1 mixture of 3,5- and 3,6-bisborylated-*N*-Boc-indole.

17. For a selective Ir-catalyzed C–H borylation of a fully protected tryptophan and *N*-TIPS protected indoles see: Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 10160–10163.

18. 10% Deuterium incorporation was initially observed at C3. Washing with H_2O reprotonated this carbon.

19. The percent deuterium incorporation was determined by integration of the ^{1}H-NMR spectrum.

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Chapter 4. Deborylation/Deuteration mediated by silver oxide and copper chloride

4.1. Introduction

Deuterium and tritium labeled compounds, including those labeled at specific positions, are widely used as probes for spectroscopy, reaction mechanisms, pharmacokinetics and enzymology.[1] As the need for specifically labeled compounds grows, reliable methods for incorporating deuterium at specific positions becomes increasingly important.[2] Traditional deuteration methods such as acid, base or transition metal promoted H/D exchange methods can suffer from harsh conditions, incomplete deuterium incorporation, poor functional group compatibility,[2] although some transition metal catalysts exhibit remarkable activities.[3] There are still relatively few examples of selective introduction of one deuterium in an aryl or heteroaryl ring. The most common means of doing so is by metal halogen exchange followed be deuterolysis of the organometallic intermediate.[2]

More recently, alternatives like metal catalyzed deuterdecarboxylation have been developed.[4] Both of these approaches require existing functionality to be present. For C–H to C–D transformations, selective examples are limited to ortho deuterations using stoichiometric or catalytic metal organometallic reagents.[2,5] Many of the conditions employed for deborylation are harsh and virtually all examples involve boronic acids in aqueous media. For applications using products of C–H borylation, protolytic deborylation of aryl boronic esters in organic solvents is desirable.

During the development of C-H borylation, Dr. Shi noticed that in some cases significant quatities of starting material at the end of the reaction , even there were evidence showed starting substrates had been completely consumed during the Ir-catalyzed C-H borylation. It indicated that the starting material was being regenerated by protolytic deborylation and given by the fact of pure boronic ester did not suffer suggested it might be an Ir-catalyzed process. Thus, given the observation of

deborylation during transformations crude mixtures, they subjected the crude reaction mixture from C–H borylation of 1,2-dichlorobenzene to deutorolyis to assess the potential one-pot borylation/deuterodeborylation in Figure 33. Sucessfully, they found after heating in THF/D_2O for 30 min the arylboronate was fully converted to corresponding deuterium-labeled arene.

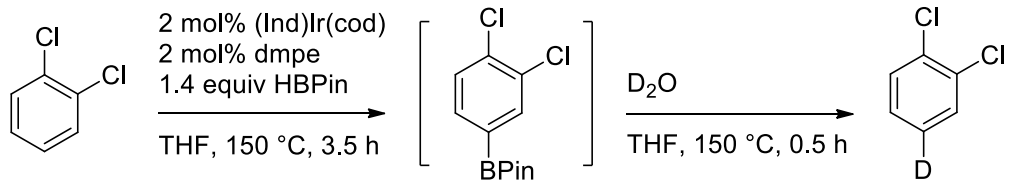
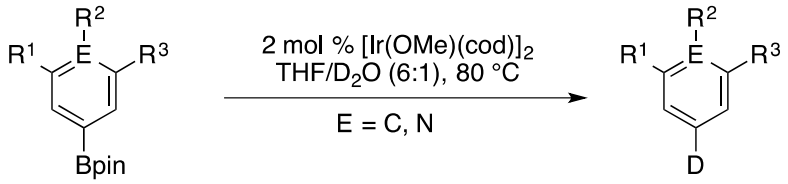
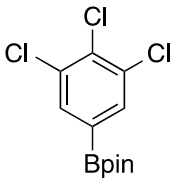
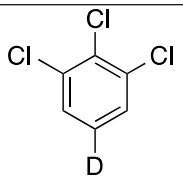
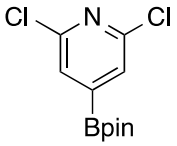
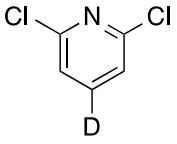
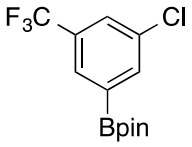
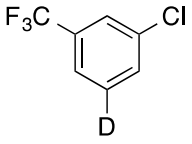
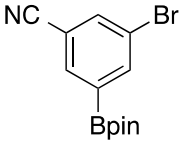
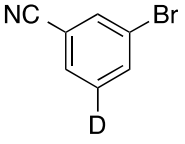
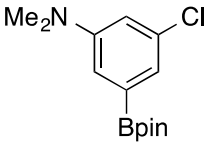
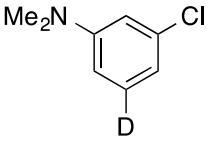
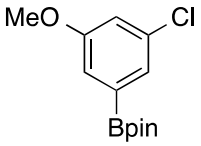
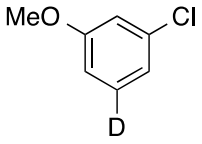


Figure 33. Proposed transition structure of 2-substituted indole during the deborylation

With these conditions in hand, substrates were screened against this one-pot C-H Borylation/deuteration protocol (Table 8).[6] The overall reactions were clean, producing the deuterated arenes as the only aromatic products in high yields and with greater than 95% deuterium incorporation. Even under relatively forcing borylation/deborylation conditions, functional groups such as halogens, nitriles, amines and ethers were tolerated.

Table 8. Selective deuterodeborylation reactions[a]

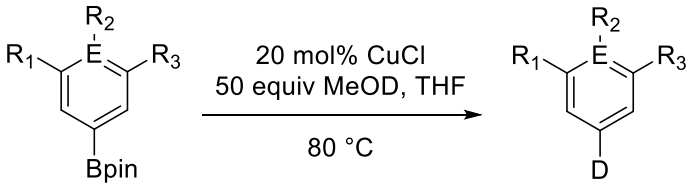


entry	arene	deuteration time	product	yield[b], %D[c]
1		2 h		80%, >98[d]
2		2 h		82%, 96
3		2 h		65%,[e] >98
4		2 h		60%, >98
5		4.5 h		74%, 96
6		3 h		74%, 93

[a]All reactions were run with 2 mmol of organoboronate. [b]Isolated yields. [c]Determined by integration of ^{13}C NMR spectra; see SI for details for method of calculation. [d]~4% 4-deuterated product was observed due to ~4% 4-borylated isomer in the starting material. [e]Owing to product volatility, solvent impurities were present.4.2. Results of Copper chloride and Silve oxide mediated Deborylation/Deuteriation

4.2. Results of Copper chloride and Silver oxide mediated Deborylation/Deuteration

Table 9. Deuteration protocol for synthesizing deuterated aromatics



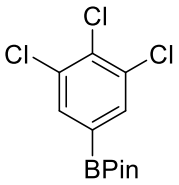
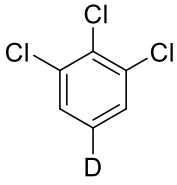
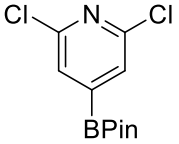
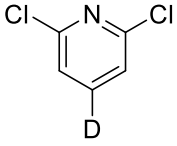
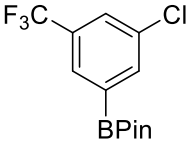
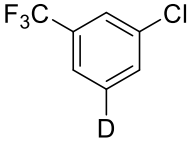
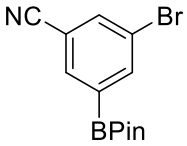
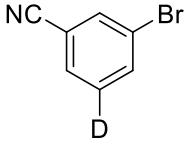
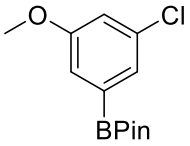
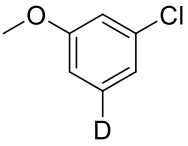
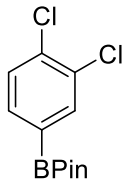
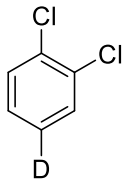
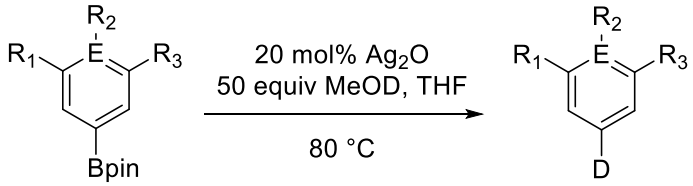
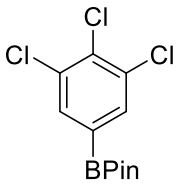
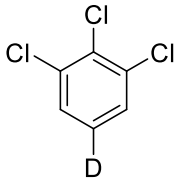
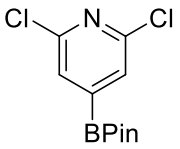
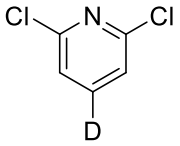
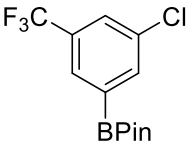
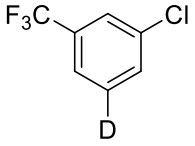
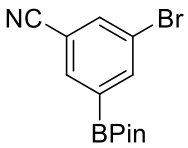
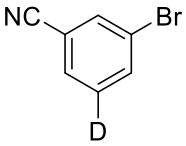
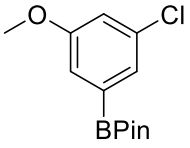
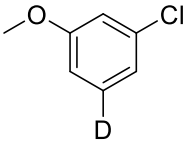
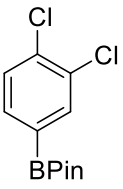
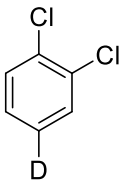
entry	arene	deuteration time	product	conversion
1		2 h		60%
2		2 h		100%
3		3 h		complex mixture
4		3 h		complex mixture
5		3.5 h		28%,
6		3 h		complex mixture

Table 10. Deuteration protocol for synthesizing deuterated aromatics



entry	arene	deuteration time	product	yield % D
1		1 h		55%,[a] 98
2		1 h		40%,[a] 98
3		2.5 h		78%,[b] 99
4		3 h		60%,[a] 97
5		2 h		62%,[a] 96
6		3 h		91%,[b] 98

[a] Isolated yields. [b]Crude yields.

In Table 10, we show that Ag-catalyzed deborylation can be utilized to isotopically label arenes. The overall reactions were clean, producing the deuterated arenes as the only aromatic products in high yields and with greater than 94% deuterium incorporation. Functional groups such as halogens, nitriles, amines and ethers were tolerated. Compare the results to Ir borylation/Deuteration.

4.3. Conclusions

As illustrated in Figure 34, deborylation can be coupled to diborylation to prepare monoborylated compounds that where the regioselectivities complement those found in the monoborylation of the parent substrates. Both Ag-catalyzed borylation and Bi-catalyzed deborylation proceed under mild conditions and can be applied to structurally complex molecules.

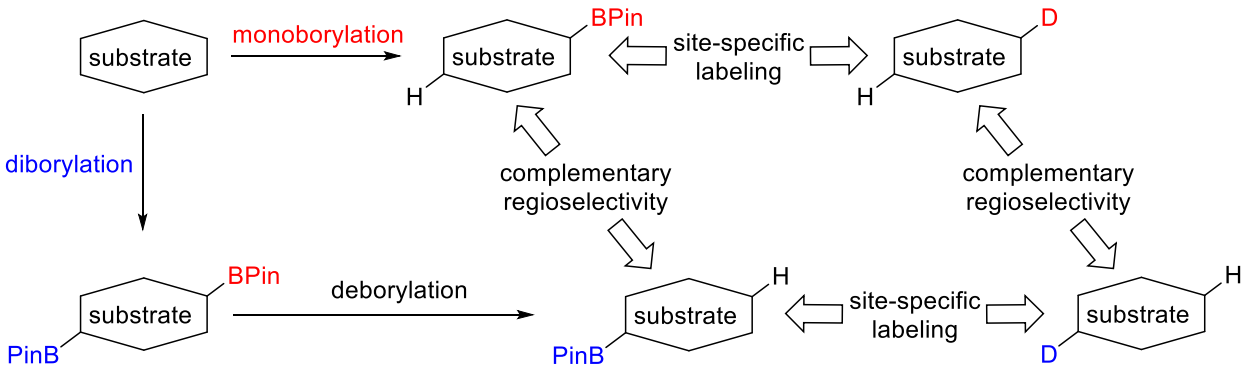


Figure 34. Potential application (isotopic labeling and regioselective synthesis)

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Chapter 5. Experimental details and characterization data

5.1. General Methods

Unless otherwise stated, the reported yields refer to chromatographically and spectroscopically pure compounds. Pinacolborane (HBPin) and B_2pin_2 were generously supplied by BoroPharm and used as received. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) ([Ir(OMe)(cod)]$_2$), was prepared per the literature procedures.[1] 4,4′-Di-*t*-butyl-2,2′-bipyridine (dtbpy) was purchased from Aldrich. $IrCl_3•(H_2O)_x$ was purchased from Pressure Chemical Co.. 2,7-bis(BPin)-*N*-Boc-L-tryptophan methyl ester was prepared according to the literature procedure.[2] All substrates were purified by column chromatography. For all Ir-catalyzed reactions, tetrahydrofuran (THF) was obtained from a dry still packed with activated alumina and degassed before use. For all Bi-catalyzed deboronations, THF was reagent grade and used as received. Acetonitrile (MeCN), triethylamine (NEt_3), and dichloromethane (DCM) were reagent grade. In addition, some of the solvents were degassed by a Freeze-Pump-Thaw method. Silica gel was purchased from EMD™ (230-400 Mesh).

Reactions were monitored by thin layer chromatography on precoated silica gel plates (Merck), using UV light or phosphomolybdic acid stain for visualization. Column chromatography was performed on 60 Å silica gel (230–400 mesh). NMR spectra were recorded on Varian VXR-500, Varian Unity-500-Plus (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C chemical shifts (in ppm) were referenced to the residual protonated or natural abundance solvent signals: $CDCl_3$ (δ 7.26 for ^{1}H and 77.0 for ^{13}C). ^{11}B spectra were recorded at 160.32 MHz. All coupling constants are apparent *J* values measured at the indicated field strengths. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus (Barnstead|Thermolyne, Dubuque, IA) and are uncorrected. High-resolution mass spectrum was acquired at the MSU Mass

Spectrometry facility using a Waters GCT Premier GC/TOF instrument (in ESI mode) (Waters Milford, MA). Low-resolution mass spectra were performed at the Molecular Metabolism and Disease Collaborative Mass Spectrometry Core facility at MSU on a Thermo Scientific LTQ-Orbitap Velos using the Ion Trap analyzer in positive ionization mode by nano-ESI.

5.2. Experimental details for Chapter 2

2,7-bis(Bpin)-Boc-L-tryptophan methyl ester (2-5). In a glove box, the starting material Boc-L-tryptophan methyl ester 2-4 (318 mg, 1.0 mmol, 1 equiv) and B_2Pin_2 (508 mg, 2.0 mmol, 2 equiv) was weighed in a 20 mL vial. Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (20 mg, 0.03 mmol, 6 mol % Ir) and d^{t}bpy (16 mg, 0.06 mmol, 6 mol %). HBPin (40 mL, 0.28 mmol, 0.28 equiv) along with 1 mL of THF was added to the $[Ir(OMe)(COD)]_2$ test tube. THF (1 mL) was added to the d^{t}bpy test tube in order to dissolve the dtbpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to the 20 mL reaction vial containing indole substrate and B_2Pin_2. Additional THF (3 mL) was used to wash the test tubes and the washings were transferred to the reaction vial. The reaction vial was stirred at room temperature inside the glove box for 20 h. At this point the volatile materials were removed and the crude material was purified via a gradient column (10% ethyl acetate/hexanes to 30% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (359 mg, 63% yield, mp 88-94 °C). Regiochemistry of the diborylated product was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.21 (br s, 1H, H_a), 7.78-7.76 (d, J=7.9 Hz, 1H, H_b/H_d), 7.70-7.69 (d, J=6.8 Hz, 1H, H_b/H_d), 7.13-7.10 (t, J=7.8 Hz, 1H, H_c), 5.99-5.97 (d, J=6.7 Hz, 1H, NH), 4.34-4.30 (m, 1H, CH), 3.70 (s, 3H, CH_3 of Me), 3.43-3.30 (m, 2H, CH_2), 1.41 (br s, 6H, 2 CH_3 of BPin), 1.39 (br s, 18H, 6 CH_3 of BPin), 1.34 (br s, 9H, CH_3 of ^{t}Bu); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 173.5 (C═O), 155.6 (C═O), 142.9 (C), 131.7 (CH), 126.8 (C), 123.0

(CH), 122.9 (C), 119.2 (CH), 84.3 (C), 83.8 (C), 79.2 (C), 55.3 (CH), 52.1 (CH_3), 28.3 (3 CH_3 of ^{t}Bu), 27.2 (CH_2), 25.0 (4 CH_3 of BPin), 24.9 (2 CH_3 of BPin), 24.6 (2 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.2; FT-IR (neat) $\tilde{n}_{max}$: 3453, 3391, 3056, 2980, 2934, 1754, 1719, 1551, 1514, 1497, 1441, 1416, 1391, 1368, 1337, 1294, 1207, 1167, 1136, 1101, 853, 683 cm^{-1}; $[\alpha]^{20}D$+15.2(c 0.4, CH_2Cl_2)

7-Bpin-Boc-L-tryptophan methyl ester (2-6). To an air-free flask containing a degassed solution of 2, 7-bis(Bpin)-Boc-L-tryptophan methyl ester 2-5 (172.0 mg, 0.302 mmol) in methanol (1.0 mL) and dichloromethane (0.5 mL) was added in one portion $[Ir(OMe)COD]_2$ (3.0 mg, 0.004 mmol). The flask was purged and refilled with nitrogen three times and the resulting mixture was heated in oil bath at 55 °C for 3 hours. The reaction mixture was then filtered through a short plug of silica gel eluting with dichloromethane to remove the iridium residue. The crude material was concentrated by rot vap, and purified by column chromatography eluting with 20% ethylacetate/hexanes (R_f = 0.4) furnished the product as a white solid (73.3 mg, 0.165 mmol, 55% yield, mp 177-179 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.12 (s, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.63 (d, *J* = 7.1 Hz, 1 H), 7.11 (dd, *J* = 7.8, 7.1 Hz, 1 H), 7.04 (s, 1 H), 5.05 (d, *J* = 7.8 Hz, 1 H), 4.63 – 4.61 (m, 1 H), 3.66 (s, 3 H), 3.29 (d, *J* = 4.9 Hz, 2 H), 1.41 (s, 9 H), 1.37 (s, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 155.2, 141.3, 129.5, 126.6, 122.7, 122.3, 119.1, 109.6, 83.8, 79.7, 54.2, 52.2, 28.3, 27.9, 24.9; ^{11}B NMR ($CDCl_3$, 96 MHz) δ 30.6; FT-IR (neat) $\tilde{n}_{max}$: 3453, 2981, 2919, 2853, 2252, 1742, 1708, 1599, 1492, 1437, 1373, 1331, 1167, 1135, 799, 735 cm^{-1}; $[\alpha]^{20}_D$ +39.3 (*c* 1.0, $CHCl_3$); HRMS (ESI+): (m/z) calculated for $[C_{23}H_{34}BN_2O_6]^+$ 445.2510, found 445.2519.

7-BPin-L-tryptophan methyl ester (2-7). 7-Bpin-Boc-L-tryptophan methyl ester 2-6 (330 mg, 0.75 mmol) was suspended in Acetonitrile (10 ml) and water (0.2 ml), and then the containing flask was sealed and placed in an oil bath at 60 ºC in order to provide a homogenous solution. A second

portion $BiCl_3$ (284 mg, 0.9 mmol) was added into the flask, the mixture was stirred at that temperature for 30 min. And an additional $BiCl_3$ (284 mg, 0.9 mmol) was added and the mixture was stirred for a further 15 min. The reaction was monitored by TLC. Volatile solvent were removed on a rotary evaporator. The crude material was suspended in MeOH (5 ml) and placed on a celite bed followed by washing with MeOH (twice with 3 times the volume of solvent). The filtrate was dried over anhydrous $MgSO_4$, after filtration and solvent removal gave product 2-7, acetonitrile and presumably inorganic salts (350 mg, 1 mmol, 133% yield). Regiochemistry of the crude product was assigned by NMR spectroscopy. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.68-7.66 (d, *J* = 7.9 Hz, 1H), 7.54-7.52 (d, *J* = 7.0 Hz, 1H), 7.34 (s, 1H), 7.11-7.04 (t, *J* = 7.3 Hz, 1H), 4.38 (s, *J* = 5.8, 1H), 3.73 (s, 3H), 3.51-3.39 (m, 2H), 1.42-1.31 (m, 9H), 1.19 (d, *J* = 9.9 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 170.7 (C=O), 142.4 (C), 130.3 (CH), 127.4 (C), 126.2 (CH), 122.7 (CH), 119.91 (CH), 107.29 (C), 85.1 (2 C), 54.72 (CH), 53.64 (OCH_3), 31.1 (CH_3 of BPin), 28.83 (CH_3 of BPin), 27.33 (CH_2), 25.2 (2 CH_3 of BPin); ^{11}B NMR (CD_3OD, 160 MHz) δ 29.8; HRMS (ESI): *m/z* calculated for $C_{18}H_{26}BN_2O_4$ $[M+H]^+$ 345.1986, found 345.1992. This crude material was used directly in the following step without further purification and assuming a quantitative yield.

(S)-O-TBS-N-Boc-3-bromotyrosine (2-9). To a solution of (*S*)-*N*-Boc-3-bromotyrosine (1.30 g, 3.61 mmol) in DMF (15 mL) were successively added imidazole (0.74 g, 10.83 mmol) and TBSCl (1.20 g, 7.94 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was then treated with water (15 mL), stirred for 30 min, and extracted with diethyl ether (3 × 30 mL). Combined ether layers were successively washed with 1N aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Once dried over Na_2SO_4, the organic extract was concentrated *in vacuo*. The resulting yellowish oil was redissolved in THF

(10 mL), treated with potassium carbonate 1 M in water (11 mL, 11 mmol), and stirred at room temperature for 1 hour. The mixture was acidified to pH 3 by addition of 1M aqueous HCl and then extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexanes/EtOAc/HOAc 8:1.9:0.1 to provide (*S*)-*O*-TBS-*N*-Boc-3-bromotyrosine 2-9 as a slightly yellowish oil that became a foam under high vacuum and hardened upon standing to form a white solid (1.20 g, 2.53 mmol, 70% yield), mp 116–118 ºC; R_f = 0.35 (hexanes/EtOAc/HOAc 8:1.9:0.1); $[\alpha]^{20}_D$ +14.5° (*c* 0.54, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (apparent s, 1 H), 6.97 (dd, *J* = 8.1, 2.0 Hz, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 4.95 (d, *J* = 7.7 Hz, 1 H), 4.52 (m, 1 H), 3.11 (dd, *J* = 13.7, 4.4 Hz, 1 H), 2.94 (dd, *J* = 13.7, 6.3 Hz, 1 H), 1.41 (s, 9 H), 1.01 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 155.4, 151.7, 134.1, 129.9, 129.1, 120.1, 115.3, 80.5, 54.3, 36.6, 28.3, 25.7, 18.3, 4.2; IR (neat) $\tilde{\nu}_{max}$ 3307, 2957, 2930, 2859, 1684, 1654, 1496, 1395, 1366, 1289, 1255, 1167, 1046 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{33}NO_5BrSi$ $[M+H]^+$ 474.1311, found 474.1313.

Preparation of dipeptide (2-11): To a stirring solution of 2-9 (0.996 g, 2.1 mmol) and *N*-hydroxysuccinimide (0.302 g, 2.63 mmol) in DME (21 mL) at 0 °C was added DCC (0.542 g, 2.63 mmol) in one portion. The containing flask was sealed and the reaction mixture was stirred at 0 ºC overnight. The resulting suspension was filtered and the solid (urea) was rinsed with cold DME (3 × 5 mL). The filtrate together with the rinses was concentrated *in vacuo*, redisolved in dioxane (9 mL), and cooled to about 10 °C. To this solution was added a solution of L-asparagine (1.67 g, 12.60 mmol) and sodium bicarbonate (1.06 g, 12.60 mmol) in water (6 mL) in small portions.

After 1 h of vigorous stirring, most of the dioxane was removed under vacuum and the remaining aqueous phase was acidified to pH 3.5 and extracted three times with EtOAc. The combined extracts were washed with water and brine, dried over $MgSO_4$, and evaporated to yield a white foam that was subjected to flash chromatography eluting with hexanes/EtOAc/HOAc 8:1.9:0.1 to afford dipeptide 2-11 (972 mg, 1.651 mmol, 79% yield) as a white solid, mp 147–147.5 ºC; R_f = 0.21 (hexanes/EtOAc/HOAc 8:1.9:0.1); $[\alpha]^{20}_D$ +16.5° (*c* 0.49, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br, 1 H), 7.31 (s, 1H), 6.99 (br, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.70 (dd, *J* = 8.0, 3.0 Hz, 1 H), 5.69 (br, 1H), 5.56 (br, 1H), 4.71 (m, 1 H), 4.40 (m, 1H), 3.06 (apparent d, *J* = 13.5 Hz, 1 H), 2.92–2.69 (m, 3 H), 1.26 (s, 9 H), 0.98 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 172.3, 171.9, 156.1, 151.3, 134.2, 131.0, 129.2, 120.0, 115.1, 80.4, 55.6, 50.2, 37.3, 37.0, 28.3, 25.7, 18.3, 4.2; IR (neat) $\tilde{\nu}_{max}$ 3449, 3297, 3055, 2957, 2857, 1734, 1669, 1604, 1495, 1473, 1437, 1372, 1329, 1292, 1254, 1205, 1167, 1047 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{24}H_{39}N_3O_7BrSi$ $[M+H]^+$ 588.1741, found 588.1742.

Tripeptide (2-2): To a stirred slurry of crude 7-BPin-L-tryptophan methyl ester 2-7 (assumed to contain 49.3 mg, 0.142 mmol, 1.2 equiv) and dipeptide 2-10 (70.2 mg, 0.119 mmol) in THF (6 mL) were added EDC (45.8 mg, 0.239 mmol) and HOBT (36.6 mg, 0.239 mmol). The mixture was stirred and cooled to 0 °C under nitrogen atmosphere. Triethylamine (166 µL, 1.194 mmol) was added in one portion via syringe and the mixture was allowed to slowly warm to room temperature and stirred for 24 h. The reaction mixture was concentrated *in vacuo*, adsorbed onto a minimum amount of silica gel, dried under high vacuum, and directly subjected to column chromatography eluting with ether and then ether/EtOAc (1:1 to 0:1) to afford tripeptide 2-2 (63.1

mg, 0.069 mmol, 58% yield) as an off-white slightly orange solid, mp 131.5–133.5 ºC; R_f = 0.32 (EtOAc); $[\alpha]^{20}_D$ +20.5° (*c* 0.21, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.76 (br d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 7.0 Hz, 1 H), 7.46 (br d, *J* = 6.5 Hz, 1 H), 7.27 (d, *J* = 2.0 Hz, 1 H), 7.11 (s, 1 H), 7.09 (dd, *J* = 8.0, 7.0 Hz, 1 H), 6.89 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 5.95 (br, 1 H), 5.52 (br, 1 H), 4.96 (br d, *J* = 7.5 Hz, 1 H), 4.76 (m, 1 H), 4.73 (m, 1 H), 4.26 (m, 1 H), 3.60 (s, 3 H), 3.27 (apparent d, *J* = 6.0 Hz, 2 H), 2.92 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.82 (m, 1 H), 2.79 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.46 (dd, *J* = 16.0, 6.5 Hz, 1 H), 1.37 (s, 9 H), 1.35 (s, 12 H), 1.00 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.9, 171.4, 170.2, 155.5, 151.5, 141.2, 134.0, 130.5, 129.4, 129.0, 126.2, 123.3, 122.0, 120.1, 119.0, 115.3, 109.0, 83.8, 80.5, 55.6, 53.2, 52.4, 49.6, 36.5, 36.45, 28.2, 27.3, 25.7, 25.0, 18.3, −4.3; IR (neat) $\tilde{\nu}_{max}$ 3397, 2956, 2916, 2849, 1577, 1540, 1459, 1419, 1355 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{42}H_{62}BN_5O_{10}SiBr$ $[M+H]^+$ 914.3542, found 914.3549.

5.3. Experimental details for Chapter 3

General procedure for borylation with $[Ir(OMe)(COD)]_2$ and d^{t}bpy. In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with the substrate (1mmol). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (1 mol% Ir) and d^{t}bpy (1 mol%). When B_2pin_2 was used as the borylating agent, HBPin (2.8 x Ir mol%) was used to generate active catalyst. THF (2 × 200 µL) was added to the d^{t}bpy containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the $[Ir(OMe)(cod)]_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to the vial. Additional THF (3 × 200 µL) was used to wash the test tubes and the washings were transferred to the vial. The vial was sealed, brought out of the glove box and the reaction was carried out at the specified temperature. After completion

of the reaction, the volatile materials were removed on a rotary evaporator followed by removing the dark brown red color from the crude material with a silica plug. The crude material was purified by column chromatography.

General procedure for deborylation with $Bi(OAc)_3$ and MeOH. A vial equipped with a magnetic stirring bar was charged with substrate (1 mmol, 1 equiv) and $Bi(OAc)_3$ (0.2 mmol, 20 mol %). Solvent mixture MeOH and THF (4 mL) was added to the vial. The vial was sealed and the reaction was carried out at the 80 °C. The reaction was monitored by TLC. After completion of the reaction, the crude material was passed through a plug of celite and washed three times by ethyl acetate. After the volatile materials were removed on a rotary evaporator the crude material was purified by column chromatography.

General procedure for deborylation with $[Ir(OMe)(COD)]_2$ and MeOH. A Schlenk flask equipped with a magnetic stirring bar was charged with substrate (1.0 mmol, 1.0 equiv) and $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol % Ir). The Schlenk flask was then evacuated and backfilled with nitrogen (this sequence was carried out two times). Solvent mixture (methanol/dichloromethane 2:1, 5 mL) was degassed by a Freeze-Pump-Thaw method then added to the Schlenk flask and flushed under nitrogen twice as mentioned previously. The Schlenk flask was sealed and the reaction was carried out at the 60 °C. The reaction was monitored by TLC, after completion of the reaction; the volatile materials were removed on a rotary evaporator. The crude material was purified by column chromatography.

7-Bpin-Boc-L-tryptophan methyl ester (3-2). The general procedure was applied to 2, 7-bis(Bpin)-Boc-L-tryptophan methyl ester 3-1 (39 mg, 0.068 mmol) and $Bi(OAc)_3$ (5.3 mg, 0.0137 mmol, 20 mol%) with solvent mixture MeOH /THF (0.34 mL /0.27 mL) at 80 °C for 7 h. The crude material was concentrated and purified by column (20% ethyl acetate/hexanes) on silica gel. The product

was isolated as white solid (27 mg, 90%). Regiochemistry of the crude product was assigned by NMR spectroscopy. ^{1}H NMR (CD_3OD, 500 MHz) δ 9.13 (br s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 5.06 (d, *J* = 7.8, 1H), 4.64 (m, 1H), 3.67 (s, 3H), 3.31 (d, *J* = 4.9, 2H), 1.43 (s, 9H), 1.39 (s, 12H); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.7, 155.2, 141.3, 129.5, 126.6, 122.7, 122.3, 119.1, 109.6, 83.8, 79.7, 54.2, 52.2, 28.3, 27.9, 25.0. The spectral data were in accordance with literature.[3]

7-BPin-L-tryptophan methyl ester (3-3): 7-Bpin-Boc-L-tryptophan methyl ester 3-2 (330 mg, 0.75 mmol, 1 equiv) was suspended in acetonitrile (10 ml) and water (0.2 ml), and then the containing flask was sealed and placed in an oil bath at 60 ºC in order to provide a homogenous solution. $BiCl_3$ (142 mg, 0.45 mmol, 0.6 equiv) was added into the flask, the mixture was stirred at that temperature for 30 min. And an additional $BiCl_3$ (142 mg, 0.45 mmol, 0.6 equiv) was added and the mixture was stirred for a further 30 min. The reaction was monitored by TLC. Volatile solvent were removed on a rotary evaporator. The crude material was suspended in MeOH (5 ml) and placed on a celite bed followed by washing with MeOH (twice with 3 times the volume of solvent). The filtrate was dried over anhydrous $MgSO_4$, after filtration and solvent removal gave product and presumably inorganic salts (350 mg, 1 mmol, 133% yield). Regiochemistry of the crude product was assigned by NMR spectroscopy. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.31 (s, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 4.37 (m, 1H), 3.71 (s, 3H), 3.42 (m, 2H), 1.35 (s, 9H), 1.16 (d, *J* = 9.8 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 170.7 (C=O), 142.4, 130.3, 127.4, 126.2, 122.7, 119.9, 107.3, 85.1, 54.7 , 53.7, 31.1, 28.8, 27.33, 25.2; ^{11}B NMR (CD_3OD, 160 MHz) δ 29.8; HRMS (ESI): *m/z* calculated for $C_{18}H_{26}BN_2O_4$ $[M+H]^+$ 345.1986, found 345.1992.

2,7-bis(BPin)-indole (3-6). The borylation step was carried out neat with indole 3-5 (585 mg, 5 mmol, 1 equiv), B_2Pin_2 (2.54 mg, 10 mmol, 2 equiv), HBPin (210 μL, 1.4 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (17 mg, 0.025 mmol, 1 mol % Ir) and d^{t}bpy (13 mg, 0.05 mmol, 1 mol %) at 80 °C for 48 h and worked up as described in the general procedure. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (1.9 g, 77%, mp 147 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.35 (br s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.72 (dd, J = 6.9, 1.0 Hz, 1H), 7.12 (m, 2H), 1.42 (s, 12 H, 4 CH_3 of BPin), 1.38 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.3, 131.4, 127.5, 125.3, 119.5, 113.9, 84.1(2 C), 83.9 (2 C), 25.1 (4 CH_3 of BPin), 24.9 (4 CH_3 of BPin). The spectral data were in accordance with literature.[4]

2,4,7-tri(BPin)-indole (3-7). The borylation step was carried out neat with 2,7-bis(BPin)-indole 3-6 (554 mg, 1.5 mmol, 1 equiv), B_2Pin_2 (381 mg, 1.5 mmol, 1 equiv), HBPin (63 μL, 0.42 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (5 mg, 0.015 mmol, 1 mol % Ir) and d^{t}bpy (4 mg, 0.015 mmol, 1 mol %) at 80 °C for 12 h and worked up as described in the general procedure. The crude material was purified by silica gel chromatography (10% ethyl acetate/hexanes) on silica gel to afford the product as white powder (713 mg, 96%).

Alternative procedure, 2,4,7-tri(BPin)-indole (3-7). In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with indole 3-5 (585 mg, 5 mmol, 1 equiv) and B_2Pin_2 (3.81 g, 10 mmol, 3 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (100 mg, 0.15 mmol, 6 mol % Ir) and d^{t}bpy (80 mg, 0.3 mmol, 6 mol %). HBPin (210 μL, 1.4 mmol, 0.28 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. THF (2 mL) was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$

and HBPin mixture. After mixing for 1 min, the resulting solution was transferred to the vial containing the indole substrate. Additional THF (3 mL) was used to wash the test tubes and the washings were transferred to the vial. The vial was well sealed, brought out of the glove box and stirred at 70 °C. After 48 h, the reaction was stopped followed by removing the dark brown red color from the reaction solution with silica bed. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (1.5 g, 60%, mp 255°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (br s, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 1.42 (s, 12 H, 4 C*H*$_3$ of BPin), 1.39 (s, 24 H, 4 C*H*$_3$ of BPin), 1.39 (s, 24 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.5, 131.6, 130.2, 127.2, 115.4, 84.0(2 C), 83.9 (2 C), 83.5 (2 C), 25.0 (8 CH_3 of BPin), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160MHz): δ 30.6; FT-IR (neat) $\tilde{\nu}_{max}$: 3461, 2979, 1538, 1372, 1327, 1292, 1137, 973, 855, 693 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{26}H_{41}B_3NO_6$ $[M+H]^+$ 496.31, found 496.3.

2,7-di(BPin)-6-fluoroindole (3-9). The borylation step was carried out neat with 6-fluoroindole 3-8 (675 mg, 5 mmol, 1 equiv), B_2Pin_2 (2.54 g, 10 mmol, 2 equiv), HBPin (210 μL, 1.4 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (17 mg, 0.05 mmol, 1 mol % Ir) and d^{t}bpy (13 mg, 0.05 mmol, 1 mol%) at 80 °C for 24 h and worked up as described in the general procedure. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. The product was afforded as a foamy solid (1.59 g, 82%, mp 117-119 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (br s, 1H, NH), 7.71 (dd, *J* = 8.3, 5.4 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 10.3, 8.8 Hz, 1H), 1.44 (s, 12H, 4 C*H*$_3$ of BPin), 1.38 (s, 12H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1 (d, *J* = 247 Hz), 143.1 (d, *J* = 13.4 Hz), 126.2 (d, *J* = 11.4 Hz), 123.9, 113.7, 108.7 (d, *J* = 27.7 Hz), 84.0 (2 C),

83.8 (2 C), 24.9 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160MHz): δ 30.5; FT-IR (neat) $\tilde{\nu}_{max}$: 3445, 2980, 1569, 1540, 1387, 1418, 1288, 1235, 1166, 1020, 966, 852, 701 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{29}B_2FNO_4$ $[M+H]^+$ 387.22, found 388.3.

2,4,7-tri(BPin)-6-fluoroindole (3-10). The borylation step was carried out neat with 2,7-bis(BPin)-6-fluoroindole 3-9 (1.48 g, 3.82 mmol, 1 equiv), B_2Pin_2 (970 mg, 3.82 mmol, 1 equiv), HBPin (160 μL, 1.1 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (12.7 mg, 0.019 mmol, 1 mol % Ir) and d^{t}bpy (10 mg, 0.038 mmol, 1 mol %) at 80 °C for 12 h and worked up as described in the general procedure. The crude material was purified by silica gel chromatography (10% ethyl acetate/hexanes) on silica gel to afford the product as white powder (1.82 g, 92%).

Alternative procedure, 2,4,7-tri(BPin)-6-fluoroindole (3-10). In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with 6-fluoroindole 3-8 (675 mg, 5 mmol, 1 equiv) and B_2Pin_2 (3.81 g, 15 mmol, 3 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (100 mg, 0.15 mmol, 6 mol % Ir) and d^{t}bpy (80 mg, 0.3 mmol, 6 mol %). HBPin (210 μL, 1.4 mmol, 0.28 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. THF (2 mL) was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for 1 min, the resulting solution was transferred to the vial containing the indole substrate. Additional THF (3 mL) was used to wash the test tubes and the washings were transferred to the vial. The vial was well sealed, brought out of the glove box and stirred at 70 °C. After 24 h, the reaction was stopped followed by removing the dark brown red color from the reaction solution with silica bed. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. The product was crystallized out from MeOH as white crystals (1.59 g, 62%, mp 278°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.50

(br s, 1H, NH), 7.54 (d, *J* = 2.1 Hz, 1H), 7.32 (d, *J* = 10.3 Hz, 1H), 1.43 (s, 12H, 4 C*H*$_3$ of BPin), 1.38 (s, 24H, 8 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4 (d, *J* = 247 Hz), 142.7 (d, *J* = 12.4 Hz), 128.4, 115.7 (d, *J* = 25.8 Hz), 115.3, 84.0 (2 C), 83.9 (2 C), 83.8 (2 C), 25.0 (8 CH_3 of BPin), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.1; FT-IR (neat) $\tilde{\nu}_{max}$: 3455, 2979, 1540, 1510, 1387, 1323, 1292, 1235, 1137, 1042, 966, 852, 702 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{26}H_{40}B_3FNO_6$ $[M+H]^+$ 514.30, found 514.3.

4,7-bis(BPin)-2-carboethoxy-indole (3-12). The borylation step was carried out neat with 7-BPin-2-fluoroindole 3-11 (189 mg, 1 mmol, 1 equiv), B_2Pin_2 (508 mg, 2 mmol, 2 equiv), HBPin (42 μL, 0.28 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (3.3 mg, 0.01 mmol, 1 mol % Ir) and d^{t}bpy (2.6 mg, 0.01 mmol, 1 mol %) at 80 °C for 12 h and worked up as described in the general procedure. The crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) on silica gel to afford the product as white powder (146 mg, 81%, mp 163 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (br s, 1H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.67 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2 H, *CH*$_2$CH$_3$), 1.46 (t, *J* = 7.1 Hz, 3 H, CH$_2$*CH*$_3$), 1.41 (s, 12 H, 4 C*H*$_3$ of BPin), 1.41 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3 (C=O), 141.0, 131.7, 130.7, 128.1, 127.5, 110.0, 84.1 (2 C), 83.7 (2 C), 60.8 (CH_2), 24.9 (8 CH_3 of BPin), 14.4 (CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 31.3; FT-IR (neat) $\tilde{\nu}_{max}$: 3448, 2978, 1721, 1512, 1385, 1347, 1292, 1136, 973, 855, 763, 695 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{23}H_{34}B_2NO_6$ $[M+H]^+$ 442.25, found 442.3.

4,7-bis(BPin)-3-methyl-indole (3-14). The borylation step was carried out neat with 2-methylindole 3-13 (131 mg, 1 mmol, 1 equiv), B_2Pin_2 (508 mg, 2 mmol, 2 equiv), HBPin (42 μL, 0.28 mmol, 0.28 equiv), $[Ir(OMe)(COD)]_2$ (3.3 mg, 0.01 mmol, 1 mol % Ir) and d^{t}bpy (2.6 mg, 0.01 mmol, 1 mol %) at 80 °C for 24 h and worked up as described in the general procedure. The

crude material was purified by silica gel chromatography (20% ethyl acetate/hexanes) on silica gel to afford the product as white powder (271 mg, 71%, mp 353 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (br s, 1H), 7.55 (d, *J* = 6.9 Hz, 1H), 7.54 (d, *J* = 6.9 Hz, 1H), 6.68 (s, 1H), 2.52 (s, 3H), 1.40 (s, 12 H, 4 C*H*$_3$ of BPin), 1.38 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.7, 135.7, 132.9, 127.0, 126.5, 101.7, 83.8 (2 C), 83.3 (2 C), 25.0 (8 CH_3 of BPin), 14.2 (CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.5; FT-IR (neat) $\tilde{\nu}_{max}$: 3449, 2976, 1610, 1511, 1372, 1332, 1304, 1167, 1136, 968, 856, 697 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{21}H_{32}B_2NO_4$ $[M+H]^+$ 384.24, found 384.3.

3,5-bis(BPin)-6-fluoro-indole (3-15). In a glove box, a 20 mL vial, equipped with a magnetic stirring bar. The 6-fluoroindole 3-8 (54 mg, 0.4 mmol, 1 equiv) was stirred in HBPin (240 μL, 1.6 mmol, 4 equiv) at r.t. for 1 h followed by adding B_2Pin_2 (2.54 g, 10 mmol, 2 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (100 mg, 0.15 mmol, 6 mol % Ir) and d^{t}bpy (80 mg, 0.3 mmol, 6 mol %). HBPin (210 μL, 1.4 mmol, 0.28 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. THF (1 mL) was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for 1 min, the resulting solution was transferred to the vial containing the indole substrate. Additional THF (1 mL) was used to wash the test tubes and the washings were transferred to the vial. The vial was well sealed, brought out of the glove box and stirred at 80 °C. After 5 h, the reaction was stopped followed by removing the dark brown red color from the reaction solution with silica bed. The crude material was concentrated and purified by column (30% ethyl acetate/hexanes) on silica gel. The product was isolated as a colorless oil (112 mg, 90%). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (br s, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 7.61 (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J*

= 10.3 Hz, 1H), 1.38 (s, 12 H, 4 CH_3 of BPin); 1.37 (s, 12 H, 4 CH_3 of BPin) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, *J* = 242 Hz), 139.2 (d, *J* = 13.4 Hz), 134.6 (d, *J* = 2.9 Hz), 130.9 (d, *J* = 9.5 Hz), 127.7, 97.1 (d, *J* = 29.6 Hz), 83.5 (2 C), 83.0 (2 C), 24.9 (4 CH_3 of BPin), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.7; FT-IR (neat) $\tilde{\nu}_{max}$: 3423, 2980, 1625, 1475, 1373, 1145, 982, 851, 674 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{29}B_2FNO_4$ $[M+H]^+$ 387.22, found 388.3.

3,5-bis(BPin)-N-Boc-indole (3-17). In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with N-Boc-6-fluoroindole 3-16 (471 mg, 2 mmol, 1 equiv) and B_2Pin_2 (1 g, 4 mmol, 2 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (40 mg, 0.06 mmol, 6 mol % Ir) and d^{t}bpy (32 mg, 0.12 mmol, 6 mol %). HBPin (84 μL, 0.56 mmol, 0.28 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. THF (1 mL) was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for 1 min, the resulting solution was transferred to the vial containing the indole substrate. Additional THF (3 mL) was used to wash the test tubes and the washings were transferred to the vial. The vial was well sealed, brought out of the glove box and stirred at 80 °C. After 3 h, the reaction was stopped followed by removing the dark brown red color from the reaction solution with silica bed. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (780 mg, 80%, mp 163°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (d, *J* = 5.9 Hz, 1H), 7.95 (s, 1H), 7.85 (d, *J* = 10.8 Hz, 1H), 1.65 (s, 9 H, 3 CH_3 of Boc), 1.39 (s, 12 H, 4 CH_3 of BPin); 1.38 (s, 12 H, 4 CH_3 of BPin) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7 (d, *J* = 244 Hz), 149.0, 135.6, 130.3 (d, *J* = 9.5 Hz), 129.3, 102.0 (d, *J* = 31.5 Hz), 84.3 (C), 83.7 (2 C), 83.5 (2 C), 28.1 (3 CH_3 of Boc), 24.9 (8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 29.8; FT-IR (neat) $\tilde{\nu}_{max}$: 3447, 2978, 1740, 1636, 1559, 1443, 1363, 1322,

1255, 1139, 1063, 853, 668 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{25}H_{37}B_2FNO_6$ $[M+H]^+$ 488.27, found 488.3.

7-BPin-indole (3-18). The general procedure was applied to 2,7-bis(BPin)-indole 3-6 (36.9 mg, 0.1 mmol, 1 equiv) and $Bi(OAc)_3$ (7.72 mg, 0.02 mmol, 20 mol%) with solvent mixture MeOH /THF (0.5 mL /0.4 mL) at 80 °C for 17 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. The product was isolated as white solid (20 mg, 82%). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.25 (br s, 1 H), 7.79 (d, *J* = 7.9 Hz, 1 H), 7.68 (d, *J* = 7.0 Hz, 1 H), 7.28 (dd, *J* = 2.8 Hz, 1 H), 7.15 (dd, *J* = 7.5 Hz, 1 H), 6.57 (dd, *J* = 2.8 Hz, 1 H), 1.41 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 141.0 (C), 129.2 (CH), 126.8 (C), 124.2 (CH), 124.0 (CH), 119.3 (CH), 102.0 (CH), 83.8 (2 C), 25.0 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.8. The spectral data were in accordance with literature.[4]

7-BPin-indole-2d (3-18-d_1). A vial equipped with a magnetic stirring bar was charged with 2,7-bis(BPin)-indole 3-6 (185 mg, 0.5 mmol, 1 equiv) and $Bi(OAc)_3$ (38.6 mg, 0.1 mmol, 0.2 equiv). Solvent mixture CD_3OD (810 μL, 20 mmol, 40 equiv) and THF (2 mL) was added to the vial. The vial was sealed and the reaction was carried out at the r.t. The reaction was monitored by TLC. After completion of the reaction, the crude material was passed through a plug of celite and washed three times by ethyl acetate. After the volatile materials were removed on a rotary evaporator the crude material was purified by column chromatography eluting with 5% ethylacetate/hexanes. The product was isolated as a white solid (96 mg, 79%, mp 87-88 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (br s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 6.9 Hz, 1H), 7.31 (t, *J* = 2.9 Hz, 0.13H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$,125 MHz): δ 140.9, 129.2, 126.7, 124.2, 123.9 (t, *J* =

25.8 Hz), 119.2, 101.9, 101.7, 83.8 (2 C), 25.0 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 31.2; FT-IR (neat) $\tilde{\nu}_{max}$: 3457, 2977, 1592, 1503, 1367, 1314, 1130, 978, 845, 805, 753, 678 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}DBNO_2$ $[M+H]^+$ 245.15, found 245.1. Percent D incorporation (based on quantitative ^{1}H NMR): 92%

4,7-bis(BPin)-indole (3-19). The general procedure was applied to 2,4,7-tri(BPin)-indole 3-7 (100 mg, 0.2 mmol, 1 equiv) and $Bi(OAc)_3$ (15.4 mg, 0.04 mmol, 20 mol%) with solvent mixture MeOH /THF (1 mL /0.8 mL) at 80 °C for 17 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. The product was isolated as white solid (55.4 mg, 75%, mp 225°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.24 (br s, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 5.4, 2.9 Hz, 1H), 7.03 (t, *J* = 4.9, 2.9 Hz, 1H), 1.40 (d, *J* = 2.5 Hz, 24 H, 8 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3, 131.5, 128.2, 126.9, 124.4, 103.9, 83.9 (2 C), 83.4 (2 C), 25.0 (8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 31.6; FT-IR (neat) $\tilde{\nu}_{max}$: 3426, 2978, 1400, 1325, 1137, 1067, 968, 856 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{30}B_2NO_4$ $[M+H]^+$ 370.23, found 370.3.

4-BPin-6-fluoro-indole (3-20). The general procedure was applied to 2,4,7-tri(BPin)-6-fluoroindole 3-10 (513 mg, 1 mmol, 1 equiv) and $Bi(OAc)_3$ (77.2 mg, 0.2 mmol, 20 mol%) with solvent mixture MeOH /THF (10 mL /4 mL) at 80 °C for 15 h. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. The product was isolated as white solid (205 mg, 80%, mp 114°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (br s, 1H), 7.46 (dd, *J* = 10.3, 2.5 Hz, 1H), 7.18 (dd, *J* = 2.9 Hz, 1H), 7.14 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.07 (dd, *J* = 2.5 Hz, 1H), 1.43 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 159.3 (d, *J* = 237 Hz), 135.3 (d, *J* = 11.5 Hz),

129.1, 125.1 (d, J = 3.8 Hz), 115.3 (d, J = 22.9 Hz), 104.3, 100.3 (d, J = 25.8 Hz), 83.7 (2 C), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 31.3; FT-IR (neat) $\tilde{\nu}_{max}$: 3344, 2979, 1612, 1384, 1264, 1137, 1064, 966, 849, 782, 682 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}BFNO_2$ $[M+H]^+$ 261.13, found 262.1.

4,7-bis(BPin)-6-fluoro-indole (3-21). The general procedure was applied to 2,4,7-tri(BPin)-6-fluoroindole 3-10 (513 mg, 1 mmol, 1 equiv) and $Bi(OAc)_3$ (77.2 mg, 0.2 mmol, 20 mol%) with solvent mixture MeOH /THF (2.5 mL /4 mL) at 80 °C for 5 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. The product was isolated as white solid (259 mg, 67%, mp 185°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.34 (br s, 1H), 7.33 (d, J = 10.3 Hz, 1H), 7.27 (dd, J = 2.9, 2 Hz, 1H), 6.98 (dd, J = 2.9, 2 Hz, 1H), 1.42 (s, 12 H, 4 CH_3 of BPin), 1.39 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 164.3 (d, J = 246 Hz), 140.4, 128.1, 124.6 (d, J = 3.8 Hz), 114.9 (d, J = 25.8 Hz), 103.9, 83.9 (2 C), 83.8 (2 C), 25.0(8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.4; FT-IR (neat) $\tilde{\nu}_{max}$: 3125, 2923, 1559, 1401, 1256, 1139, 1063, 853 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{29}B_2FNO_4$ $[M+H]^+$ 387.22, found 388.3.

Optimized procedure, 4-BPin-2-carboethoxy-indole (3-22). The deborylation step was carried out neat with 4,7-bis(BPin)-2-ethyl ester-indole 3-12 (220.5 mg, 0.5 mmol)), $[Ir(OMe)(COD)]_2$ (10 mg, 0.03 mmol, 6 mol % Ir) in MeOH (800 μL, 20 mmol, 40 equiv) and THF (5 mL) at r.t. for 12 h and worked up as described in the general procedure. The crude material was concentrated by rot vap, and purified by column chromatography eluting with 5% ethylacetate/hexanes. The product was isolated as a white solid (85 mg, 54 %, mp 139 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.14 (br s, 1H), 7.70 (m, 1H), 7.68 (dd, J = 6.9, 1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.34 (dd, J = 8.3, 7.3 Hz, 1H), 4.45

(q, *J* = 6.9 Hz, 2 H, *CH*$_2$CH$_3$), 1.45 (t, *J* = 7.3 Hz, 3 H, CH$_2$*CH*$_3$), 1.41 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3 (C=O), 136.2, 131.7, 129.0, 127.6, 124.6 (C), 114.8, 110.5, 83.6 (2 C), 61.0 (CH_2), 24.9 (4 CH_3 of BPin), 14.4 (CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.8; FT-IR (neat) $\tilde{\nu}_{max}$: 3331, 2979, 1686, 1521, 1250, 1146, 1022, 980, 852, 769, 681 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{17}H_{23}BNO_4$ $[M+H]^+$ 316.16, found 316.2.

4-BPin-2-methyl-indole (3-23). The deborylation step was carried out neat with 4,7-BPin-2-methylindole 3-14 (38 mg, 0.1 mmol, 1 equiv), $[Ir(OMe)(COD)]_2$ (1 mg, 0.003 mmol, 3 mol % Ir) in MeOH and DCM at 60 °C for 2 h and worked up as described in the general procedure. The crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) on silica gel to afford the product as white solid (20 mg, 74%, mp 157–160 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (br s, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.71 (s, 1H), 2.47 (s, 3H), 1.39 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.7, 135.4, 133.9, 127.6, 120.3, 113.0, 102.4, 83.3 (C), 25.0 (4 CH_3 of BPin), 13.8(CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.9; FT-IR (neat) $\tilde{\nu}_{max}$: 3436, 2976, 1549, 1371, 1269, 1130, 1064, 973, 858, 637 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{15}H_{21}BNO_2$ $[M+H]^+$ 258.16, found 258.2.

5-BPin-6-fluoro-indole (3-24). The deborylation step was carried out neat with 3,5-bis(BPin)-6-fluoro-indole 3-15 (193 mg, 0.5 mmol, 1 equiv), $[Ir(OMe)(COD)]_2$ (5 mg, 0.015 mmol, 3 mol % Ir) in MeOH and DCM at 60 °C for 2 h and worked up as described in the general procedure. The crude material was purified by silica gel chromatography (30% ethyl acetate/hexanes) on silica gel to afford the product as white solid (86 mg, 66%).

Alternative procedure, 5-BPin-6-fluoro-indole (3-24). The general procedure was applied to 3,5-bis(BPin)-6-fluoro-indole 3-15 (77 mg, 0.2 mmol, 1 equiv) and $Bi(OAc)_3$ (15.4 mg, 0.04 mmol,

20 mol%) with solvent mixture MeOH /THF (0.8 mL /0.4 mL) at 80 °C for 3 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (46 mg, 88 %, mp 159-162°C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1H), 8.05 (d, *J* = 5.4 Hz, 1H), 7.17 (dd, *J* = 3.4, 2.5 Hz, 1H), 7.04 (d, *J* = 10.3 Hz, 1H), 6.53 (dd, *J* = 2.5 Hz, 1H), 1.38 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (d, *J* = 242 Hz), 138.2 (d, *J* = 13.4 Hz), 129.6 (d, *J* = 10.5 Hz), 128.3, 124.7 (d, *J* = 3.8 Hz), 103.1, 97.1 (d, *J* = 29.6 Hz), 83.5 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.7; FT-IR (neat) $\tilde{\nu}_{max}$: cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}BFNO_2$ $[M+H]^+$ 261.13, found 262.1.

Optimized procedure, 5-BPin-N-Boc-indole (3-25). The deborylation step was carried out neat with 3,5-bis(BPin)-N-Boc-indole 3-17 (195 mg, 0.4 mmol), $[Ir(OMe)(COD)]_2$ (8 mg, 0.024 mmol, 6 mol % Ir) in MeOH (800 μL, 20 mmol, 50 equiv) and THF (4 mL) at r.t. for 10 h and worked up as described in the general procedure. The crude material was concentrated by rot vap, and purified by column chromatography eluting with 5% ethylacetate/hexanes. The product was isolated as a colorless oil (67 mg, 47%). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, *J* = 5.9 Hz, 1H), 7.82 (br d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 2.9 Hz, 1H), 6.53 (d, *J* = 3.9 Hz, 1H), 1.66 (s, 9 H, 3 C*H*$_3$ of Boc), 1.38 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.1 (d, *J* = 244 Hz), 149.4, 129.1 (d, *J* = 9.5 Hz), 126.6, 126.2 (d, *J* = 3.8 Hz), 107.2, 102.2 (d, *J* = 31.5 Hz), 84.1 (C), 83.7 (2 C), 28.1 (3 CH_3 of Boc), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.1; FT-IR (neat) $\tilde{\nu}_{max}$: 3443, 2979, 1737, 1622, 1446, 1359, 1257, 1143, 1085, 959, 860, 732 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{19}H_{26}BFNO_4$ $[M+H]^+$ 362.19, found 362.3.

4,7-bis(BPin)-6-fluoro-N-Boc-indole (3-26). A round bottom flask equipped with a magnetic stirring bar, a condenser and an additional funnel was charged with 4,7-bis(BPin)-6-fluoro-indole 3-21 (217 mg, 0.56 mmol, 1 equiv), MeCN (1 mL) and NEt_3 (1.6 mL, 11.2mmol, 20 equiv) were injected into the flask followed with refluxing the solution at 80 °C for 0.5 h. DMAP (137 mg, 1.12 mmol, 2 equiv) and Boc_2O (2.4 g, 11.2 mmol, 20 equiv) were weighted together in one vial, after adding the MeCN (1 mL), allowing the mixture stirred at r.t. until it became a yellow homogenous solution. Then this solution was introduced to an additional funnel and allowed it flow at the rate of 1 drop/ 2 min to the round bottom flask, the reaction was refluxed at 80 °C for another 10 h. Until the reaction was judged to be complete by TLC, it was concentrated and purification by column chromatography eluting with 5% acetones/heptanes. The product was isolated as white solid (250 mg, 80%, mp 158 °C). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, *J* = 3.4 Hz, 1H), 7.37 (d, *J* = 9.8 Hz, 1H), 7.01 (d, *J* = 3.9 Hz, 1H), 1.62 (s, 9 H, 3 C*H*$_3$ of BPin), 1.45 (s, 12 H, 4 C*H*$_3$ of BPin), 1.37 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 163.6 (d, *J* = 237 Hz), 150.1, 136.7, 131.0, 125.0 (d, *J* = 3.8 Hz), 117.2 (d, *J* = 25.8 Hz), 109.6, 84.0 (2 C), 83.9 (C), 83.8 (2 C), 28.2 (3 CH_3 of Boc), 25.6 (4 CH_3 of BPin), 25.0 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 29.1; FT-IR (neat) $\tilde{\nu}_{max}$: 3422, 2979, 1723, 1540, 1458, 1039, 1233, 1145, 935, 852, 769, 668 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{25}H_{37}B_2FNO_6$ $[M+H]^+$ 488.27, found 488.2.

7-BPin-6-fluoro-N-Boc-indole-4-d (3-27). The deborylation step was carried out neat with 4,7-bis(BPin)-6-fluoro-N-Boc-indole 3-26 (76 mg, 0.156 mmol, 1 equiv), $[Ir(OMe)(COD)]_2$ (0.78 mg, 0.00234 mmol, 1.5 mol% Ir) in CD_3OD (253 μL, 6.24 mmol, 40 equiv) and THF (253 μL) at r.t. for 10 h and worked up as described in the general procedure. The crude material was concentrated by rot vap, and purified by column chromatography eluting with 10% ethyl

acetate/hexanes. The product was isolated as a colorless oil (44 mg, 78%). Regiochemistry of the borylated products was assigned by NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (d, *J* = 3.4 Hz, 1H), 6.95 (d, *J* = 9.3 Hz, 1H), 6.50 (d, *J* = 3.4 Hz, 1H), 1.62 (s, 9 H, 3 C*H*$_3$ of Boc), 1.47 (s, 12 H, 4 C*H*$_3$ of BPin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 164.1 (d, *J* = 237 Hz), 150.0, 125.8, 125.0 (d, *J* = 3.8 Hz), 110.7 (d, *J* = 27.7 Hz), 107.7, 84.0 (3 C), 28.2 (3 CH_3 of Boc), 25.6 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 160 MHz): 28.4; FT-IR (neat) $\tilde{\eta}_{max}$: 3439, 2978, 1724, 1601, 1541, 1353, 1257, 1151, 1093, 984, 854, 736, 613 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{19}H_{25}DBFNO_4$ $[M+H]^+$ 363.19, found 363.2. Percent D incorporation (based on quantitative ^{1}H NMR): 84%

5.4. Experimental details for Chapter 4

General Procedure for Preparation of Deuterated Aromatics To 1 mmol borylated arene were added 20 mol% Ag_2O, 0.1 mL D_2O and 0.5 mL dry THF. The flask was sealed and heated in an oil bath to 80 °C until the reaction was judged complete by TLC thin plate. Upon completion, the mixture was filtered through 1 mL silicon gel, dried over $MgSO_4$ and evaporated. Column chromatography (5% ethyl acetate/hexane) afforded the product.

1,2,3-Trichlorobenzene-5-d. The deuteration step was then carried out at 80 °C for 1 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 100 mg of the deuterated compound (55%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, $J_{H\text{-}D}$ = 1.1 Hz). The spectral data were in accordance with literature.[3]

2,6-Dichloropyridene-4-d. The deuteration step was then carried out at 80 °C for 1 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 58 mg of the deuterated compound (40%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, $J_{H\text{-}D}$ = 1.1 Hz). The spectral data were in accordance with literature.[3]

3-Chlorobenzotrifluoride-5-d. The deuteration step was then carried out at 80 °C for 2.5 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 111 mg of the deuterated compound (78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br, 1 H), 7.54–7.48 (m, 2 H). The spectral data were in accordance with literature.[3]

3-Bromobenzonitrile-5-d. The deuteration step was then carried out at 80 °C for 3 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 109 mg of the deuterated compound (60%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (t, J = 1.6 Hz, 1 H), 7.73 (br, 1 H), 7.59 (br, 1 H). The spectral data were in accordance with literature.[3]

3-Chloroanisole-5-d. The deuteration step was then carried out at 80 °C for 2 h and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 89 mg of the deuterated compound (62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (br, 1 H), 6.88 (t, J = 2.3 Hz, 1 H), 6.77 (br, 1 H), 3.78 (s, 3 H). The spectral data were in accordance with literature.[3]

1,2-Dichlorobenzene-4-d. The deuteration step was then carried out at 80 °C for 3 h and worked up as described in the general procedure, after which the crude material was afford 135 mg of the deuterated compound (91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.44 (m, 2 H), 7.16-7.20 (m, 1 H). The spectral data were in accordance with literature.[3]