ALLIED STUDIES ON TOTAL SYTHESIS OF CYCLIC TRIPEPTIDE TMC-95 VIA AN IRIDIUM CATALYZED BORYLATION/DEBORYLATION STRATEGY AND TEACHING ORGANIC CHEMISTRY IN “WORDS”

By

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ABSTRACT

ALLIED STUDIES ON TOTAL SYTHESIS OF CYCLIC TRIPEPTIDE TMC-95 VIA AN IRIDIUM CATALYZED BORYLATION/DEBORYLATION STRATEGY AND TEACHING ORGANIC CHEMISTRY IN “WORDS”

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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.

Also, while I was a teaching assistant and a fixed-term instructor during my graduate studies at Michigan State University, I gradually realized that teaching is my passion and I am prepared to start my independent career and be an independent thinking teacher for the organic chemistry area. Owing to the nature of the subject, organic chemistry can be very visually distracting, and the image can be overpowering during student's learning. Like it or not students will try memorization first, our hypothesis is that once they know the "organic transformation formula" in words, via memorization or any other method, then introducing them to the structures of these functional groups will come with added context, and once they make that jump from word to structure they will be in a better position to understand reaction mechanisms.

By introducing functional group transformations without the "clutter" of structures, we predict that once structures are introduced students will prioritize what's important because they will have trained their minds to ask what is the functional group, not "where did I see that structure in my notes".

In short, we aim to train students to focus their attention on the reactive functional group of an organic molecule by emphasizing the use of WORDS to describe functional group transformation and teach the organic chemistry as the second language.

To my friends and families

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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 reactions 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]

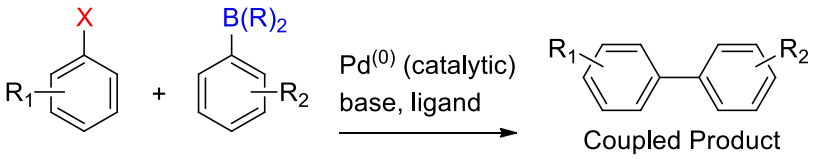


Figure 1. Suzuki cross-coupling reaction

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]

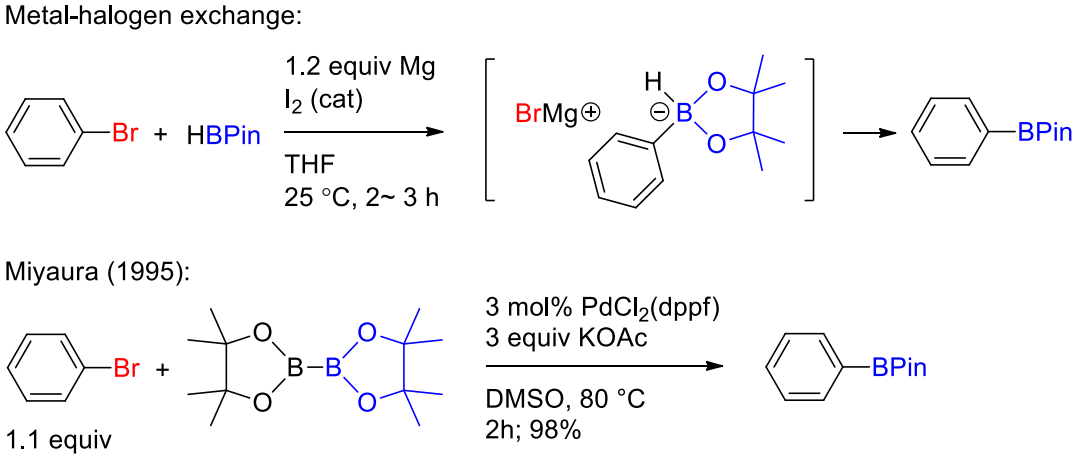


Figure 2. Preparing the aryl boronic ester

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]

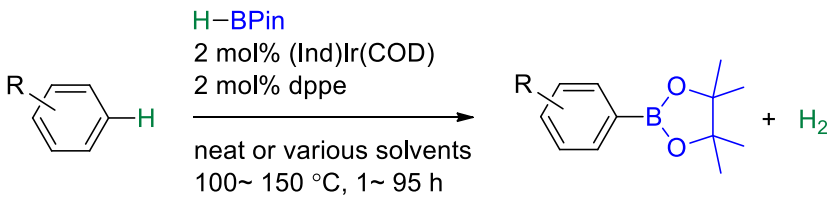


Figure 3. Example of a C–H activation/borylation

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]

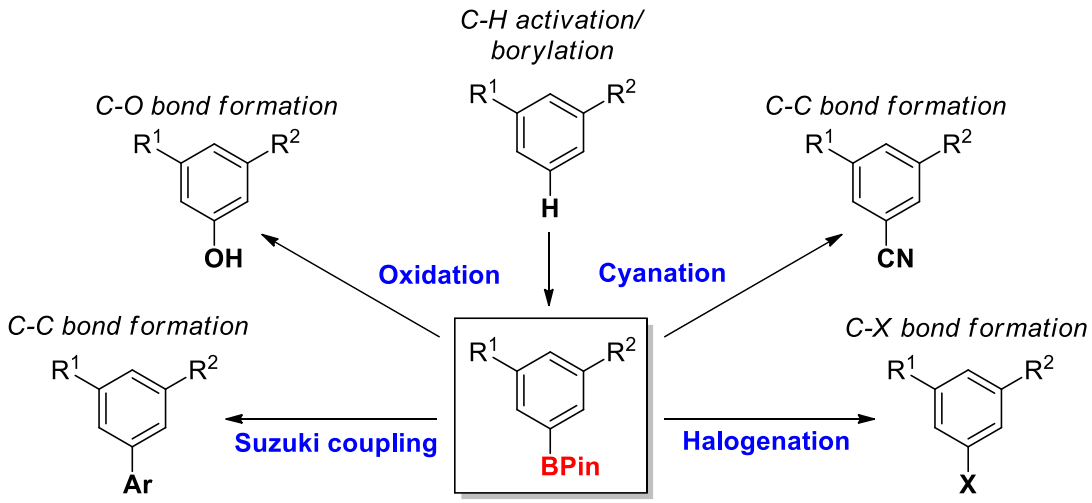


Figure 4. Synthetic utility of borylated arenes

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]

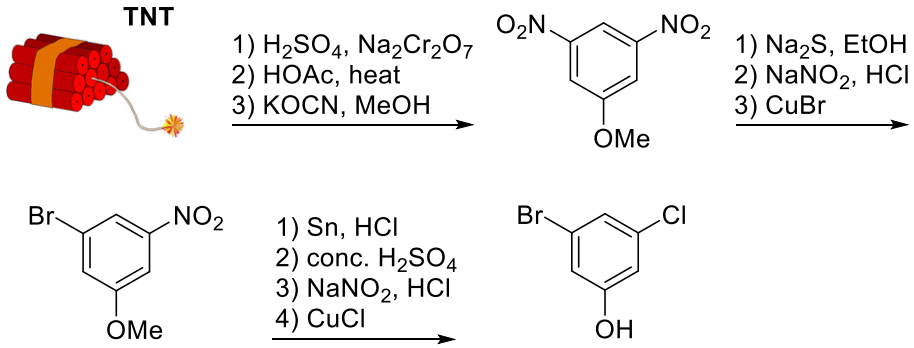


Figure 5. Synthesis 3-Bromo-5-chlorophenol via traditional route

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]

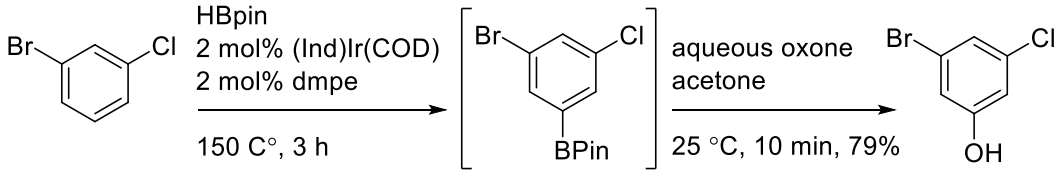


Figure 6. Synthesis 3-Bromo-5-chlorophenol via our method.

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. Besides, the transformations discussed other applications were of interest and were explored in our labs.

1.3. Iridium catalyzed deborylation

A 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 incorporation in the product was low owing to an incomplete borylation in step 1. To obtain high deuterium incorporation the borylated material was purified. Interestingly, when isolated 1,2,3-trichlorobenzene-5-Bpin was subjected to the same deuteration conditions as in step 2 protiodeborylation was not observed. However, by adding fresh Ir catalyst to a reaction with pure boronic ester, 5-deuterated-1,2,3-trichlorobenzene was generated. This indicated that the observed deborylations were Ir-catalyzed.

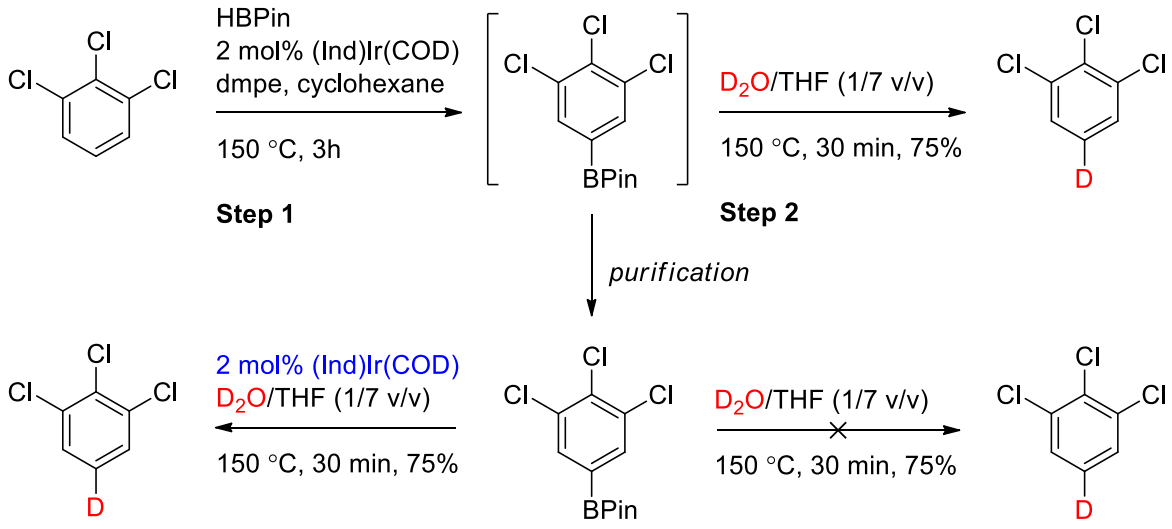


Figure 7. Discovery of Ir catalyzed deborylation during the borylation of trichlorobenzene

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

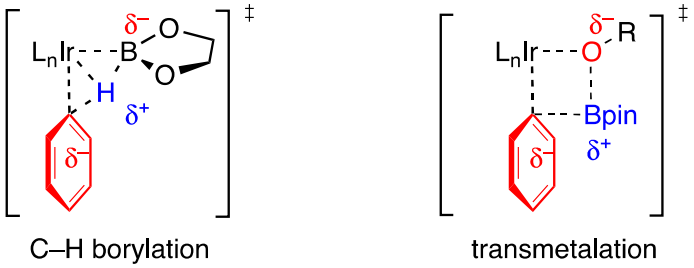
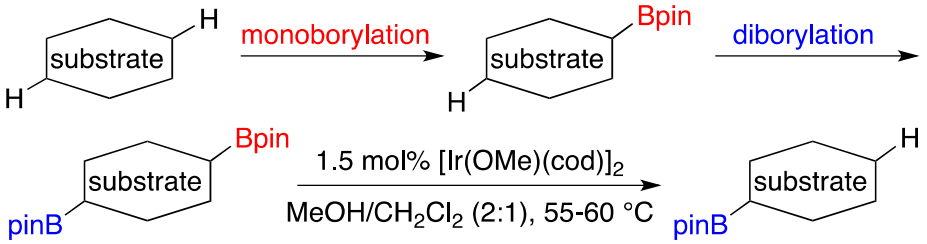


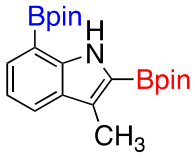
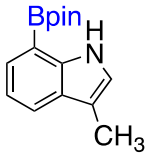
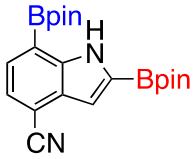
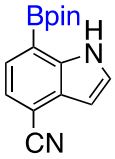
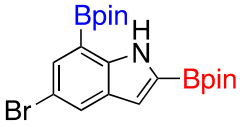
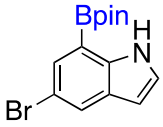
Figure 8. Putative mechanism of Ir-catalyzed borylation/deborylation

1.4. Selective deborylation of polyborylated material

It is possible to install more than one Bpin into a substrate. For example, when exposed to excess B_2pin_2 unprotected 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[8]



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 9 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 the next chapter.

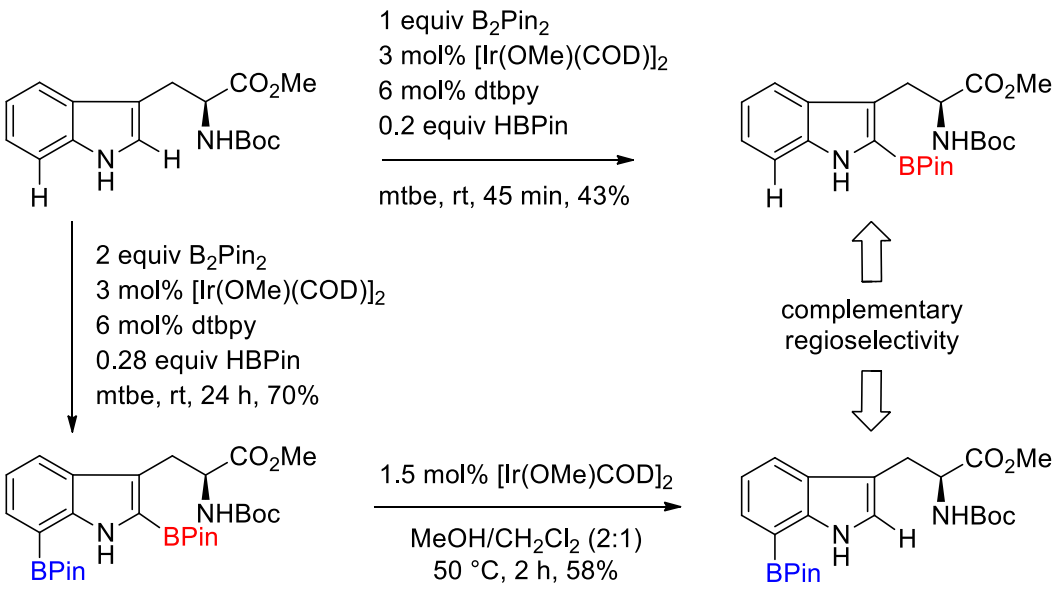


Figure 9. Ir-catalyzed borylations and deborylation on protected tryptophan

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REFERENCES

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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 95 A- D, a novel family of fungal metabolites with a distinctive cyclic peptide structure (Figure 10), 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]

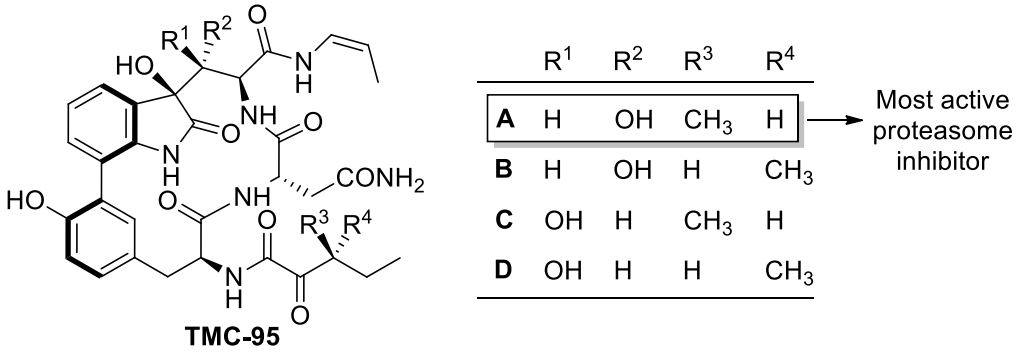


Figure 10. TMC-95 nature products.

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 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 syntheses 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 disconnections were evident for this macrocycle (Figure 11). One of the disconnections is the aryl-aryl linkage, which in the forward 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 Trp-Asp amide bond leads to a more convergent synthesis. Either formation of 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**.

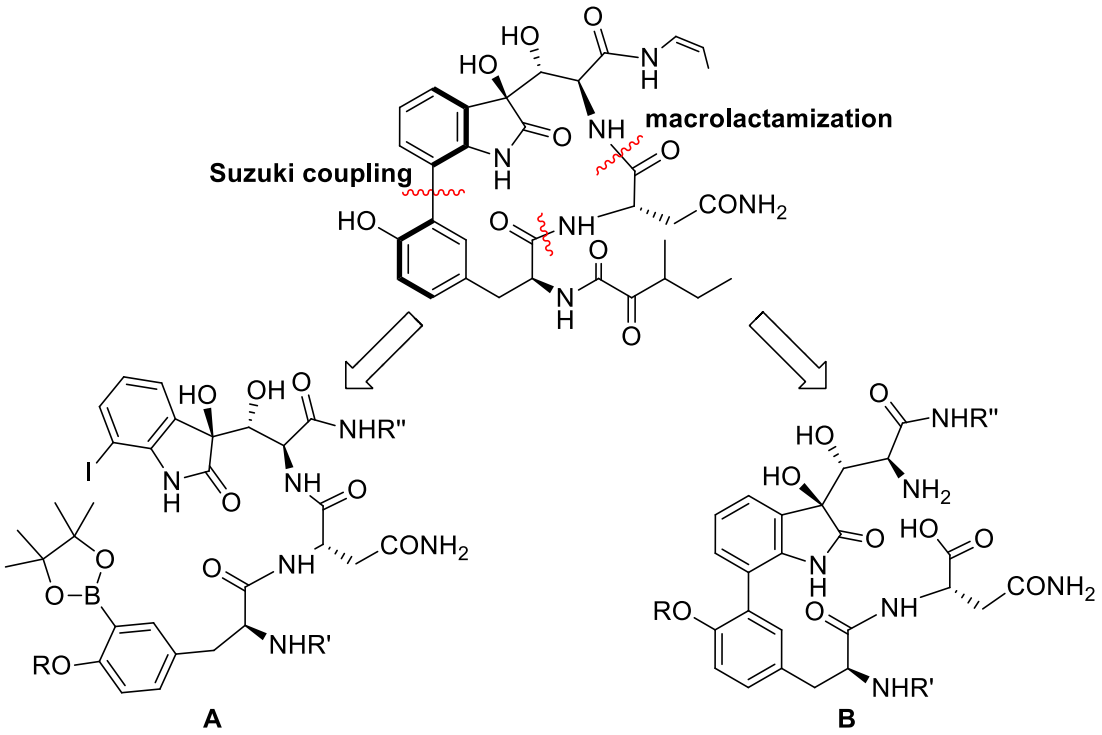
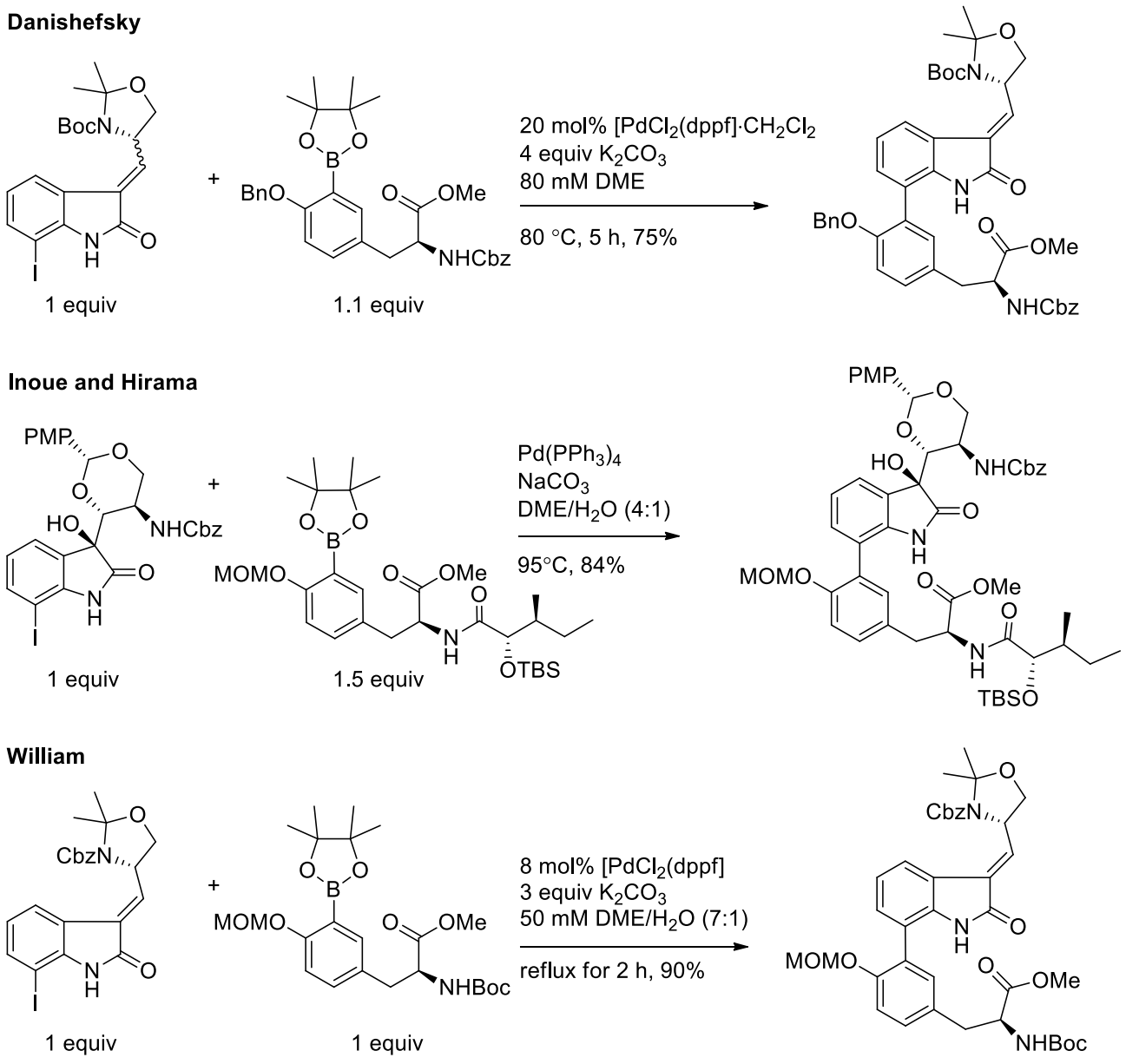


Figure 11. Synthetic pattern

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 and then closed the ring by macrolactamization (Scheme 1).

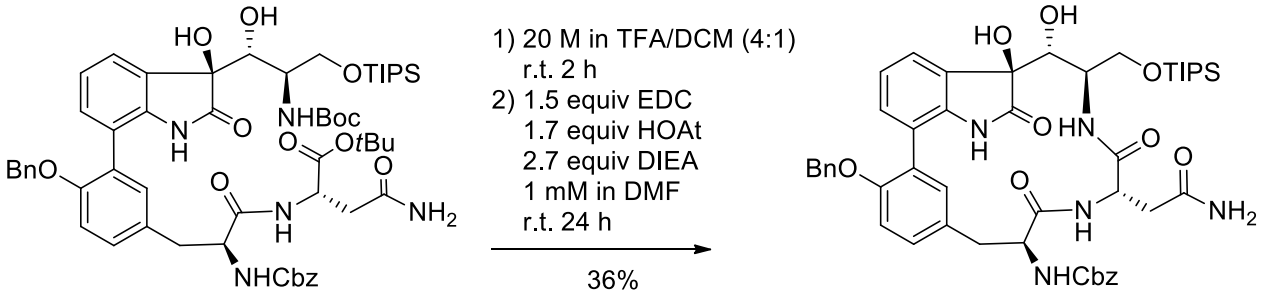


Scheme 1. Suzuki cross coupling step of prior TMC-95 synthesis

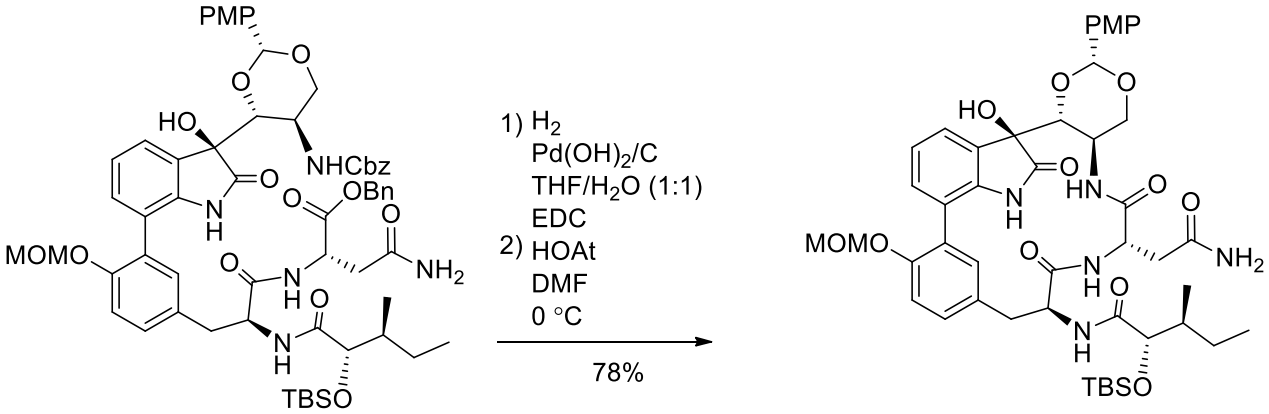
Most importantly, all three groups formed the aryloxidole linkage formation in yield greater than 75%. Notably, in all three cases the boronate was on the tyrosine unit while the electrophilic partner was on the oxidole.

For the ring closure, Danishefsky's group used EDC/HOAt-mediated amidation that afforded a 52% yield of the macrocycle. This cycloamidation pathway has been used by most of the research groups in their subsequent TMC-95 syntheses (Scheme 2).

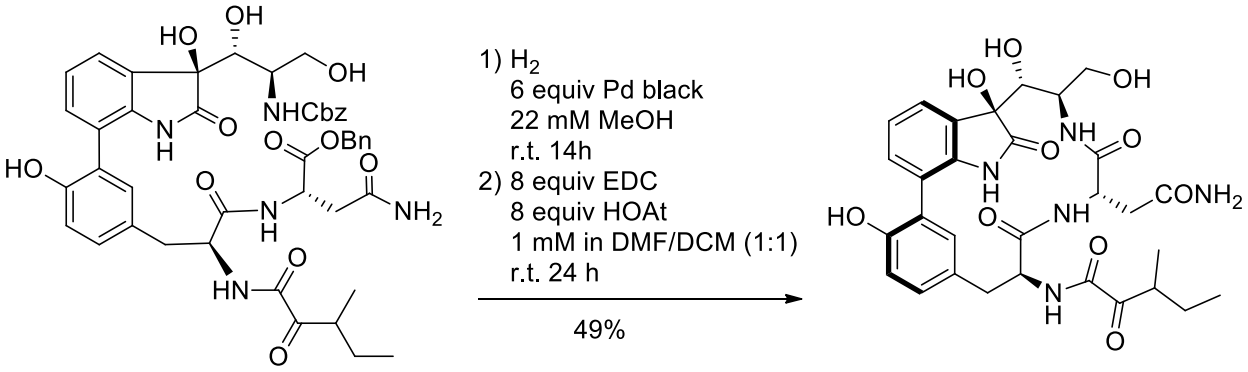
Danishefsky



Inoue and Hirama



William



Scheme 2. Macrolactamization step for TMC 95 syntheses

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]

Moroder's first approach was based on the synthesis of complestatin **A** and chloropeptin **B** (Figure 12), which bears a structure similar to TMC 95A as indicated in the square. During his early studies, the acid-catalyzed rearrangement that leads to bond-migration from the C6-indole/phenol to the C7-indole/phenol junction was a breakthrough that allowed him to synthesize chloropeptin **B** from complestatin **A.**

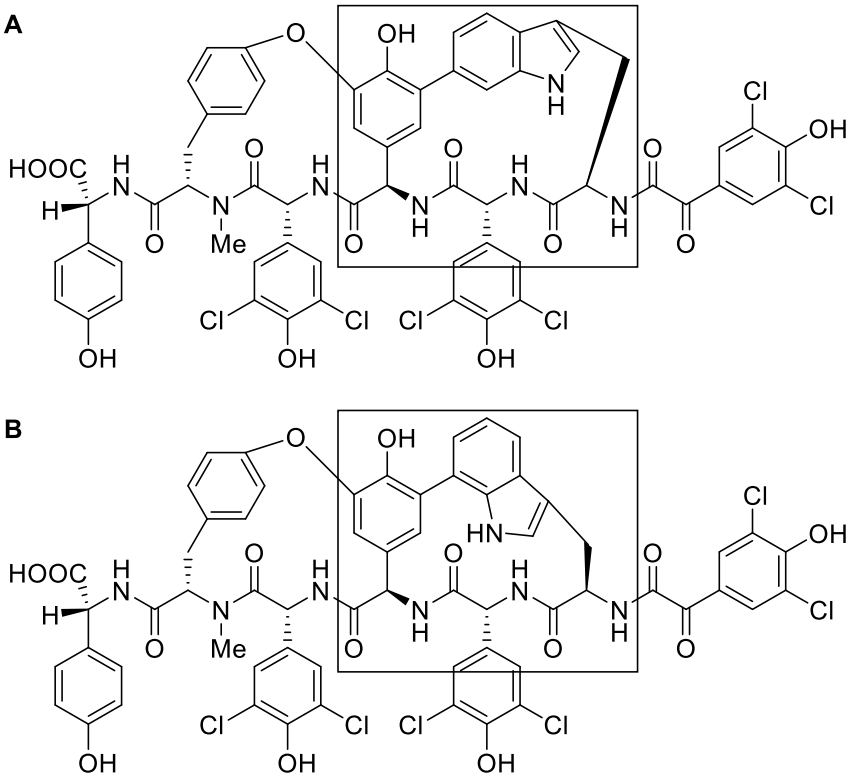
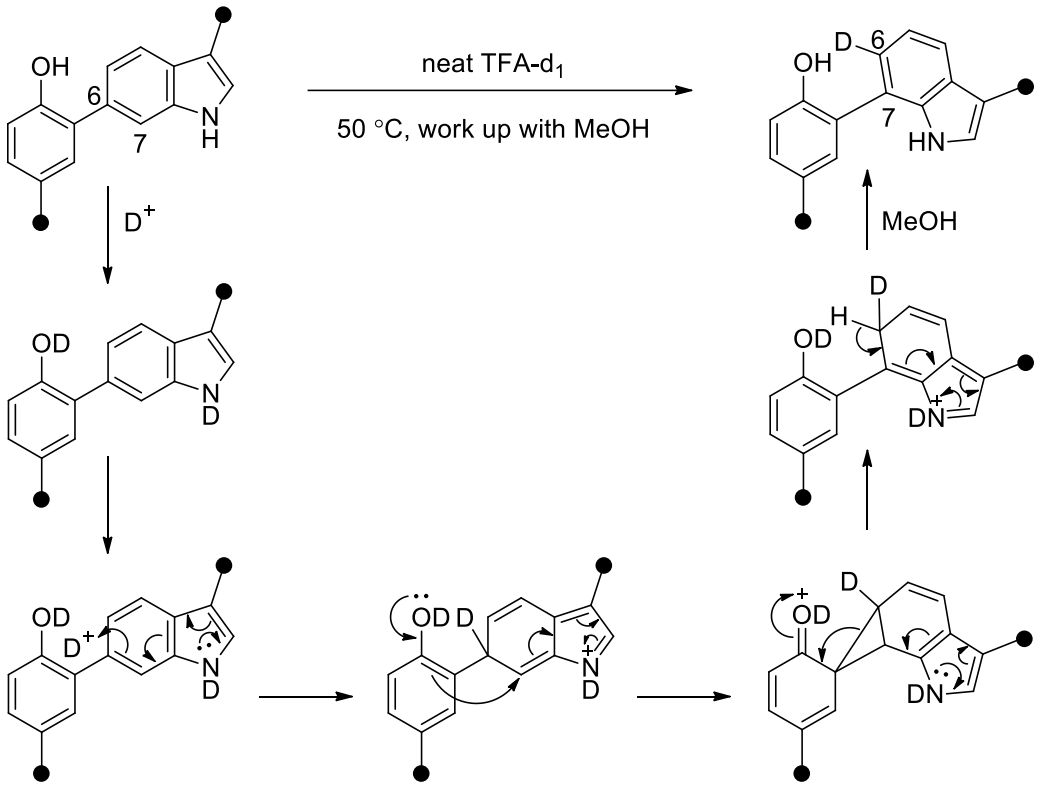


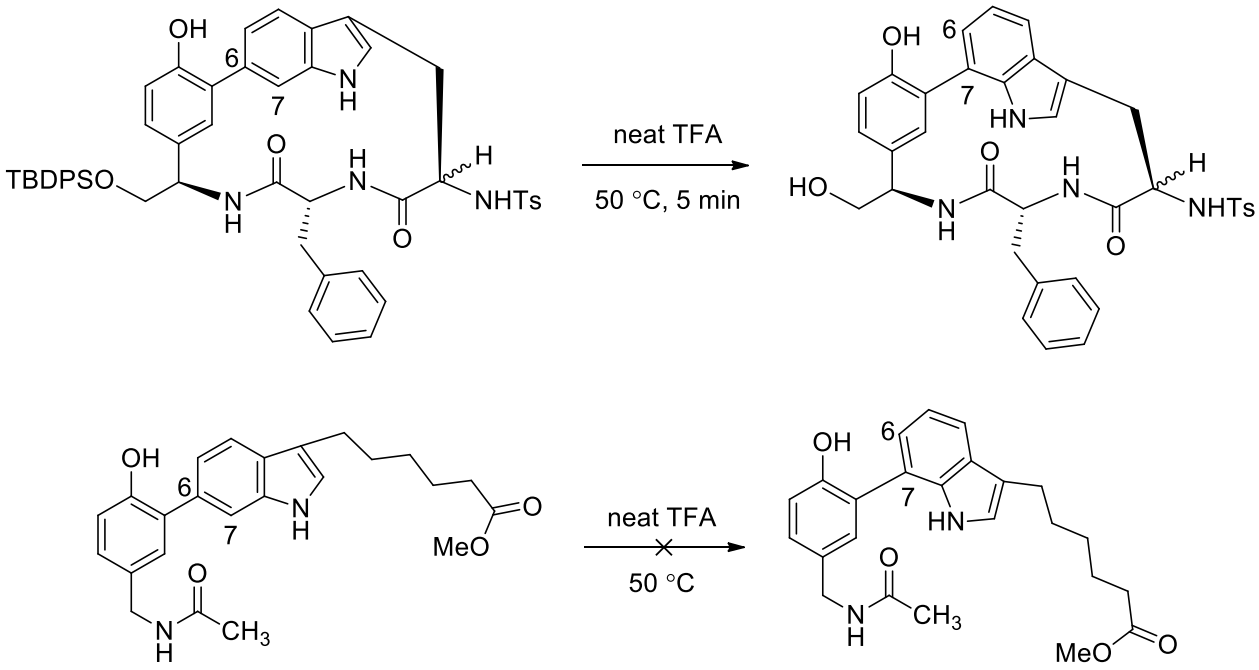
Figure 12. Structure of complestatin A and chloropeptin B

An isotope study[9] was done to understand how this acid-catalyzed rearrangement worked. By treating complestatin **A** in neat TFA-d_1 at 50 °C, the 17-membered ring system of complestatin unit was contracted to the 16-membered ring system chloropeptin and the deuterium was found on C6 of the indole moiety of chloropeptim **B**. The proposed mechanism is shown in Scheme 3.



Scheme 3. Putative mechanism of acid-catalyzed rearrangement

For comparison, a linear system was synthesized to see if migration from C6 to C7 occurred in an acyclic system (Scheme 4).[10] However, no migration from the 6-position to the 7-position was observed, which indicates that additional factors such as ring strain is needed to drive phenyl migration.



Scheme 4. Comparison between a linear and acyclic system under acidic condition

In order to test if this chemistry could enable the synthesis of a TMC 95A analog, a C6-indole/C3-tyrosine cross-linked precursor **A** was prepared and was expected to give the cyclized analog **B** (Figure 13). However, only dimerized product was observed in all macrolactamization attempts. In contrast, subjecting alternative precursor **C** to the ring closure step resulted in clean formation of the desired cyclic monomer **D**.

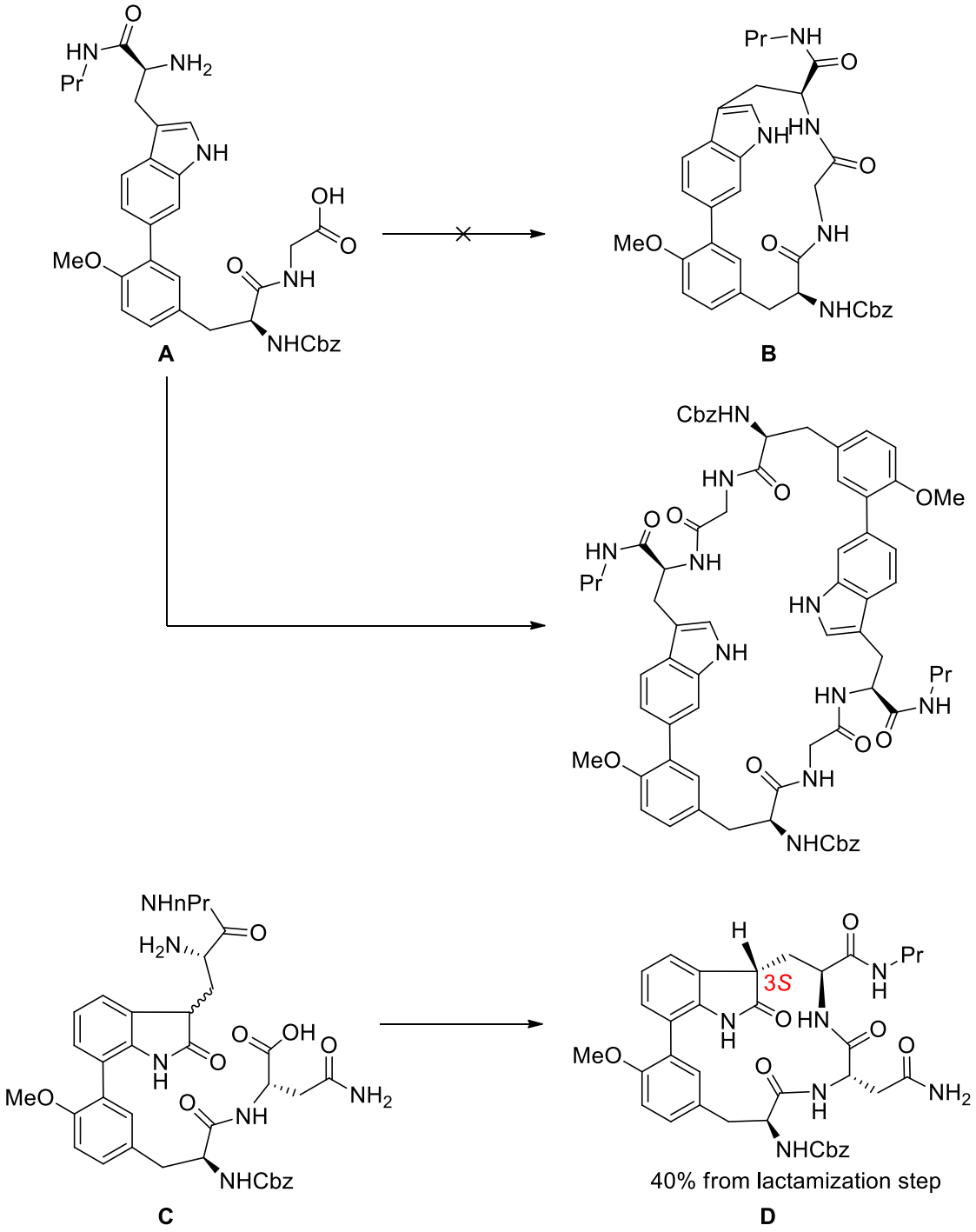


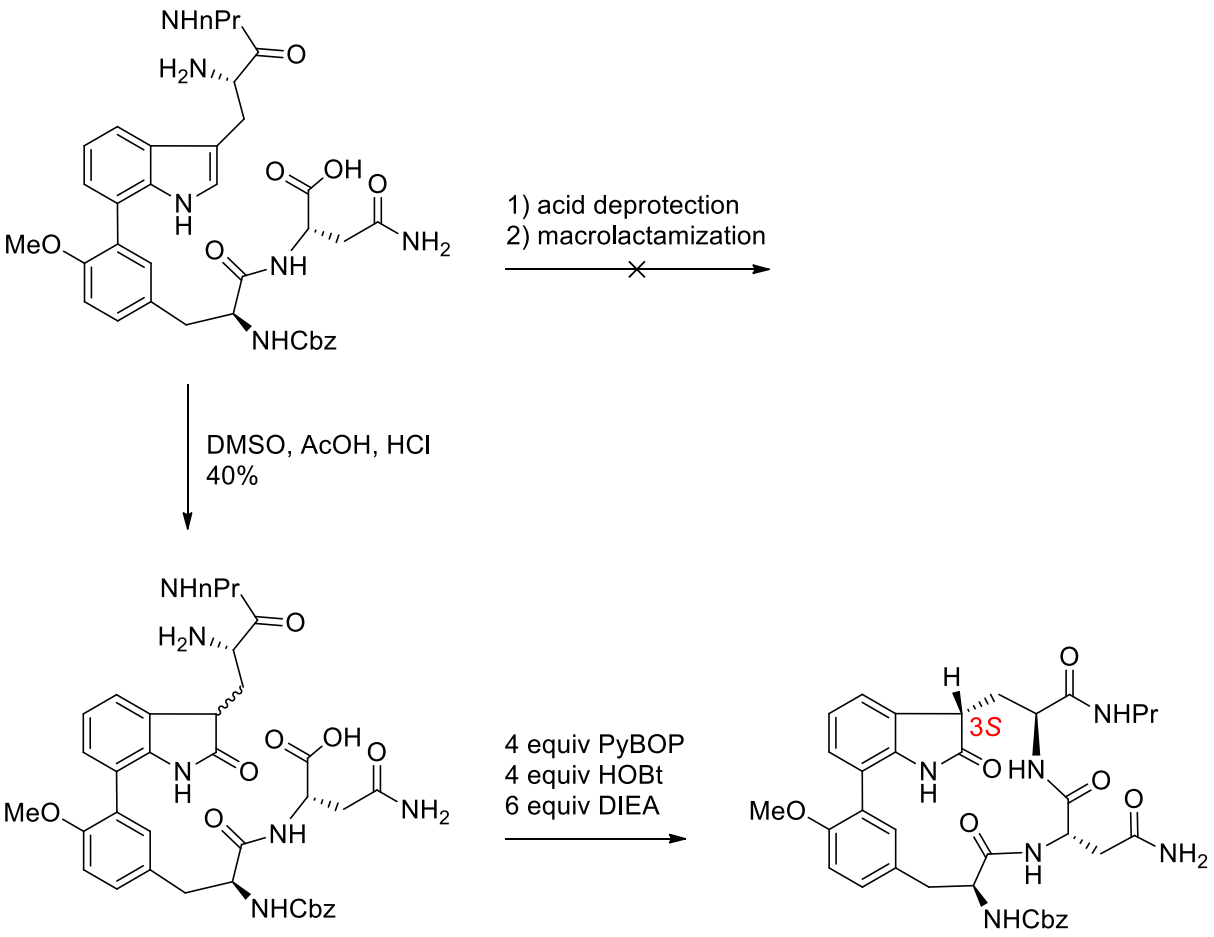
Figure 13. Reaction scheme of macrolactamization of the linear C6-indole/C3-tyrosine cross-linked precursor A and the linear C7-indole/C3-tyrosine cross-linked precursor B

In order to understand why macrolactamzion of C succeed and A failed, Moroder calculated the differences of the computed energies between open-chain precursors A and C and cyclic peptides B and D (Table 2)

Table 2. Computed energies for the lowest energy backbone conformation of the linear precursors A and C, and cyclic forms of the TMC-95A analog B and D (units in kcal/mol)

Linear precursor	Cyclic form	Energy difference
A: 191.90	**B:** 206.75	14.85
C: 130.38	**D:** 131.79	1.41

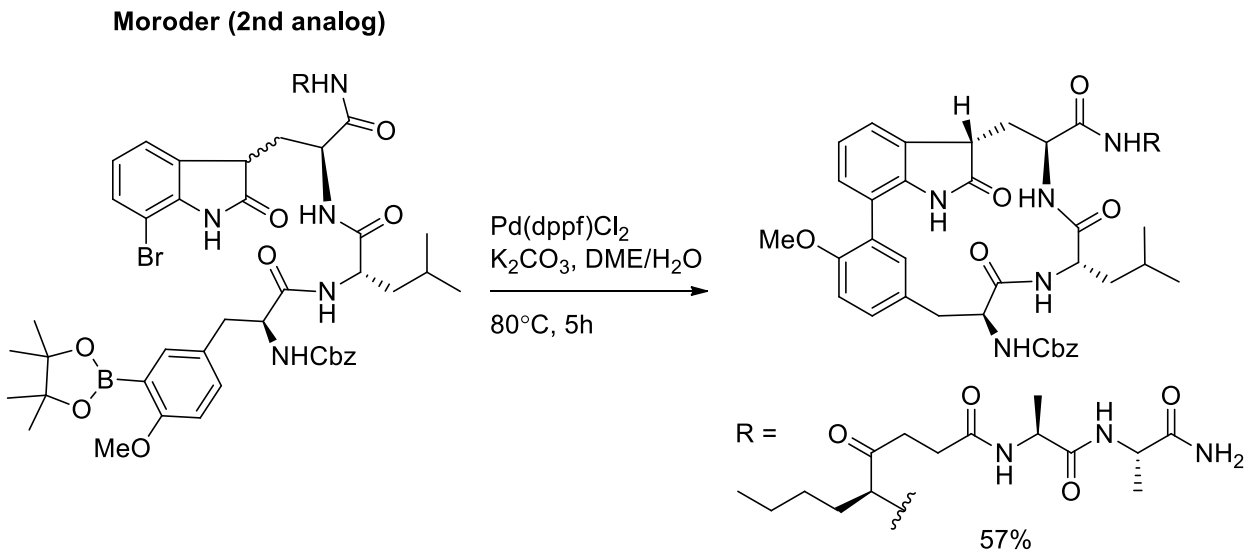
He found a significantly enhanced cyclization propensity for analog **C**, which fully agreed with the experimental results (Scheme 5). Thus, he suggested obtaining the monomeric cyclized species required a sp^3 hybridized C3 on the oxidole.



Scheme 5. Moroder's route

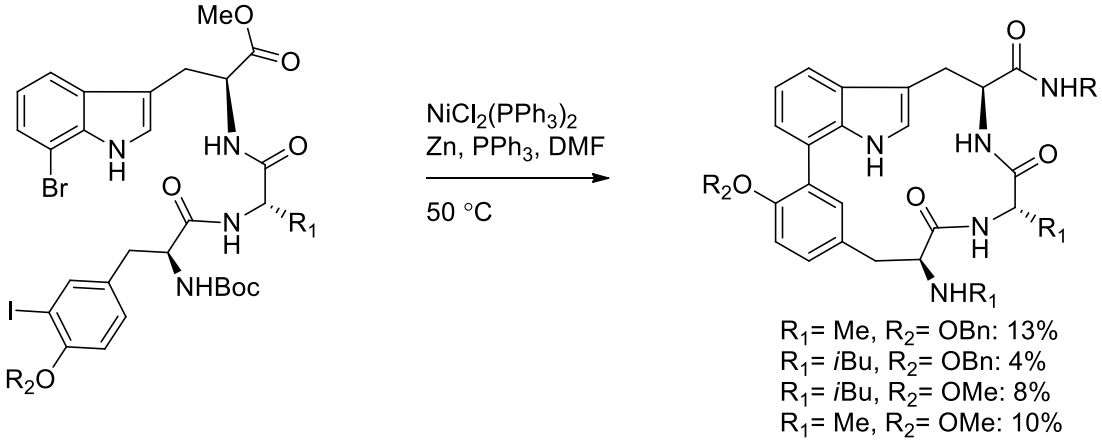
To test this hypothesis further, Moroder took advantage of the flexible nature of the key disconnection and investigated an approach where the tripeptide was formed first and the ring closed via Suzuki coupling.

In Moroder's second 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 (Scheme 6). Thus, he suggested that the ring could be closed only when a sp^3 hybridized C3 in oxidole.



Scheme 6. The second analog of Moroder

Vidal also replaced the highly oxidized tryptophan, but this action led to rather disappointingly low yields during nickel catalyzed intramolecular Negishi cross-couplings (Scheme 7). 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.



Scheme 7. Vidal's analog

2.3. Our synthetic approach to the TMC-95 core

Our proposed 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. Specifically, 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.

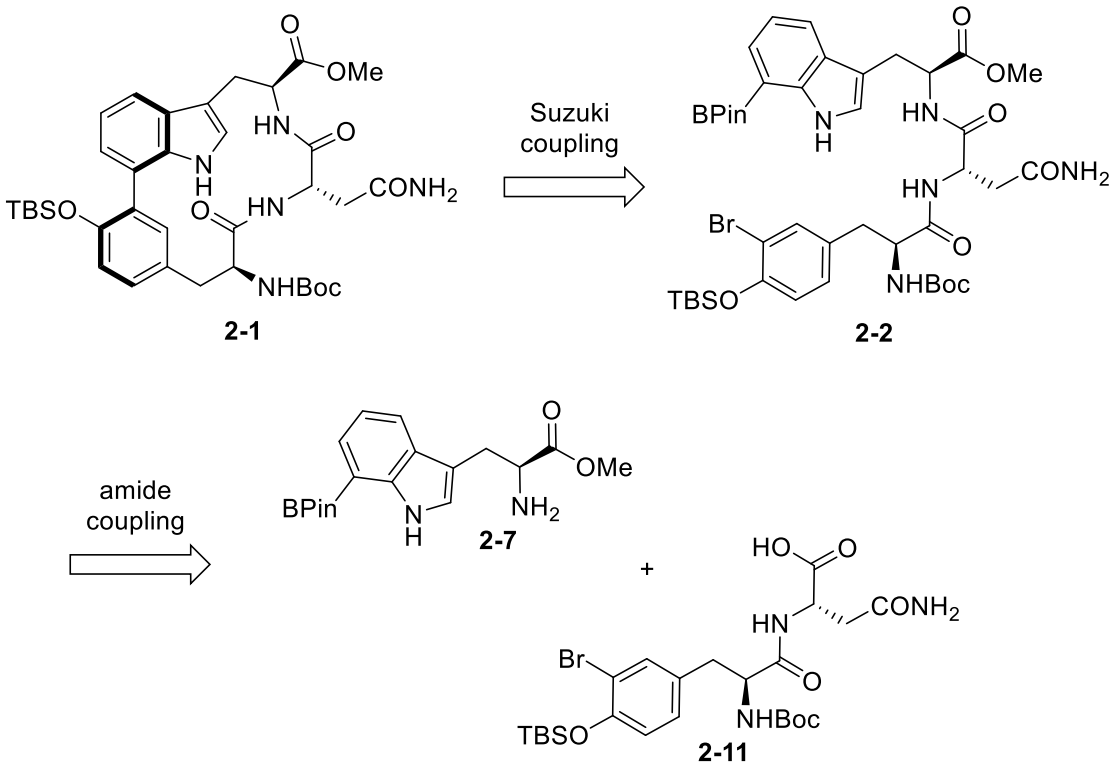
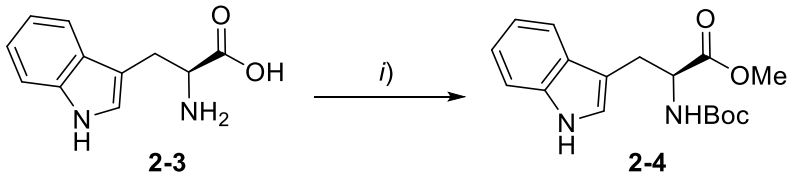


Figure 14. Retro synthetic design of our approach

2.4. Results and discussion

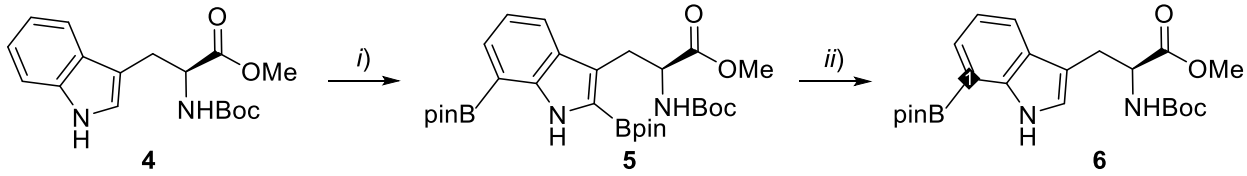
Synthesis of 7-pinacolboryl-L-tryptophan methyl ester (***2-7***). One of the building blocks for **2-2** was the N-Boc methyl ester of tryptophan **2-4**, which was converted to its 7-Bpin derivative **2-7** for a subsequent peptide coupling step. To start the synthesis of **2-7** both the amine and 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) Na_2CO_3, Boc_2O, 80%.[10]

Figure 15. Protection of L-tryptophan

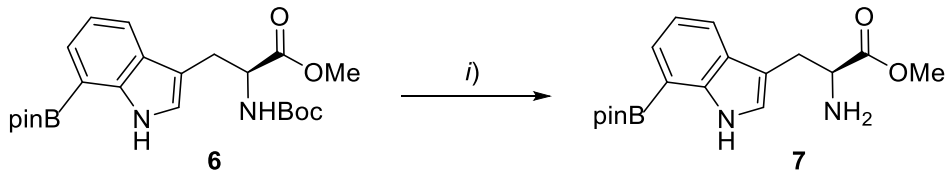
Now with compound **2-4** fully protected we were ready to apply our key borylation/deborylation sequence (Figure 16). First diborylation of **2-4** gave Bpins at the 2 and 7 positions, then 7-borylated protected tryptophan **2-6** was obtained by deborylation, which followed the rule of the first boron on during the Ir-catalyzed borylation being the first boron off in the Ir-catalyzed deborylation. The overall yield of **2-6** 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, rt. 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

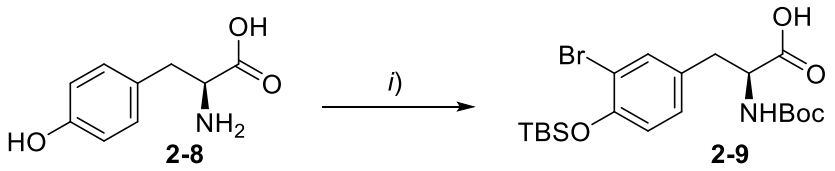
A key step in the reaction sequence to **2-1** required N-Boc deprotection of an early-stage precursor **2-6**. While TFA is the most commonly used reagent for Boc deprotection in peptide chemistry.[12] Attempts at converting **2-6** into **2-7** by treatment with TFA resulted in non-specific cleavage 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 alleviate 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, which was used directly in the next step (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

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

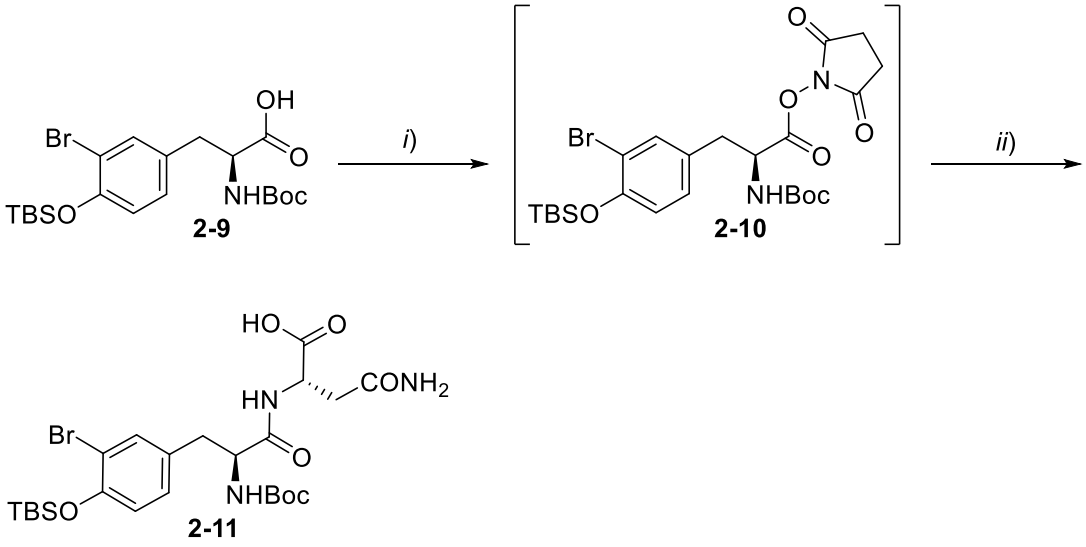
Synthesis of Dipeptide (***2-11***). To acquire dipeptide **2-11**, L-tyrosine **2-8** was converted to its arylbromo derivative by acetic acid-catalyzed bromination.[14] The resulting compound was *N*-Boc protected and then the phenol hydroxyl group was protected as a TBS ether to afford **2-9** in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



i) a) Br_2, HBr/AcOH, rt. 89%; b) 1.2 equiv Boc_2O, *t*BuOH/H_2O, pH 9, rt. 89%; c) 2 equiv TBSCl, imidazole, then K_2CO_3, H_2O, rt. 70% of **9**

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

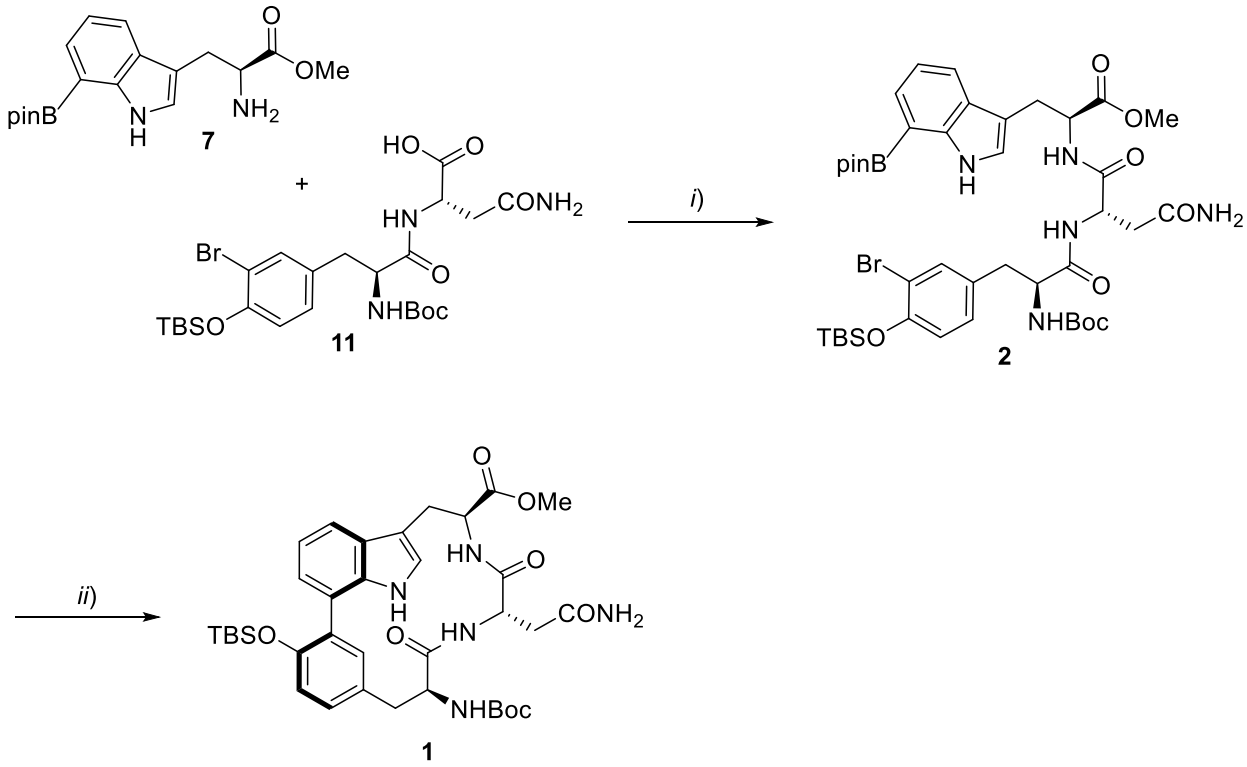
Compound **2-9** was activated to its hydroxysuccinimide ester **2-10** and coupled to L-asparagine monohydrate in one step. This method precluded the need to protect and subsequently deprotect L-asparagine as an ester. This convenient "one-step" reaction afforded dipeptide **2-11** in 79% yield (Figure 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) 1.2 equiv *N*-hydroxysuccinimide, DCC, DCM, rt. 4 h; *ii*) 10 equiv 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 rt. 68%; b) cataXium A, Pd_2dba_3, CuCl, K_2CO_3, dioxane/H_2O, at 60 °C

Figure 20. Preparation of a tripeptide followed by 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. As this is only a model study, optimization of these conditions for the selective macrocycle formation and its oxidation to afford the real TMC-95 core will explored in due course. However, the results from this model study inspired us to explore allied chemistry

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

3.1. Discovery bismuth mediated deborylation and Prior art

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 toward to TMC-95. 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.

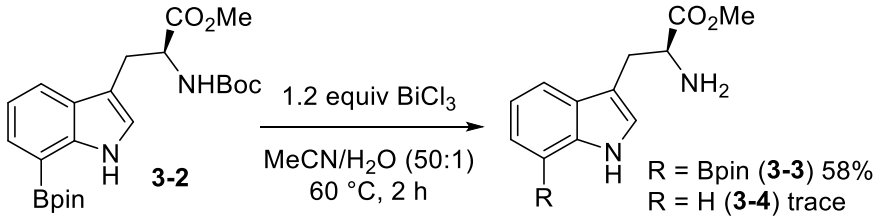


Figure 21. Discovery of Bi catalyzed protideborylations

This small amount of deborylated byproduct led us to consider whether bismuth salts could facilitate selective protideborylation in a way similar to the previously described Ir-protideborylations. Also, 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-protideborylation to selectively afford the C7-products (Figure 21).

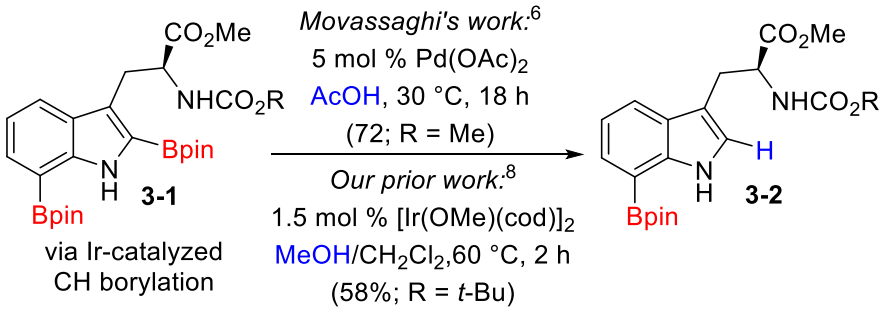


Figure 22. Prior art

While at first glance this tactic may not seem "green" owing to the loss of atom economy, from a strategic perspective such a borylation/protideborylation 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] And the rule in the deborylation seems follow the first Bpin “on” during the Ir-catalyzed borylation was the first Bpin “off” in the Ir-catalyzed protideborylation.

3.2. Development of bismuth mediated deborylation

Since we discovered that bismuth salts could facilitate selective protideborylation in a way similar to the Ir- and Pd-catalyzed protideborylations. 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]

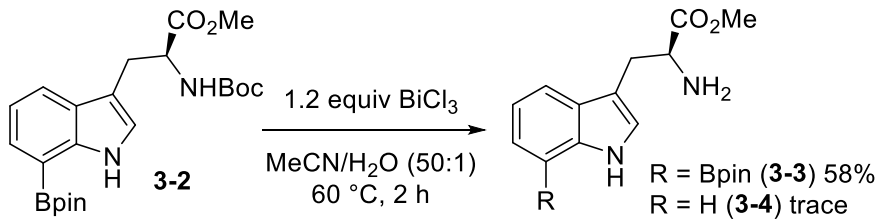
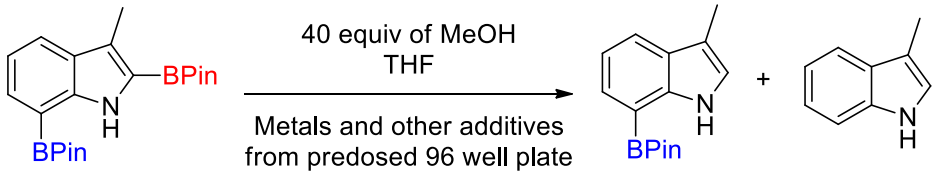


Figure 23. Discovery of Bi catalyzed protideborylations

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

Table 3. High throughput experiments on 3-methyl 2,7-bisborylatedindole deborylation conducted by Damith Perera



	1	2	3	4	5	6	7	8	9	10	11	12
A	Control	LiCl	NaF	NaBr	NaI	NaCN	Na TFA	Na TCA	$NaBF_4$	NaOTs	Na2SO3	Na_2S_2O3
B	Na_2SO_4	KCl	CsF	CsCl	$V(acac)_2$	$CrCl_2$	$MnCl_2$	$FeCl_2$	$FeCl_3$	Fe (II) acac	Fe (III) acac	Co $(acac)_2$
C	$Co(acac)_3$	NiF_2	$NiBr_2$ /DME	Ni (II) acac	(PPh_3) $NiCl_2$	CuCl	$CuCl_2$	CuBr	CuI	Cu (II) (acac)	(1,10-phenan)Br_2 Cu II	Cp_2ZrCl_2
D	Mo(acac)	$Pd(OAc)_2$	Pd $(Cl)_2$dppf DCM	$Pd_2(dba)_3$	Ag_2O	AgOTf	AuCl	$AuCl_3$	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) OTf_2	$La(OTf)_3$	$Sm(OTf)_3$	$Yb(OTf)_3$
F	$Hf(OTf)_3$	$BiOTf_3$	Boron oxide	$Al(OiPr)_3$	$Ti(OMe)_4$	$CeCl_3$	$ZnCl_2$	$K2CO_3$	$KHCO_3$	KOAc	$K3PO_4$	2,2-diphenyl ethylamine
G	proton sponge	4-phenylpy	oxalic acid	BSA	citric acid	3-phenyl propanoic acid	Bu_4NBr	$NaBH_4$	$PhI(OAc)_2$	CAN	oxone	AIBN
H	BHT	18-Crown-6	4A, MS	diamine	aminoalcohol	TPP	dppf	CataXCium A	X phos	salen	phenantroline	BINOL

Conditions: 10 µmol substrate, 100 µL THF, 40 equiv of each MeOH Standard: 0.1 equiv of 1,3,5-tri-tertbutylbenzene

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.

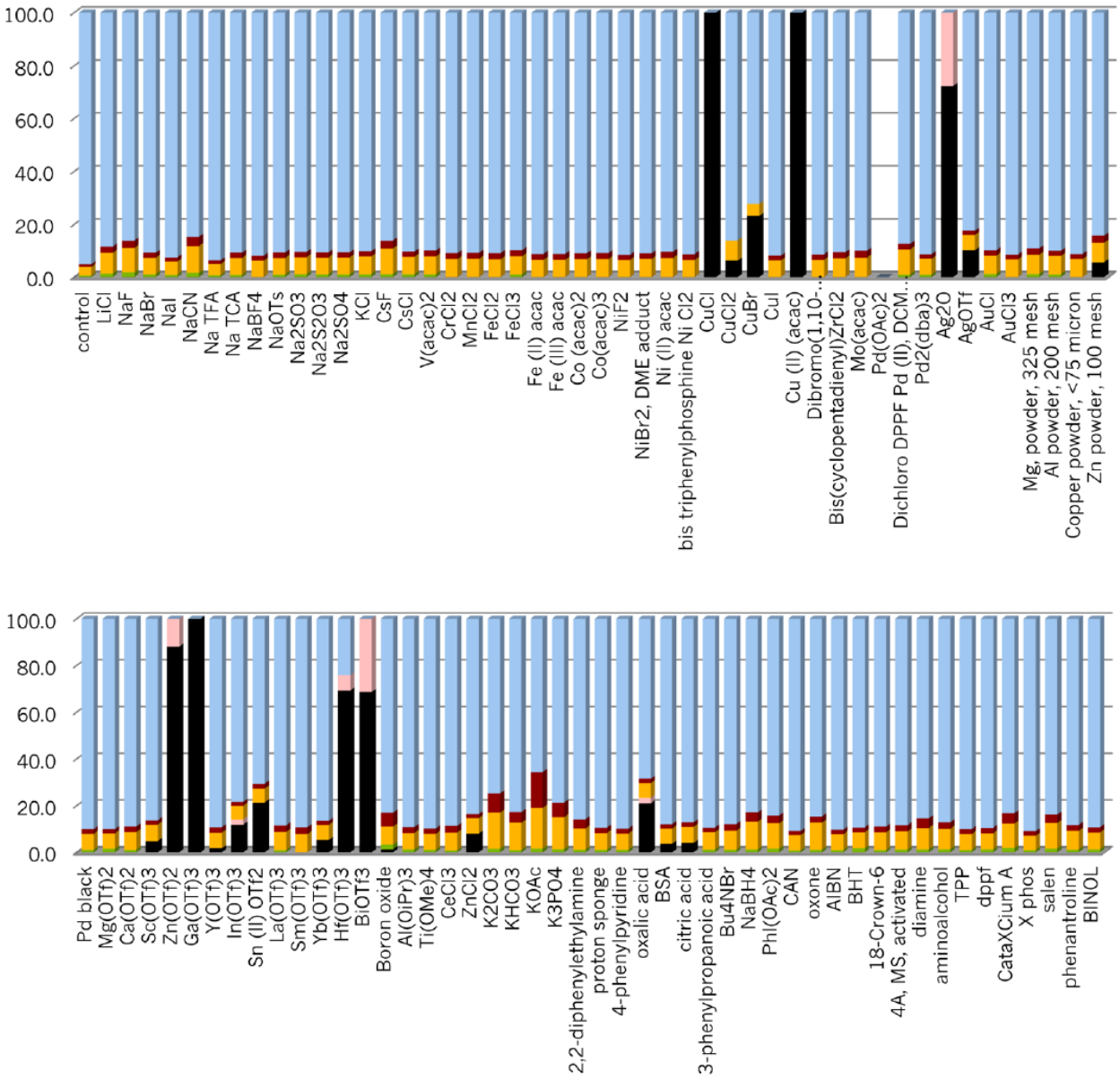


Figure 24. Deborylation feedback from high throughput screening

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.

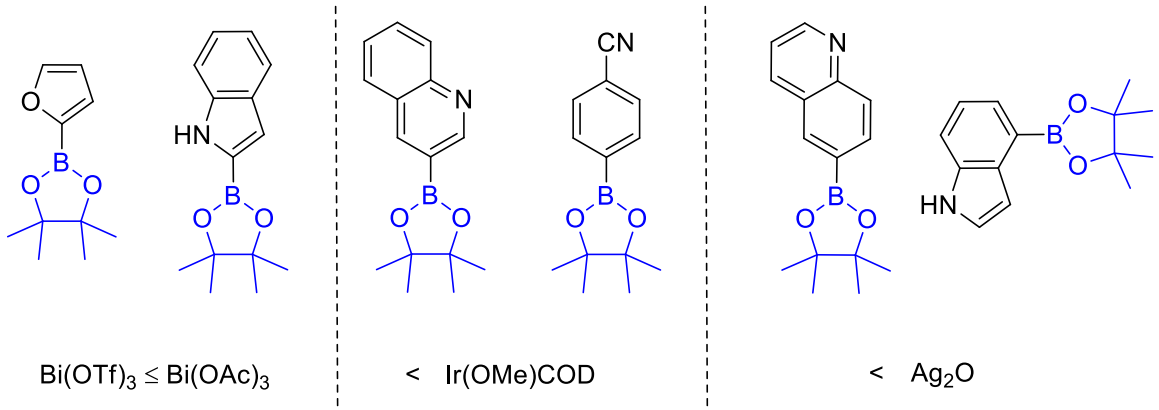


Figure 25. Study on the relative rate of deborylations

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).

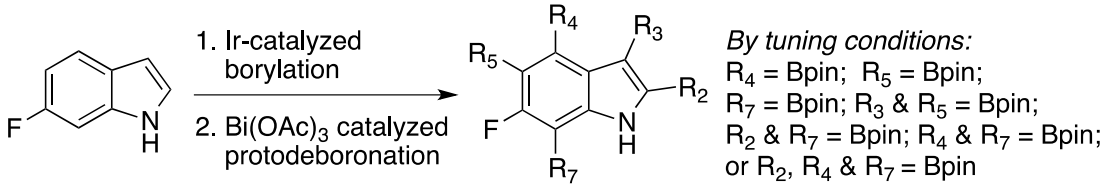


Figure 26. Utilizing combination of borylation/ deborylation to access a wide boron substrates diversity in indoles

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).

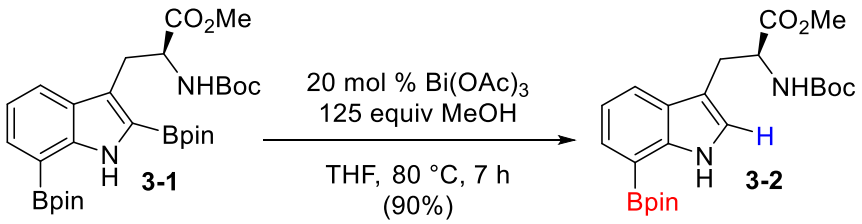
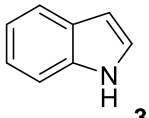
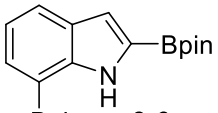
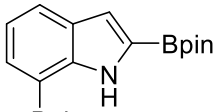
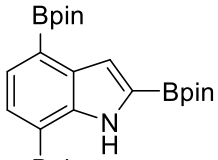
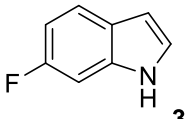
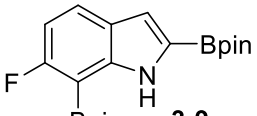
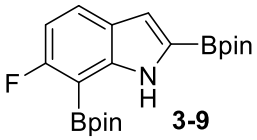
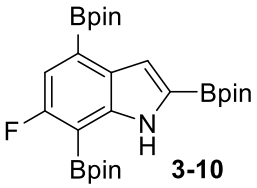
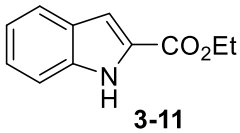
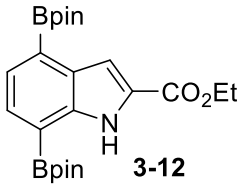
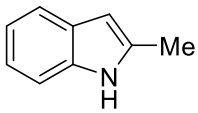
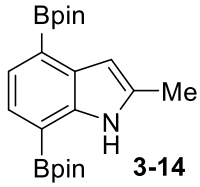
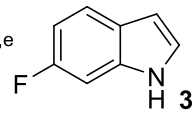
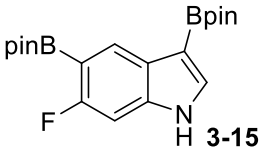
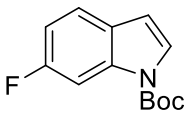
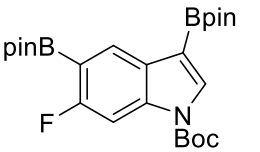


Figure 27. $Bi(OAc)_3$ catalyzed protideborylation of 3-1

Table 4. 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 protideborylations (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, protideborylation 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 described in section 3.4.).

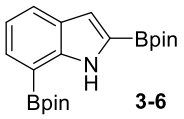
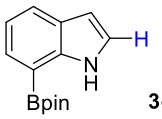
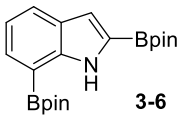
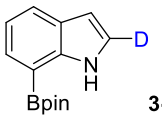
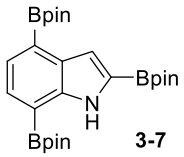
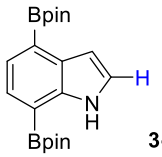
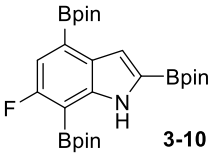
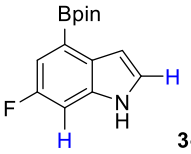
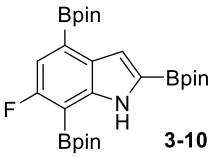
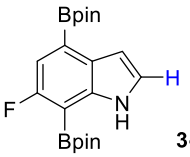
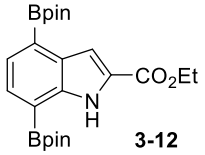
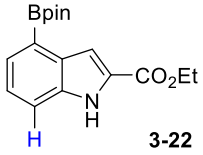
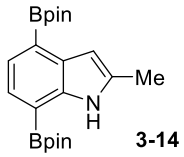
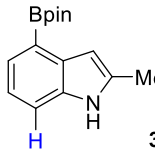
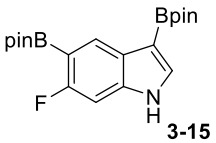
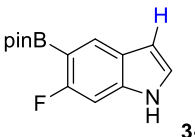
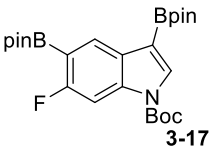
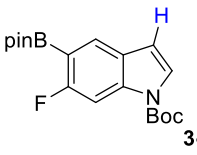
Within these parameters, 2,4,7-triborylated indole (**3-7**) was monoprotodeboronated to afford 4,7-diborylated indole (**3-19**) in 75% yield under similar conditions (entry 3). Attempts at the selective C2/C7 diprotideborylation of **3-7** were disappointing. While 4-borylated indole was formed as 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 diprotideborylation to afford **3-20** in 80% yield (entry 4). A qualitative feature of deborylating **3-10** is that upon completion, the reaction mixture takes on a slight pink color. Monoprotideborylation 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 protideborylation 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 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 protideborylation 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 protideborylation 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-protideborylation 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 5. $Bi(OAc)_3$ catalyzed protideborylations

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 experimental for details.

In contrast to **3-15**, Boc-protected **3-17** failed to undergo any protideborylation by the action of $Bi(OAc)_3$ (entry 9). This substrate was susceptible to Ir-catalyzed protideborylation, 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 protideborylation was run with 3 mol % Ir in MeOH/THF at room temperature for 10 h.

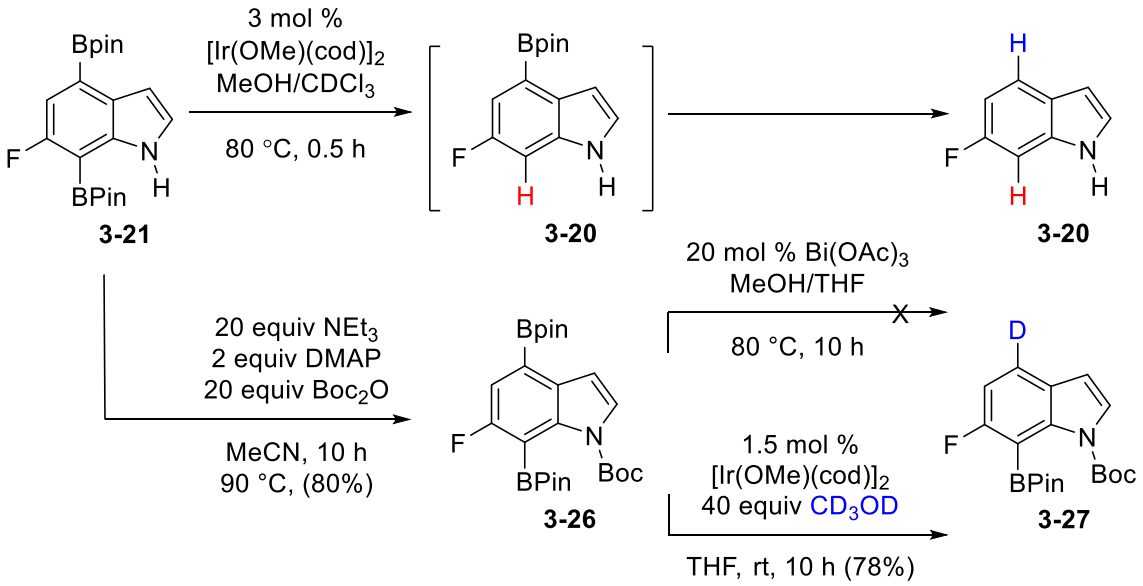


Figure 28. Changing the sequence of protideborylation

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 protideborylation 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 boron “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 the doublet of doublets at 6.95 ppm has a J value of 9.3 Hz. These data are consistent with one proton that is 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.

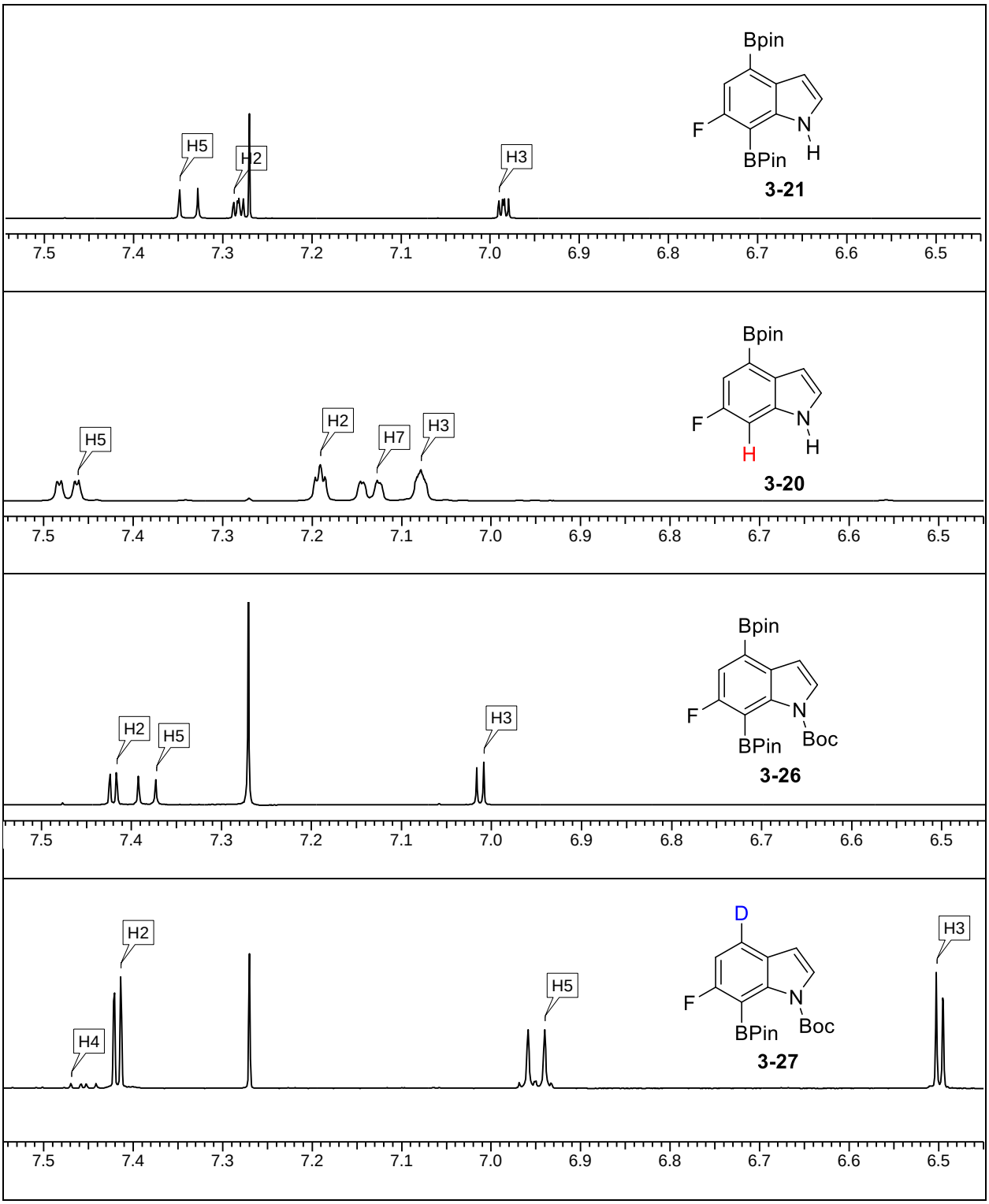


Figure 29. The protecting Boc group changed the sequence of deborylation

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]

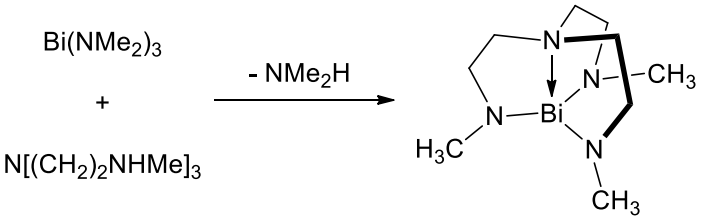


Figure 30. Figure of preparing the heterocyclic bismuth triamide

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.

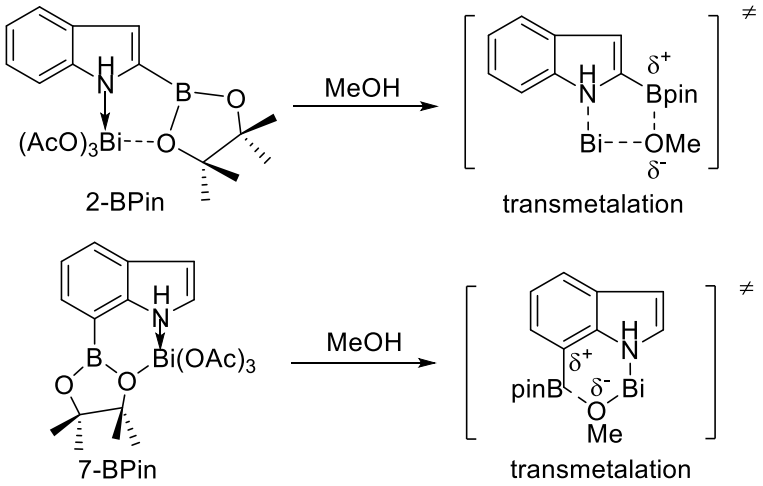
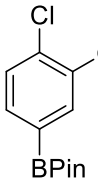
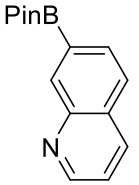
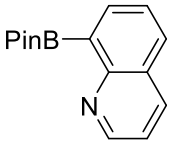
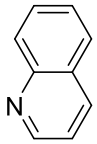
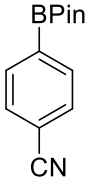
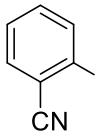
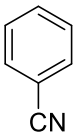
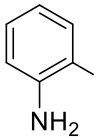
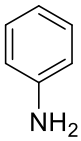
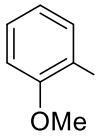
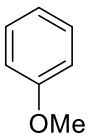


Figure 31. Putative transition states of Bi-catalyzed deborylation

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 that two boron containing materials bare nearby heteroatoms.

Table 6. 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 achieve. However, 2-Bin 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 partly supported by experiments. The exact mechanism remains an 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 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.

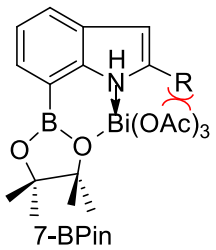


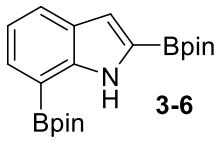
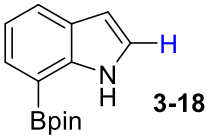
Figure 32. Proposed transition structure of 2-substituted indole during the deborylation

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

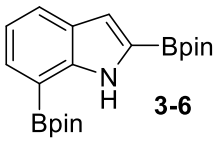
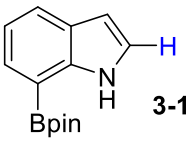
During the course of our work we determined that the grade of MeOH used in the deborylation can significantly impact the reaction rate. This issue emerged when we explored the deborylation of **3-6** to **3-18**. Experiments initially conducted at MSU required 17 h at 80 ℃ to complete the monodeborylation 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 7. 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 8. Parameters controlling experiments

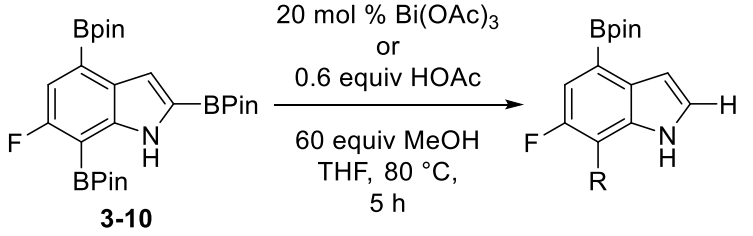
Entry	Starting Indole	Product	Conditions
1	 **3-6**	 **3-18**	20 mol % $Bi(OAc)_3$, 40 equiv MeOH, THF, rt, 2 h 45 min

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 dependent.

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



$Bi(OAc)_3$ "free" of HOAc: 90% 3:1 R = Bpin (**3-21**) / R= H (**3-20**)
$Bi(OAc)_3$ used "as is": 67% R = Bpin (**3-21**)
HOAc used in place of $Bi(OAc)_3$: no reaction

Figure 33. 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 protideborylation 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 protideborylations. 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 revealed 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 picture 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 protideborylations 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 protideborylations 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 novel deuterated product. A description of such a process is presented in the next chapter.

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REFERENCES

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9. Procedure adapted from Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389–393.

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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 experimental 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] We have desciribed some examples of selective introduction of one deuterium in an aryl or heteroaryl ring in previous chapters.

As we mentioned earlier in some cases significant quatities of starting material remained at the end of the reaction, even when spectroscopic and chromatographic evidence showed starting substrates had been completely consumed during the Ir-catalyzed C-H borylation. This 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.

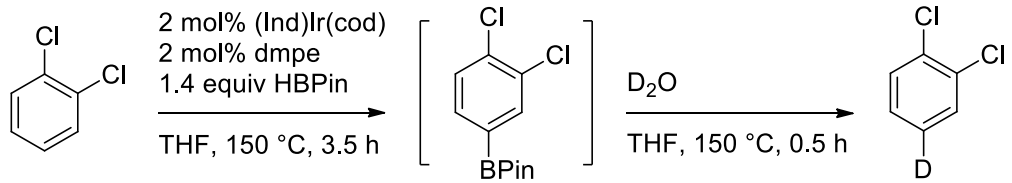
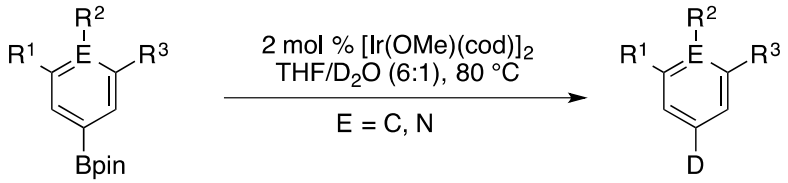
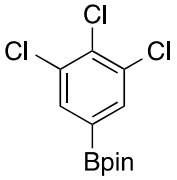
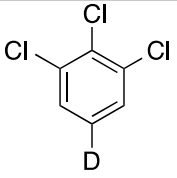
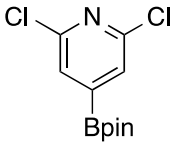
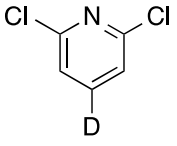
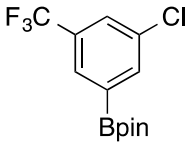
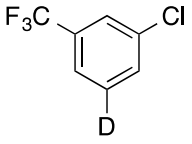
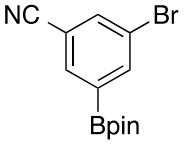
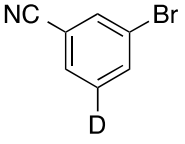
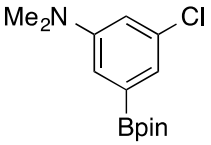
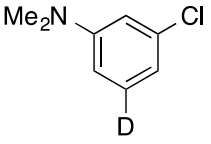
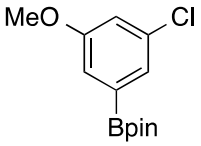
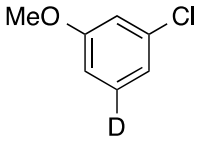


Figure 34. Proposed transition structure of 2-substituted indole during the deborylation

Sucessfully, they found after heating in THF/D_2O for 30 min the arylboronate was fully converted to corresponding deuterium-labeled arene. 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 9. Selective deuterodeborylation reactions[a]



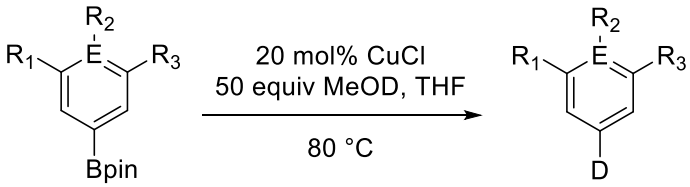
entry	arene	deuteration time	product	yield[b], %D[c]
1		2 h		80%, >98[d]
2		2 h		82%, 96
3		2 h		65%,[e] >98
4		2 h		60%, >98
5		4.5 h		74%, 96
6		3 h		74%, 93

[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

Also, with the feedback obtained from 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 (Figure 24). Unlike $Bi(OAc)_3$ showed selectivity for deborylating heterocycles when the Bpin was α to the heteroatom, Ag or Cu salts can facile deborylation but with no selectivity. However, those two salts can be apply to broader substrate range.

Table 10. Cu mediated deuteration protocol for synthesizing deuterated aromatics



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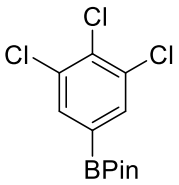
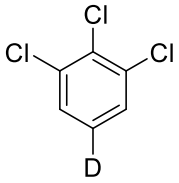
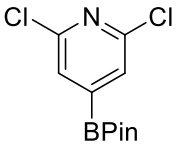
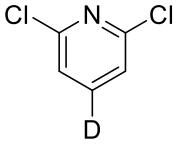
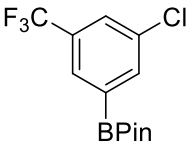
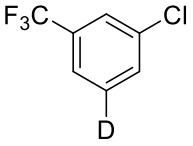
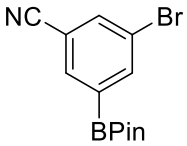
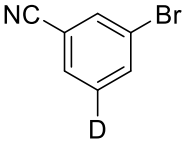
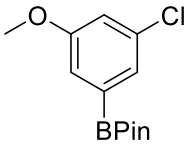
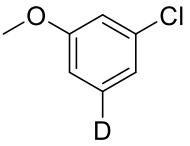
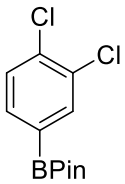
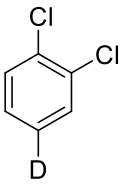
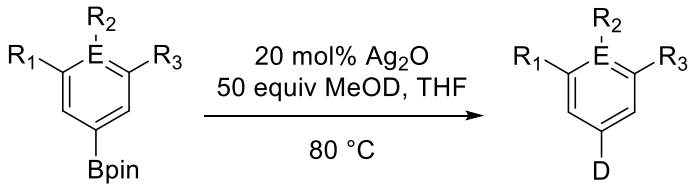
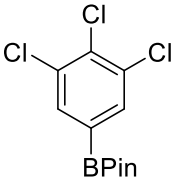
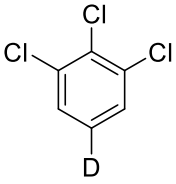
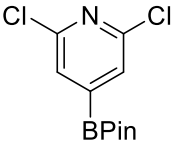
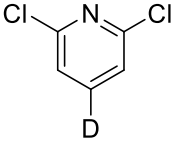
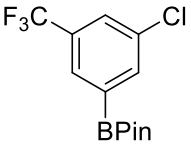
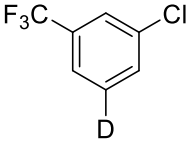
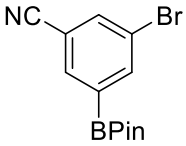
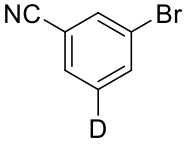
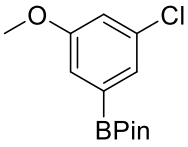
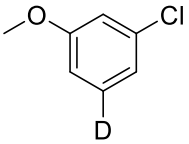
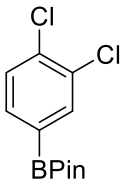
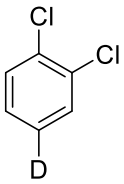
1		2 h		60%
2		2 h		100%
3		3 h		complex mixture
4		3 h		complex mixture
5		3.5 h		28%,
6		3 h		complex mixture

Table 11. Ag mediated 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 35, deborylation can be coupled to diborylation to prepare monoborylated compounds that where the regioselectivities complement those found in the monoborylation of the parent substrates. The deborylation of polyborylated arenes proceeds in order in which the borons were installed (first on first off). Bi, Ag and Cu-can catalyze borylation and Bi-catalyzed deborylation proceed under mild conditions and can be applied to structurally complex molecules. However, $Bi(OAc)_3$ is highly selective for borylated heteroarenes. Most importantly, Bi salt is not only cheap but also safe to humans.

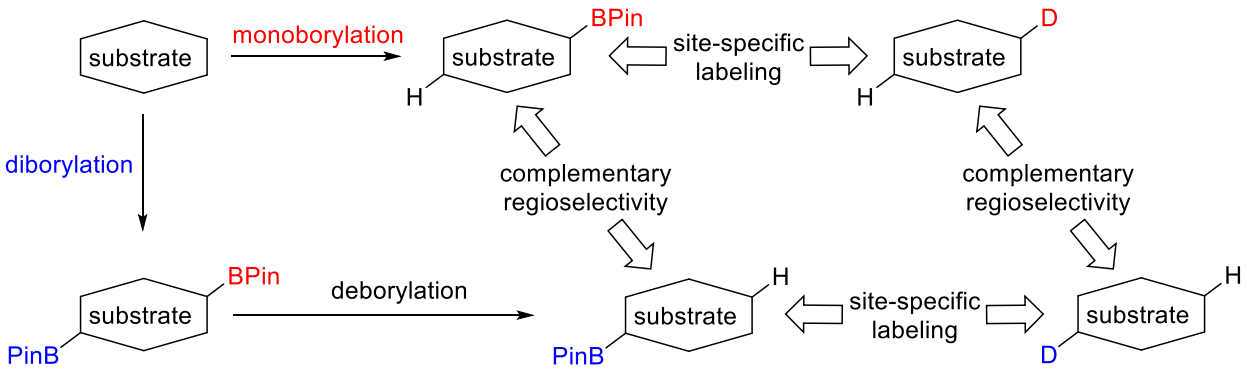


Figure 35. Potential application (isotopic labeling and regioselective synthesis)

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REFERENCES

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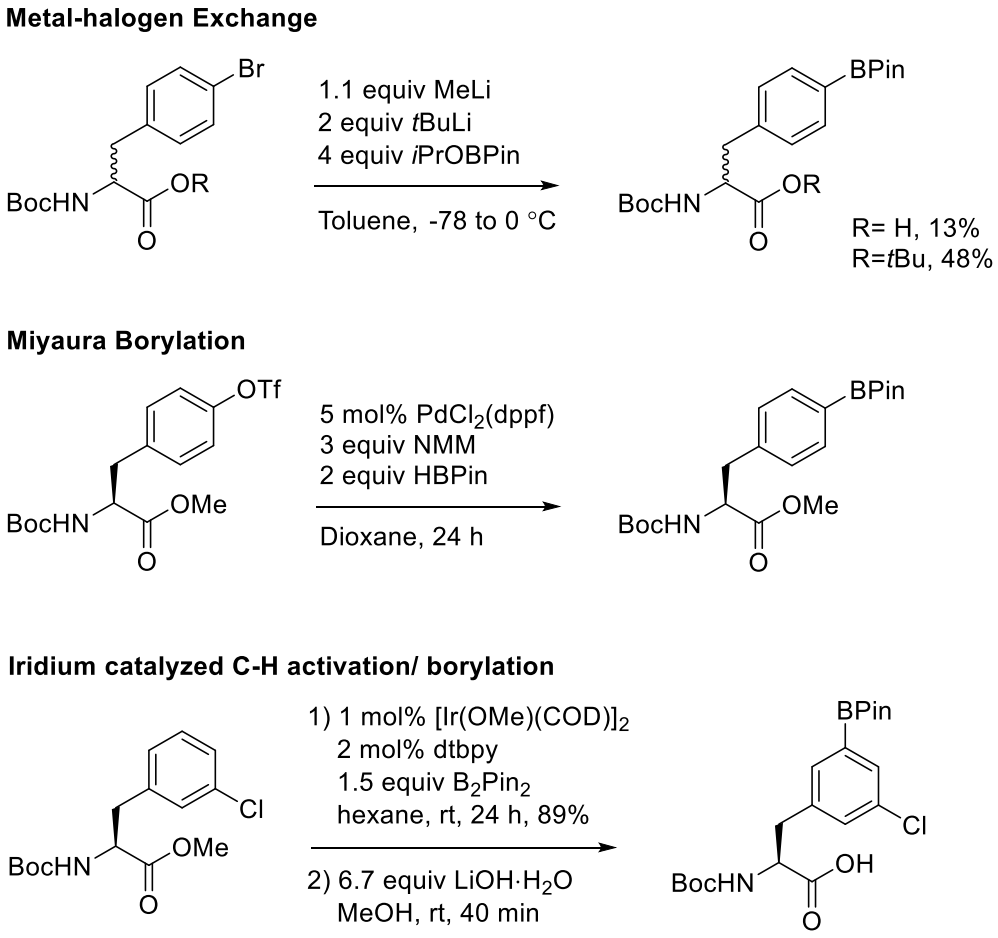
5. (a) Crabtree, R. H.; Holt, E. M.; Lavin, M.; Morehouse, S. M. *Inorg. Chem.* **1985**, *24*, 1986. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

6. Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2015**, *80*, 8341–8353.

Chapter 5. Synthesis of boron bearing peptides

5.1. Introduction

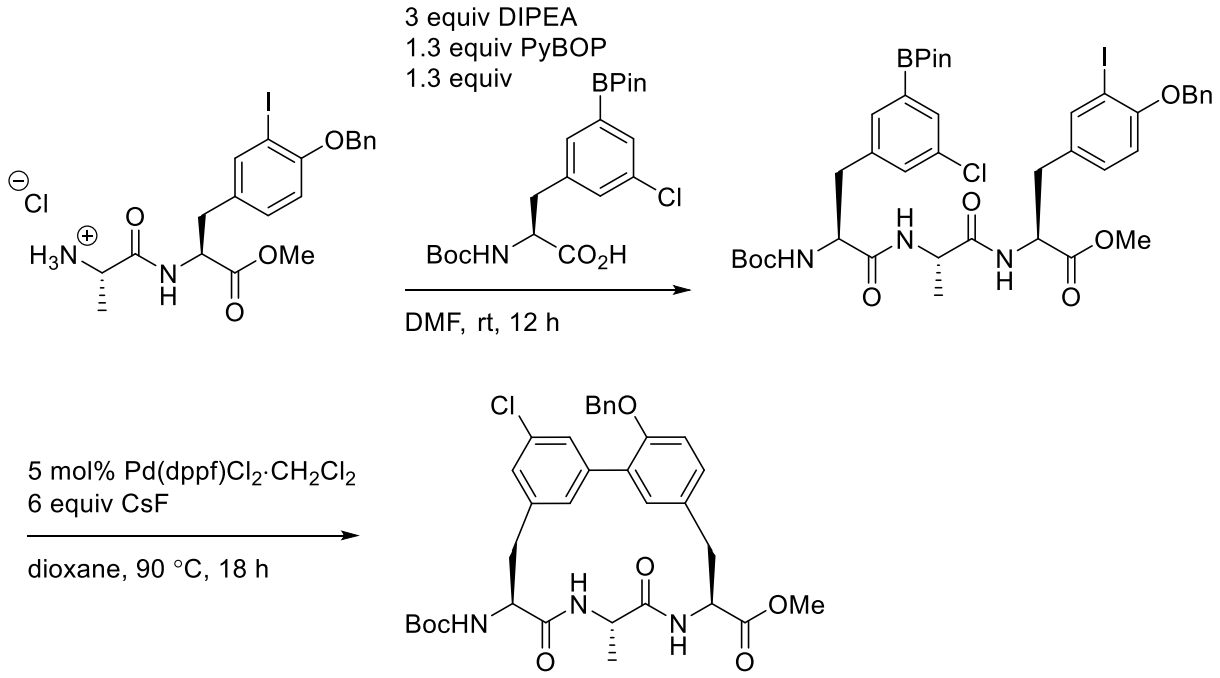
Peptides, as units of large proteins or as themselves alone are of interest in biochemical research and drug discovery.[1] Because of these uses peptides chemists have long thoughts of functionalize them. Late stage peptide modifications open new possibilities and can increase the diversity of peptide applications. Late stage synthesis of boron bearing peptides is not easy owing to the complex and highly functional nature of such compounds. As such chemists often choose to functionalize its building blocks- amino acids first and then construct the desired peptides.



Scheme 8. Synthesis of amino acid boronates

Methods for the installation of boronic esters on protected aromatic α-amino acids include (Scheme 8), metal-halogen exchange,[2] Miyaura-borylation,[3] or direct C-H activation/ borylation.[4] However, issues with the first two methodologies, include harsh reaction conditions, the incompatibility of the reaction conditions required and racemization of the α-carbon centers. Some arylpinacolboronates (Bpin) including borylated tyrosine derivatives produced have been shown to be difficult to purify and prone to degradation on silica gel.[5]

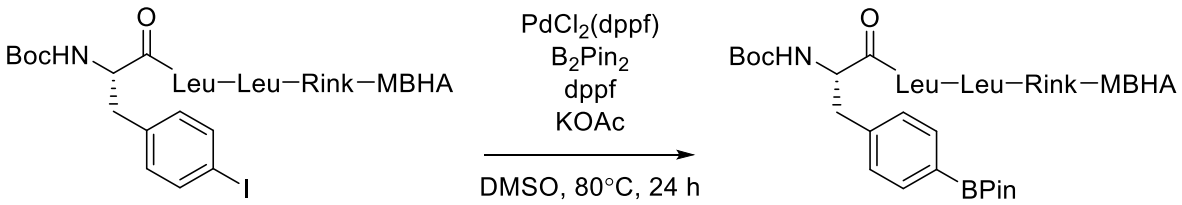
As shown in Scheme 9, the meta-meta-biaryl-bridged system demonstrates the power of Suzuki-Miyaura cross-couplings for this macrocyclization.[7] Before the ring closure the aryl iodide dipeptide was couple to borylated N-Boc amino acid to yield the boronic ester tripeptide.



Scheme 9. Synthesis of meta-meta-biaryl-bridged system

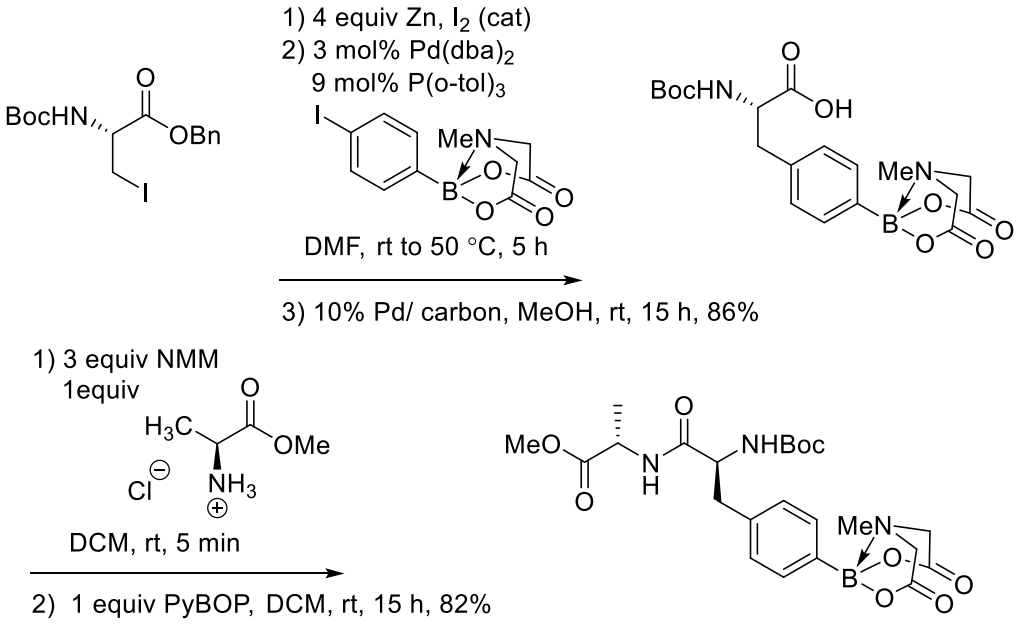
Researchers have applied similar method to peptides. Marta and Lidia established an alternative approach for the preparation of biaryl peptides through solid-phase Miyaura

borylation of a phenylalanine residue followed by Suzuki-Miyaura cross-coupling with a range of aryl halides (Scheme 10).[6] This approach is advantageous because it avoids the synthesis and purification of the amino acid boronate in solution, and is amenable to the preparation of peptide boronates in a flexible manner under mild conditions. Moreover, it allows the preparation of a large diversity of biaryl peptides from a single boronopeptide intermediate because the number of commercially available aryl halides is larger than that of arylborons.



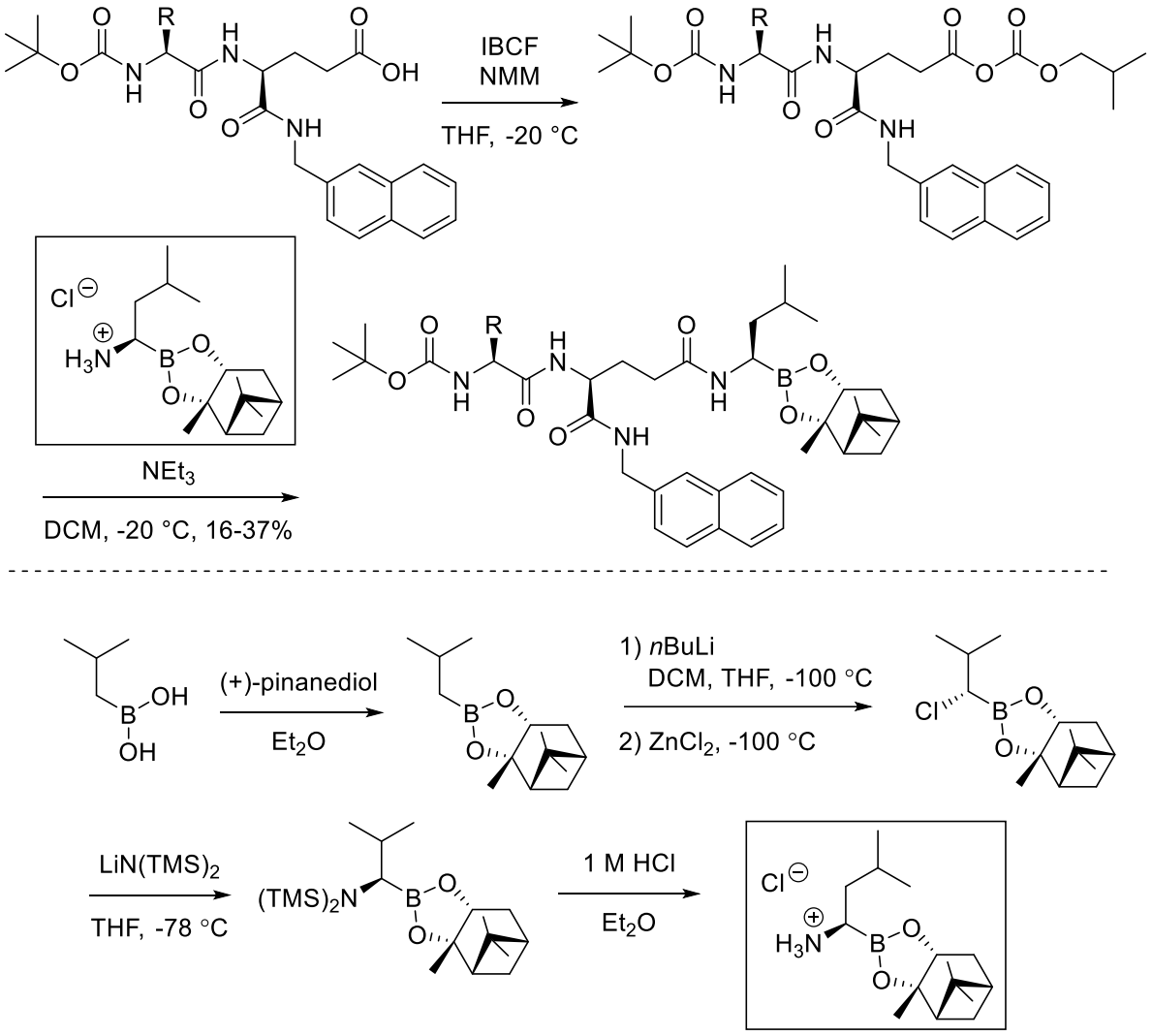
Scheme 10. Solid-phase Miyaura borylation of peptide

Steven's research group ran a standard peptide coupling with a MIDA bearing amino acid to give the MIDA boronate dipeptide in an 82% yield. The amino acid boronates were accessed from the protected iodoalanine using established Pd-catalyzed Negishi cross-coupling between a protected iodoalanine and aromatic MIDA boronates (Scheme 11).[8] No racemization of the amino acid α-carbon was observed and column purification on silica gel was possible. This methodology offers an alternative approach to access protected amino acid boronates in cases where the Bpin protecting group has been found to be unsuitable. Also, MIDA boronates afford more benchtop stability and their functionality is compatible with follow up reaction conditions, such as acid hydrolysis and Suzuki cross-couplings.



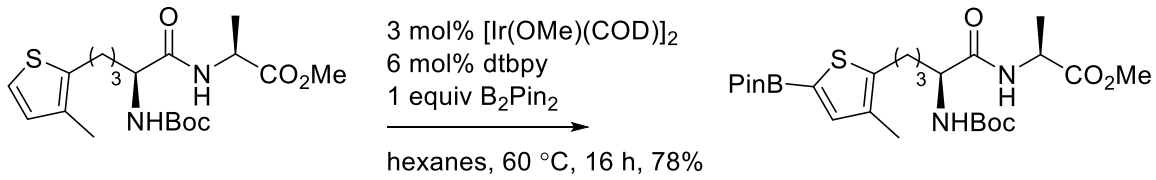
Scheme 11. MIDA boronate dipeptide

The boron ester peptide in the Scheme 12 was synthesized by activating the carboxylic acid with isobutylchloroformate (IBCF) using N-methylmorpholine (NMM) as a base. The resulting acid anhydride was reacted with the amino-boronic ester to give the corresponding target.[9] However, the end product needed to be prepared over 5 steps and moisture sensitivity is problematic in this pathway.



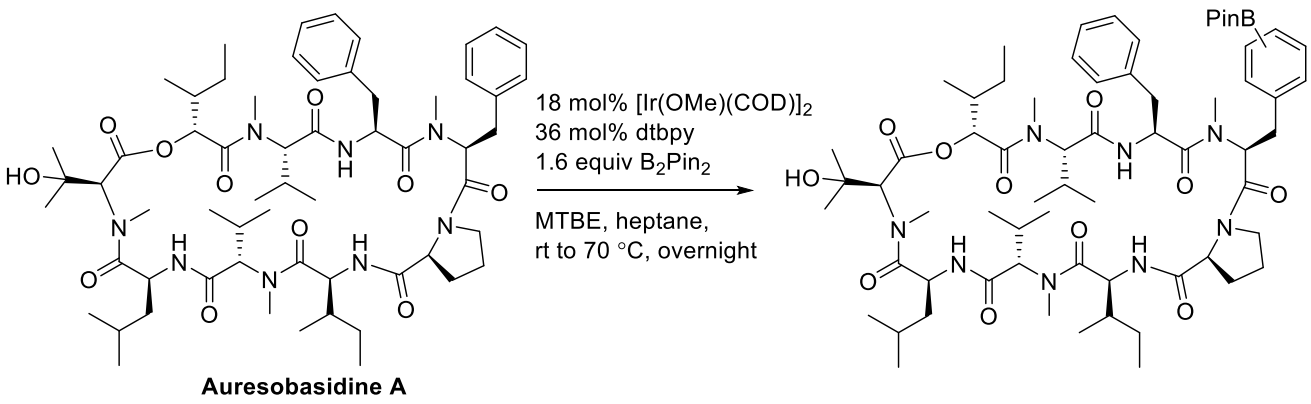
Scheme 12. The boron ester peptide was synthesized by activating the carboxylic acid

Direct Ir-catalyzed C-H activation is possible for protected peptides. Amino ester bearing a thiophene ring in the presence of iridium catalyst led to the formation of boronate dipeptide in 78% yield (Scheme 13).[10]



Scheme 13. Direct Ir-catalyzed C-H activation for protected peptides

Also, in Scheme 14 tests on aureobasidine A were undertaken via C-H activation/ borylation. Interestingly Ir-catalyzed borylation occurred only on one of the two phenylalanine rings identified as the N-Me phenylalanine ring (mix of meta-& para-isomers).[11] However, they did not give a rational for this result.

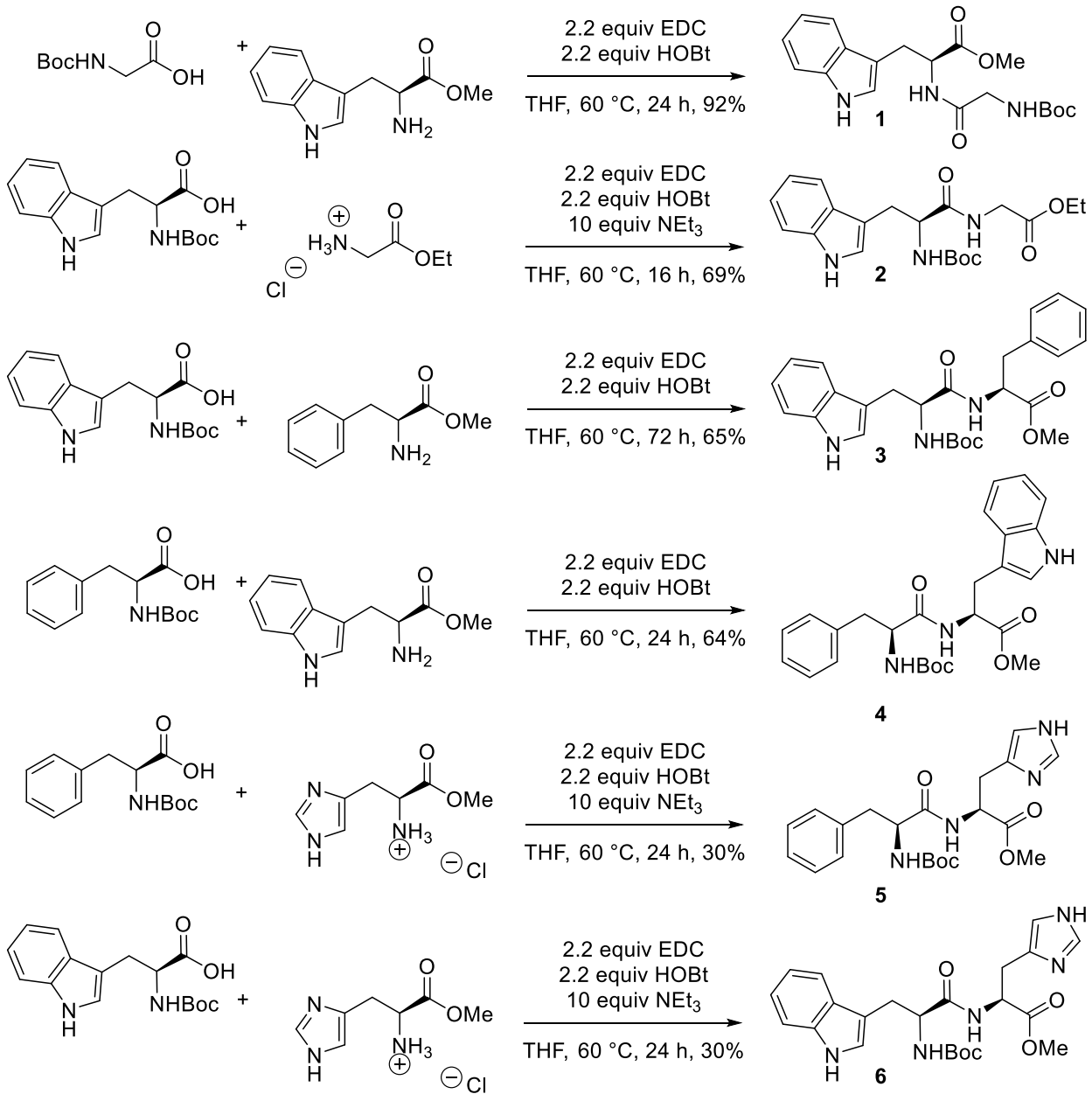


Scheme 14. Ir-catalyzed borylation on Aureobasidine A

5.2. Results and Discussion

We were also especially drawn to the generation of peptides featuring aryl boronic esters. Tryptophan derivatives represent attractive substrates, given their abundance in biologically active peptides as mentioned earlier. Due to our desire to establish a backup route to TMC-95, and considering the multiple possible positions open to Ir-catalyzed C-H activation, we sought to conduct C-H activation/ borylations on N-Boc-Gly-Trp-OMe and other aromatic peptides.

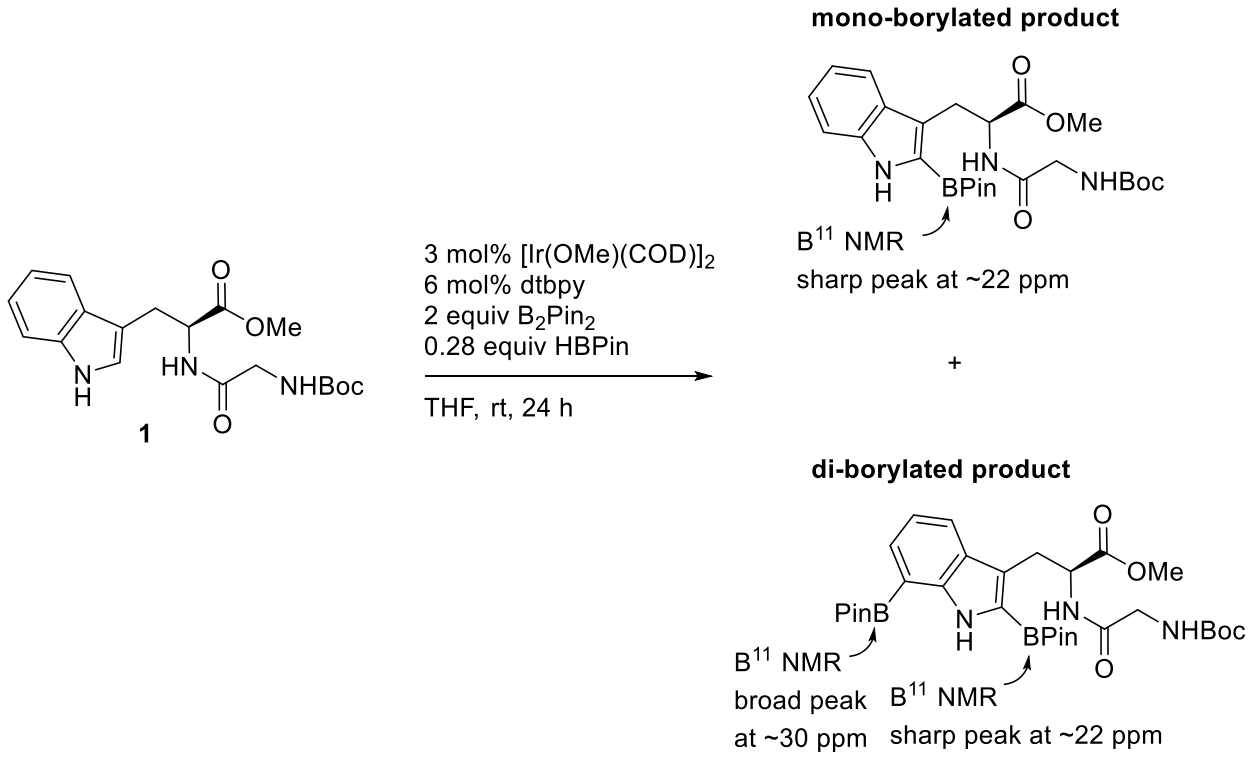
The following individual amino acids were purchased commercially. Their the N-terminal could be selectively protected as a Boc cabamate while the C-terminal could be protected through esterification. Then the corresponding peptides were prepared by standard peptide coupling (Scheme 15).



Scheme 15. Synthesis of dipeptides

Therefore, we choose those compounds to test, for dipeptide **1** and **2** (different connectivity for C- or N terminal) there is no competition between the two amino acids since we know the borylation condition we applied in this situation will preferable to install boron on aromatic ring over the sp^3 carbon. And for dipeptides **3** to **6** we picked two amino acids that might see the competition between phenyl ring, imidazole and the

indole ring. Although the borylations seemed to work, 2-Bpin BocGly–TrpOMe peptides exhibit a sharp C-B peak at 22 ppm instead of the typical 30 ppm in the boron NMR. The unusually up field and sharp boron NMR data suggested a four-coordinate product, however the exact structure of such a species could not be elucidated based on spectroscopic evidence alone.



Scheme 16. Direct Ir-catalyzed C-H activation for protected dipeptide.

Moreover, a peak at 22 ppm can be indicative of contamination by boron byproducts. Thus, we need to rule out that the peak at 22 ppm was the result of “boron junk”. After separation and purification of mono/ di-borylated products of **1** by Kugelrhor distillation, GC / mass spec and proton NMR indicated that no boron junk was present. However, the unexpected sharp boron peaks still showed at 22 ppm (Figure 35).

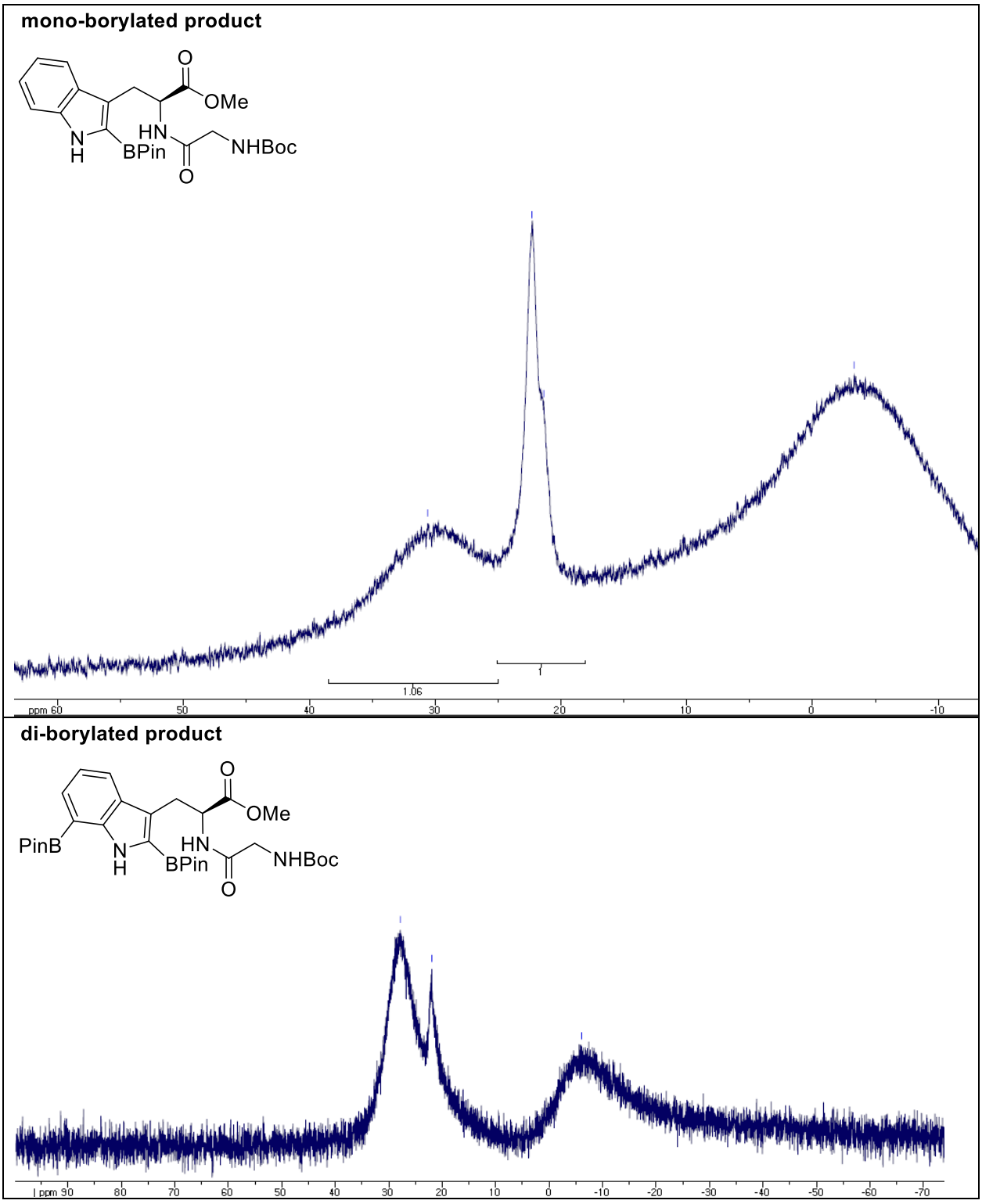


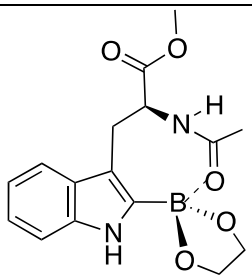
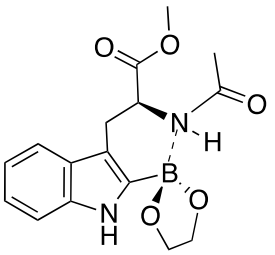
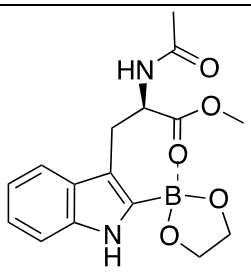
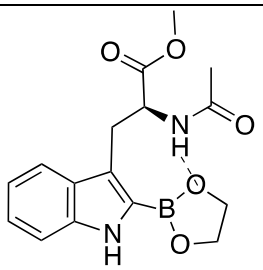
Figure 36. Boron NMR for borylated products of compound **1**

Since purified products still showed the unexpected sharp boron peaks at 22 in their B^{11} NMR spectra, we looked to computational methods to help determine the exact nature of the putative rigid structure that forms in the borylated dipeptide. As several intramolecular coordinated structures are possible, we conducted a Spartan computational analysis in attempts to determine the most likely complex structure.

Possible Intramolecular interactions:

- Boron– Amide interaction
- Peptide Chain N-B Coordination
- Boron– Ester
- Hydrogen bonding

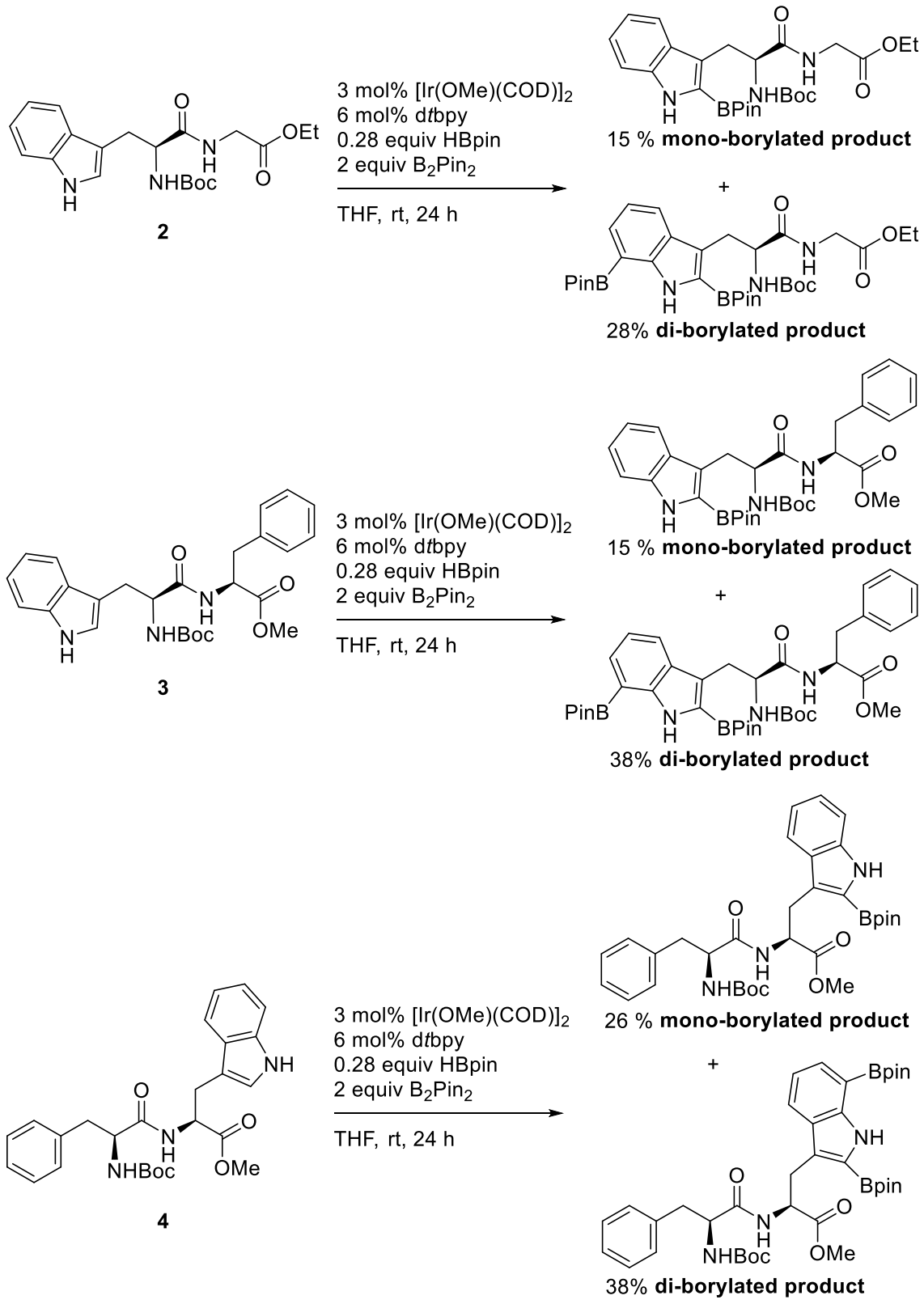
Table 12. Semi-Emperical AM1 Energy calculations on Truncated Structures

		
	Amide O-B Coordination	Peptide Chain N-B Coordination
Minimized E (kJ/mol)	270.569	478.213
Heat of Formation (kJ/mol)	– 689.066	– 458.800
Coord. Distances Å	2.86	1.894
		
	Ester O-B Coordination	H-Bonded Structure
Minimized E (kJ/mol)	348.778	23.479
Heat of Formation (kJ/mol)	-743.514	-736.586
Coord. Distances Å	2.036	2.099

Comparing bond distances and energies, the most stable calculated structures involve H-bonding between the amide NH and an oxygen in the Bpin group. Unfortunately,

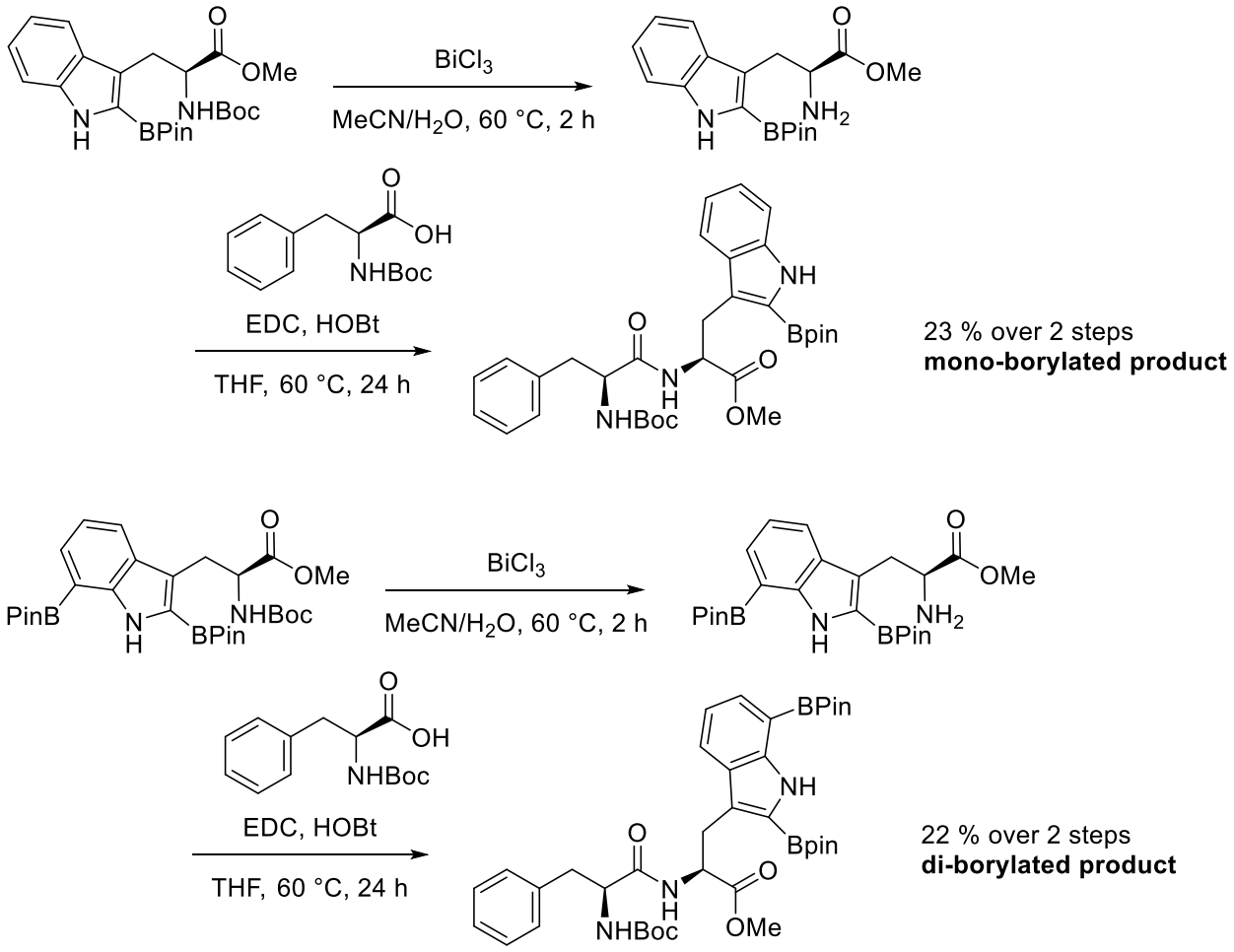
these results shed little light on the exact nature of the proposed tetrahedral complex structure.

Tryptophan moiety containing peptides yielded a mixture of 2-Bpin mono-borylated and 2,7-Bpin diborylated products, as a result of reaction at both positions adjacent to nitrogen in this fused ring system (Scheme 10). However, no borylated imidazole was observed for the peptides having histidine residuals. It is possible that nitrogen of the imidazole ring has been borylated and prone to degradation on silica gel during the purification.



Scheme 17. Direct Ir-catalyzed borylation on peptides

To confirm that the tryptophan indole moiety was borylated rather than the phenyl ring of phenylalanine, we independently synthesized borylated peptide for example **4**. Mono- and di-borylated protected tryptophan were subjected to the normal peptide coupling after Boc deprotection (Scheme 11). All proton and carbon NMR data obtained matched those from the direct C-H activation/ borylation route.



Scheme 18. Indirect synthesis for boronic ester containing peptides

In conclusion, we have demonstrated the direct C-H activation/ borylation on aryl-peptides and discovered the unusual boron peak shift. NMR indicated no diastereomers of the amide rotational isomers were formed, thus this methodology was appealing to us as the reaction has been shown to proceed without racemization of the α-carbon of the

amino acid. Future synthetic studies will further explore the scope of peptides and their deployment in the construction of larger polypeptides.

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Chapter 6. Teaching Organic Chemistry in WORDs

6.1. Introduction

As Graulich illustrated in his paper the “analogy of an iceberg could represent the nature of organic chemistry taught in a classroom context”,[1] many chemistry educators have explored new concepts and teaching styles in an attempt to better teach organic chemistry; however questions still remained as to how efficient and effective those methods are at influencing the deeper level understanding of this “iceberg” when students are presented with and asked to interpret organic structures, to make functional group–reactivity judgments or proposing mechanisms within the limits of a typical two semester organic chemistry sequence.

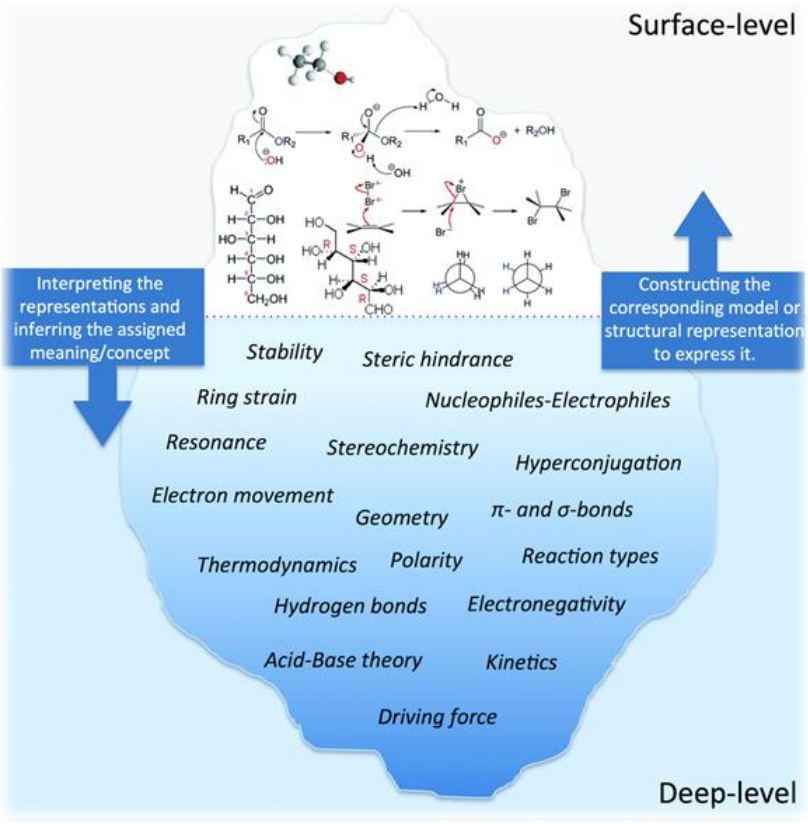
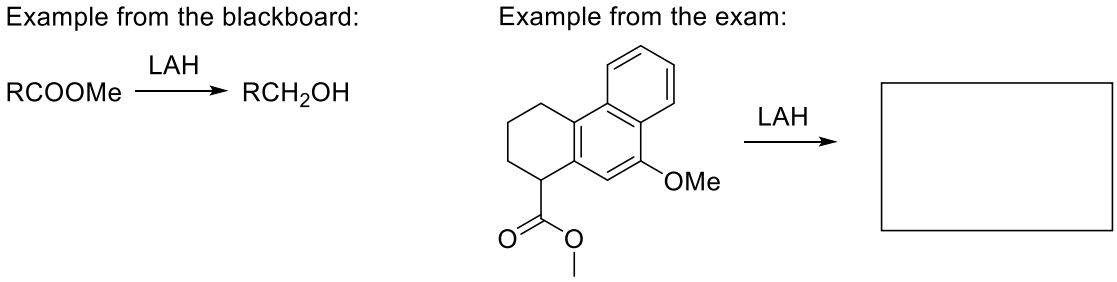


Figure 37. The iceberg of organic chemistry.[1]

As an MSU undergraduate, I was challenged, as were many of my classmates, most by our organic chemistry course. In class, reactions were often presented using truncated functional groups (e.g. RCOOMe), which did not mean anything to me besides bunch of letters that did not spell any word in the English language (Scheme 19). Even after reaction arrow pushing mechanisms were described and additional examples were shown with full structural features, when we moved on to talk about the next transformation what was on the board did not seem any different than the last example of "letters" or "chicken wire" that had been presented. No color-coding, 3-D structure, or animation helped, so my approach was to try and memorize reaction after reaction by forcing myself to try and remember structure after structure. The problem was that the structures that appeared on the exams were often different or associate with different transformations (Scheme 19). To make matters worse when those structures contained multiple functional groups, ring systems, or long alkyl chains, I would be confused as to what part of molecule was important (i.e. reactive). In short, my mind would often focus on what was visually striking and I would look to react that portion of the molecule.



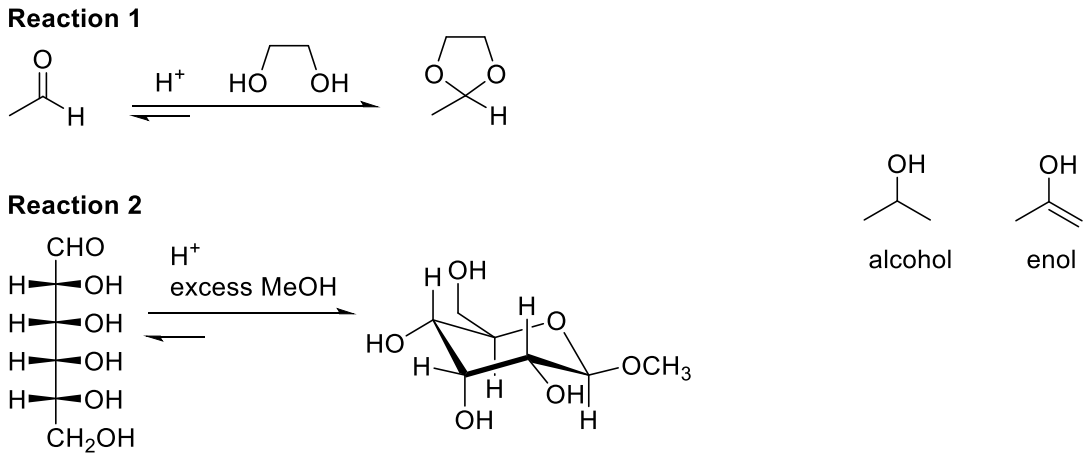
Scheme 19. Teaching examples

Despite these challenges I found organic chemistry interesting enough to pursue undergraduate research in an organic lab. That experience led to graduate school and over time I developed the ability to look at complex structures and understand where

they would react. Because I had developed this knowledge over time, when I began serving as an organic teaching assistant, I initially failed to understand why my students could not differentiate a reduction from an oxidation. Then I realized that many of my students were following the same path that I struggled when faced with those “foreign” structures for the first time. Being a TA also made me realize that I liked teaching and that I should pursue a teaching career. In doing so, I want to develop and test different approaches to delivering the content of organic chemistry with the aim of being more effective by better understanding how students learn. Of course, learning how to independently develop and assess teaching methods is not much different than learning how to independently develop and assess synthetic methods. Just as my training as a chemistry PhD student is enabling me to learn how to ask right the questions in the lab, participation and the experience in the FAST (Future Academic Scholars in Teaching) fellowship program helped train me as an independent thinking teacher.[2]

6.2. The Problem with “Orgo”

Owing to the nature of the subject, organic chemistry can be very visually distracting, and the image can be overpowering during a student’s learning. For examples, reactions in the Scheme 20 look completely different, but the functional group transformation is the same. In contrast, the molecules in the Scheme 20 look almost identical, but how they react can be very different. To make matters worse when organic structures contain multiple functional groups, ring systems, or complicated alkyl chains, students are challenged as to which part of molecule is pertinent to the question (i.e. reacting). As a result, they are often tricked into focusing on the portion of compound that is visually striking, but functionally irrelevant.



Scheme 20. Organic chemistry can be very visually distracting

I was intrigued by a talk given by Professor Vicente Talanquer (University of Arizona) that demonstrated how people prioritize different aspects of an image or an idea and carry these practices to chemical problems.[3] Thinking about this idea and then about the well-established Stroop Effect,[4] my advisor and I wanted to explore using a human's innate ability to remember and respond to words by introducing organic chemical transformations *without* using organic structures. Like it or not students will try memorization first, but this strategy largely fails owing to the lack of experience with organic structures. Our hypothesis is that once students know the organic transformation "formula" in words, via memorization or any other method, for an example that alcohols added to an aldehyde will generate an acetal (Scheme 20), etc., then introducing them to reactions with structures will come with added context and/or a place from which they are more familiar. Once they make the jump from "WORDS" to structures, they will be in a better position to answer functional group transformations (aka "sentences") and from their multi-step syntheses (aka "paragraphs"). Ultimately, we desire to have this "WORDS" approach be the first effective step on a student's way to understanding reaction mechanisms (aka "chapters"); as understanding reaction

mechanisms will best enable the student to progress to more complex topics (e.g. carbohydrates, Scheme 20 reaction 2).

However, to understand mechanisms or more broadly how “something” works one needs to have knowledge of what that “something” is. Complex theory only comes after recognizing basic words / terminology associated with the subject matter, we typically know the phenomenon before theories behind that phenomenon. In short, the origin of a theory often starts with observations without explanation. Developing the deep understanding only comes afterwards. For an example, we first recognize as a “fact” that the sun rises from the east. This observation let people’s curiosity grow and they want to dig more into this phenomenon. This it trigged more practical experiments that revised our understanding, that is the earth rotating and not the sun rising.

Considering this analogy, helping our students gain a sound mechanistic understanding of organic chemistry is the goal, helping beginning students in the beginning of their studies is the focus of this Chapter of my thesis. We propose a “WORDS” approach in introductory organic chemistry can better orient students’ focus and accelerate their awareness where they “change from being unreflected to being reflected”.[6]

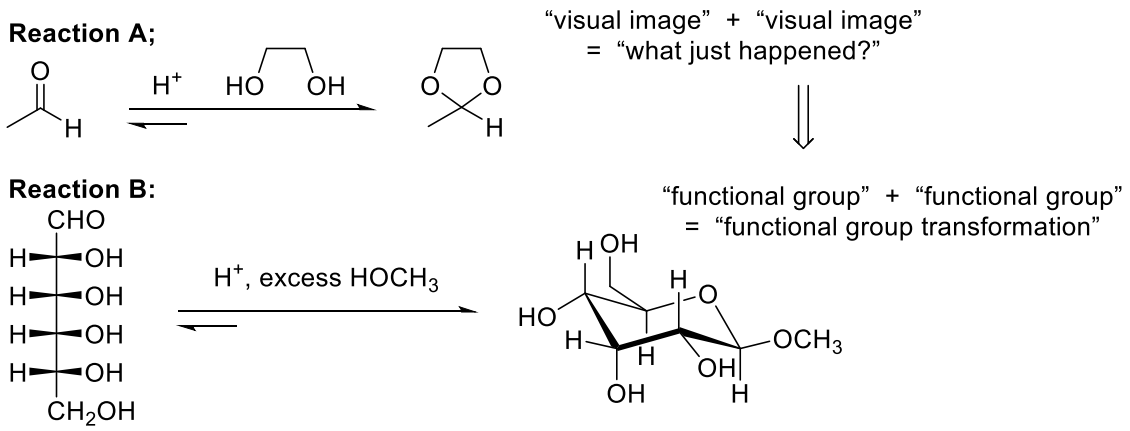
6.3. Testing My “WORDS” Hypothesis

The hypothesis was initially tested in spring 2017, where as part of my FAST (Future Academic Scholars in Teaching) fellowship I served as the primary instructor for one of three CEM 252 lecture sections taught that semester. I designed and delivered all the lectures, prepared all lecture materials including iClicker questions, wrote the exams and quizzes, held office ours, supervised the TA’s, and oversaw all grading.

6.4. Research Strategies and Questions

Organic chemistry is somewhat analogous to the math, but at the same time very different. Addition is taught in elementary math and addition reactions are taught in sophomore organic chemistry. However, in math all additions involve a combination of 10 digits (0, 1, 2, 3, 4, 5, 6, 7, 8, and 9). Therefore, once a student understands how/why 1 + 1 = 2, they are relatively quick to be able to calculate that 100 + 100 = 200. However, with organic addition reactions even when the basic reaction does not change, students become easily lost when the structures used to illustrate the addition are changed. For example, the additions of $PhC(O)CH=CHCH_2OMe + C_6H_6MgBr$ and $BnCH=C(CH_3)CH_2CHO + (CH_3)_2CHCH_2CH_2MgCl$ are essentially the same reaction, yet to beginning students they can look completely unrelated. Or the additions of $PhC(O)CH=CHCH_2OMe + C_6H_6MgBr$ and $MeOC(O)CH=CHCH_2Ph + C_6H_6MgBr$ are different transformations, but to students can look very similar. In organic chemistry, thinking is nonlinear due to the fact that molecules can be presented as flat, 3-dimensional, etc. When illustrated them with "chicken wire" drawings, the parts of the molecule that are reacting can be lost in all the "chicken wire".

Scheme 21. Organic chemistry- a “Nonlinear World”

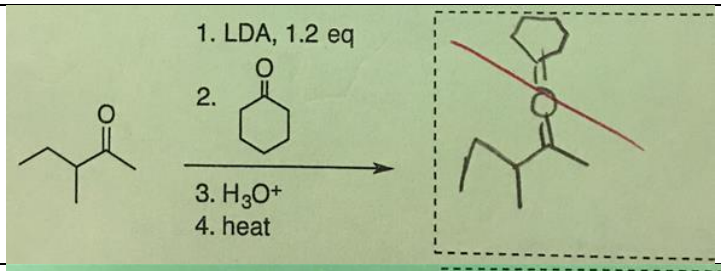
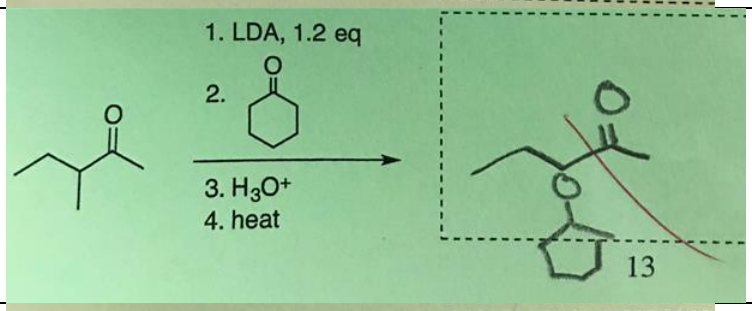
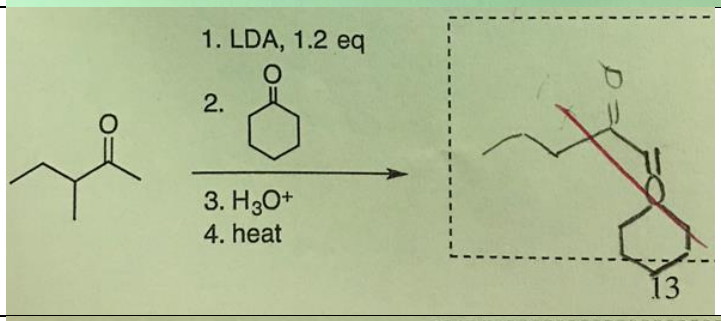
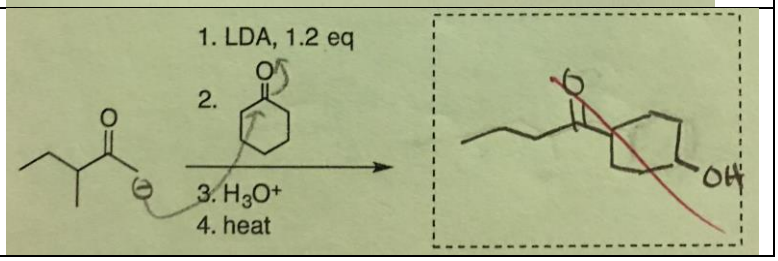


Moreover, there are almost infinite structural combinations, many of which can contain features that are visually distracting, but functionally irrelevant. This leads to students thinking “molecule” + “molecule” = “what just happened?” (Scheme 23). The difficulty seeing and analyzing the organic structure is often the first barrier for students to further understand organic chemistry. Therefore, we want to teach them from words first to better assist their ability of “seen the unseen” and accelerate students’ growing familiarity with the organic chemistry world.

6.5. Preliminary Study of Past Results

A study of students’ answers for an aldol addition problem from the FS16 control class was performed. I focused on the structures of the answer draw (Table 13). Many students’ answers’ drawings did not make chemical sense, however patterns in their answers may enable us to gain insight into their thinking process.

Table 13. Selected students' examples from the controlled class.

Example 1	
Example 2	
Example 3	
Example 4	

From examples 1 to 3 we can tell students just want to bring the pictures of the organic reactants together and are not thinking about a chemical transformation. Case 4 is notable in that the student appears to have a mechanistic understanding of the reaction yet, they still draw the wrong product. Such "decorating arrows" is well documented, Dr. Cooper at all wrote on this interesting phenomenon, "an additional 15−20% of students provided the mechanism and curved arrows only after having predicted the product,

adorning and decorating their submissions with arrows in all likelihood because we asked them to do so, not because of any inherent benefit derived from the use of such representations."[5] Sometimes "correct" mechanistic ideas do not equate to an understanding of the reaction. Students do not fully understand what arrows signify in terms of functional group transformation or even bond construction. Case 4 will be discussed in more detail later in this chapter.

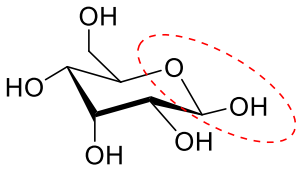
6.6. Execution of the Study

Instructional Content

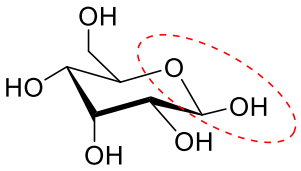
During the study, we focused on the second semester of Organic Chemistry. The topics covered in the Organic Chemistry II are conjugated pi systems (pericyclic reactions); aromaticity and electrophilic aromatic substitution; pi bond electrophiles (carbonyl chemistry, carboxylic acid derivatives); pi bond nucleophiles (alpha carbon chemistry); oxygen, nitrogen or sulfur nucleophiles and carbohydrates chemistry.

Lectures, iClickers, Quizzes, Mechanisms, and Scaffolding

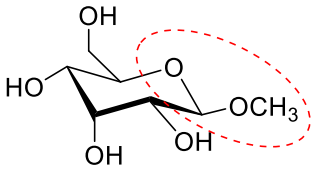
Although we term the method to be studied "teaching organic chemistry in words", chemical structures are integral to all aspects of the course and I incorporated structures from the very beginning of the course. Indeed, an essential component of the "WORDS" approach is to train students to quickly recognize functional groups within molecular structures and to immediately recall the correct name of that functional group. To accomplish this, iClicker questions were a major classroom tool for evaluating the progress and the degree of students' ability to rapidly and correctly identify functional groups with molecular structures. Examples of such an iClicker question are shown in Figure 38.

<table>
<tr>
<td> 

Clicker Q1: Is this an alcohol?

A. Yes
B. No</td>
<td> 

Clicker Q2: What is the functional group shown?

A. Acetal
B. Carboxylic acid
C. Hydrate
D. Hemiacetal</td>
</tr>
<tr>
<td> 

Clicker Q3: What is the functional group shown?

A. Acetal
B. Carboxylic acid
C. Hydrate
D. Hemiacetal</td>
<td>

Clicker Q4: What is the functional group generated during the oxidation of 1° alcohol by Jones reagents?

A. Acetal
B. Aldehyde
B. Carboxylic acid
C. Ketone
D. Hemiacetal</td>
</tr>
</table>

Figure 38. Examples of iClicker questions

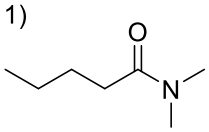
A key aspect in the use of iClicker questions, was that when the initial class vote was split, to have the students discuss among their neighbors why they selected their answer and not the others. This reinforced the training of students to describe organic chemistry and organic structures in words.

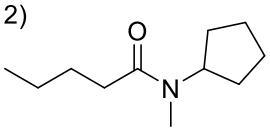
The same sort of “identify the functional group” questions were also asked on quizzes. By design quizzes were the place where we would test the students on functional group transformations in words, but then introduce structures through a series of scaffolded questions. Examples of such quiz questions are shown below.

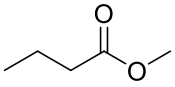
Quiz question: In the boxes provided draw an example of any compound that corresponds to the functional group indicated. (3 pts)

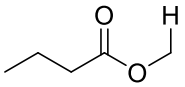
a derivative of a carboxylic acid	a hydrazone	an acid halide

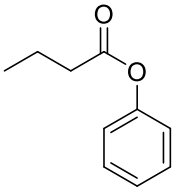
Quiz question: Provide the name of the functional group for each molecule

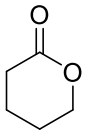
1) 

2) 

3) 

4) 

5) 

6) 

Quiz question: Which of the following is NOT an "easy" one-pot functional group transformation? Only choose one and circle your answer. (2 pts)

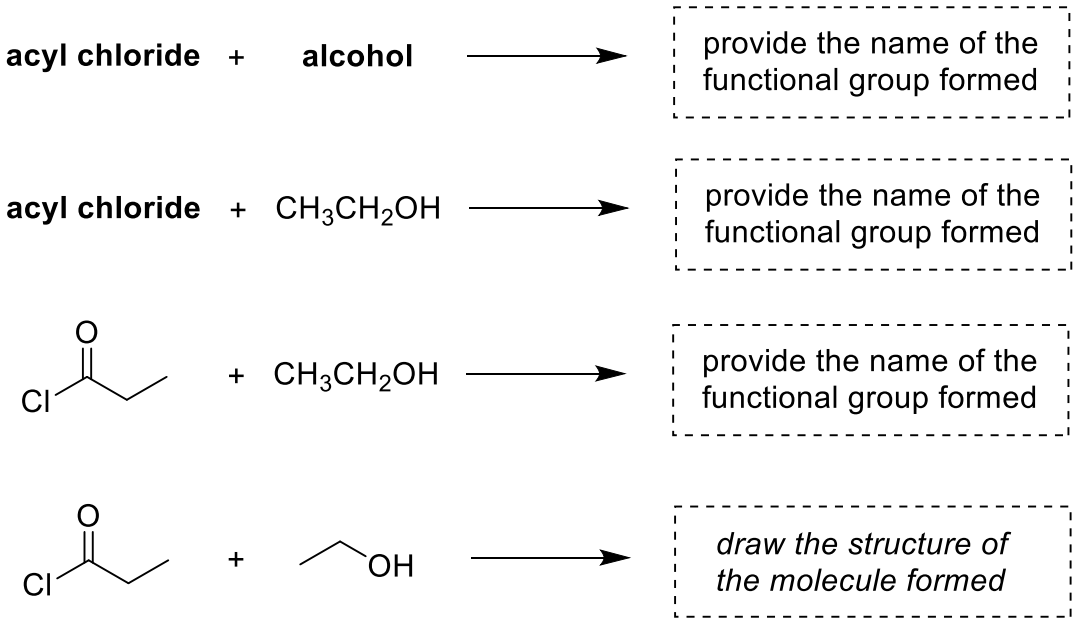
a. imine to amine b. amide to amine
c. acetal to amine d. nitrile to amine

Figure 39. Examples of such quiz questions

Scaffolding is an important component and it appears in the classroom activities and quizzes. Scaffolded questions led by the instructor can guide students' critical thing from a low level to a higher level has been shown to be powerful.

Scheme 24 illustrates how we first introduced functional group transformations without the "clutter" of structures first, and purposely training or “trick” student by switching between different structure representations and their corresponding functional group. After students feel comfortable identify that an acyl chloride reacts with an alcohol to form an ester, we will begin scaffolding the training by adding more structural representations of the reactants. We predicted that once traditional structure only questions are given on quizzes and especially on exam students would prioritize what's important because they will have trained their minds to ask what the functional groups are, not "where did I see that structure in my notes".

Scheme 22. Scaffolding training- transit from words to structure

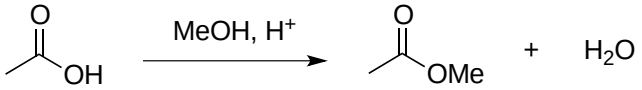


In short, we aimed to train students to focus their attention on the reactive functional group of an organic molecule by emphasizing the use of “WORDS” to describe functional group transformation and teach the organic chemistry as the second language. Once students mastered the “WORDS” and have more fluency in language of

organic chemistry for functional groups then they will be better able to move on to "sentences"- reactions; "paragraphs" – multi-step syntheses; and "chapters" – mechanistic thinking.

With respect to mechanistic thinking, the general thinking was that students would better understanding of the purpose of arrow pushing mechanisms in organic chemistry when introduced after students clearly know what new functional group generated. That said, arrow pushing mechanisms were taught and tested on. Even here though there we were aware of the literature on "decorating with arrows". Therefore, we made an effort to get students to be able to describe mechanisms in words and to translate words describing a mechanism into an arrow pushing drawing. An example of this can be seen in the quiz question shown below.

Quiz question. On the following page, please provide a detailed arrow pushing mechanism for the following reaction. (8 pts)



The following written description of the mechanism is provided to help you illustrate the proper mechanism. Acid catalyzed esterification of a carboxylic acid involves the following steps:

a) The reaction begins with protonation of the carbonyl oxygen so to increase the electrophilicity of the carbonyl carbon. The enhanced electrophilicity of the carbonyl carbon is best illustrated by the resonance form that contains a carbocation.
b) That resonance contributor (form) of the protonated carboxylic acid is attacked by the most nucleophilic atom of the methanol.
c) Proton transfer from the newly formed oxonium ion to another molecule of methanol neutralizes the carboxylic acid addition product.
d) The protonated methanol then transfers its proton to one of the hydroxyl groups. The resulting oxonium species is a good leaving group
e) Electrons from the remaining hydroxyl group attack the carbon bearing the oxonium, which results in the loss of water and formation of the protonated carbonyl.
f) Subsequent deprotonation gives the ester.

Figure 40. Examples of such quiz questions

6.7. Assessment Methods

In this study, the following questions are to be addressed:

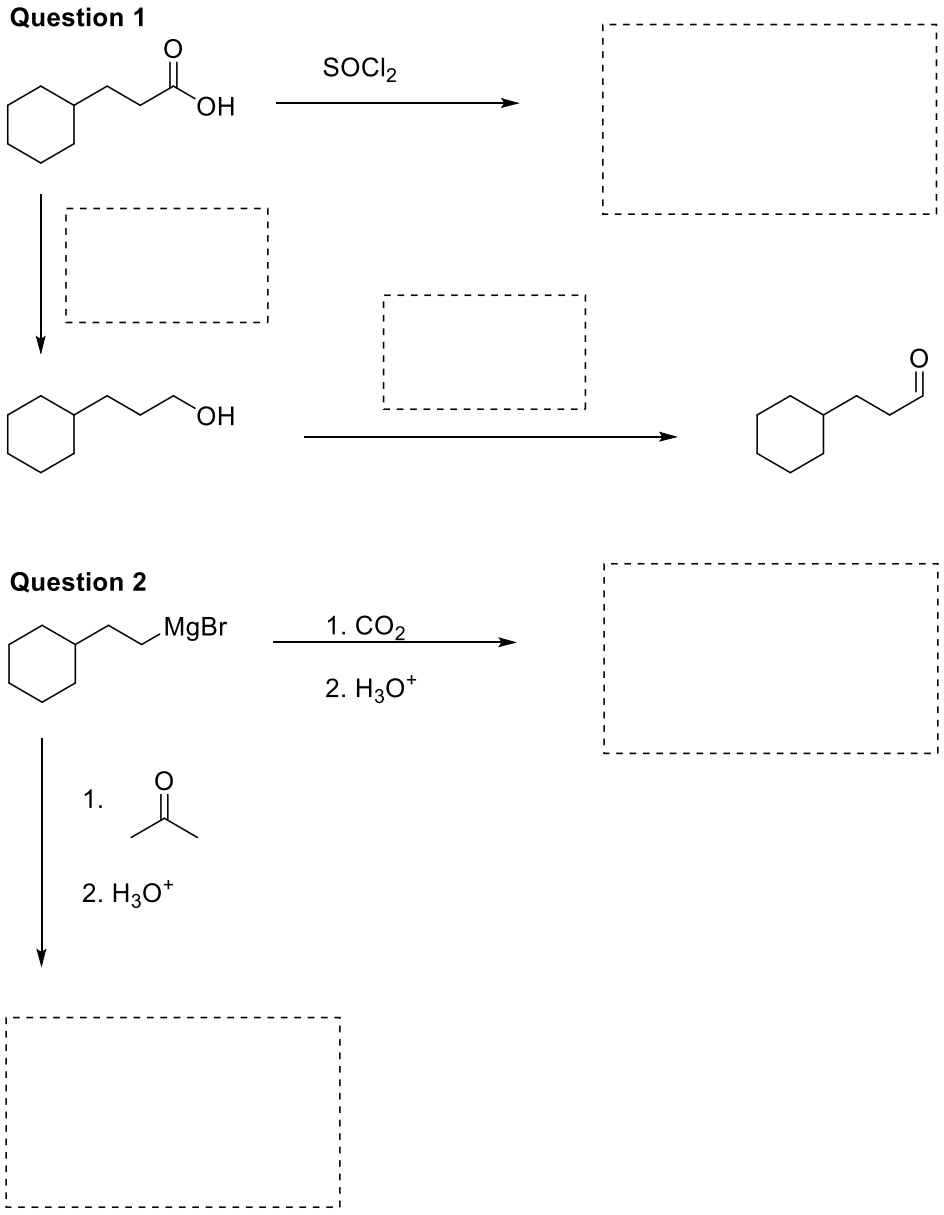
- Does an early focus on presenting functional group in words facilitate the student's ability to understand organic reactions comparing to the traditional teaching style (i.e. chemical structures)?
- Is this method transferable between different instructors/ semesters?

To address these questions, I designed an assessment method. Within the exams, I placed assessment questions where results from students taught using the "WORDS" approach would be compared against a CEM 252 control class. In designing a way to test our "WORDS" hypothesis, we used the FS16 CEM 252 class[7] as our control group. Enrollment for the FS16 class was 167 vs a final enrollment of 268 for SS17. Of course, it is impossible to have a true control as students, instructors, TA's, etc. change with every class. More details on these variables will be presented later, but the FS16 class and my SS17 test class, followed very similar syllabi (see appendix).

In practice, we took selected questions from the FS16 CEM 252 final exam and inserted them into my CEM 252 exams. Students are not given their finals back, therefore we had copies of the FS16 graded final exams, from which we could collect data on point given for each problem. We selected the FS16 assessment problems at the time we were writing the exams, that is after the lectures on those chapters so as to teaching to the exam. We also did not inform the teaching assistants as to which were the specific assessment questions or share the exam with them prior to it being administered, so that they would not teach to the exam in recitation or office hours. Meanwhile we applied the grading rubrics that established by the FS16 instructor of the control class in

our exam for those selected problems. Teaching assistants followed rubric, but again did not know at the time of grading which selected problems were the assessment problems. Only after all the grading was complete, would we compare how students performed on those questions from one semester to the next.

Scheme 23. Questions chosen for assessment and findings by exam analysis



The questions chosen are shown above. These problems were given to students on mid-term exam 2. Question one asked students to provide the product for the conversion of a carboxylic acid to an acid chloride. It also tested their knowledge on what reagents will enable the reduction of that carboxylic acid and oxidation of the intermediate alcohol. Following the FS16 grading rubric, students failing to provide a reasonable reagent, or the correct functional group earned zero points, while those with fully correct answers for all three parts of the questions earned 3 points. Students who recognized the need for a reductant or an oxidant, but not a reductant or oxidant that would afford the product lost 1 point as did those who had “typos” (e.g. gained or lost a carbon).

Question 2 asked for the products formed via the Grignard reactions shown. The grading rubric for partial credit was similar to that described for question one. Notably the starting materials while functionally very different share a cyclohexyl ring and alky chain. In this way, we sought to assess if our method would allow students to better differentiate the functional group difference on molecules that are visually similar.

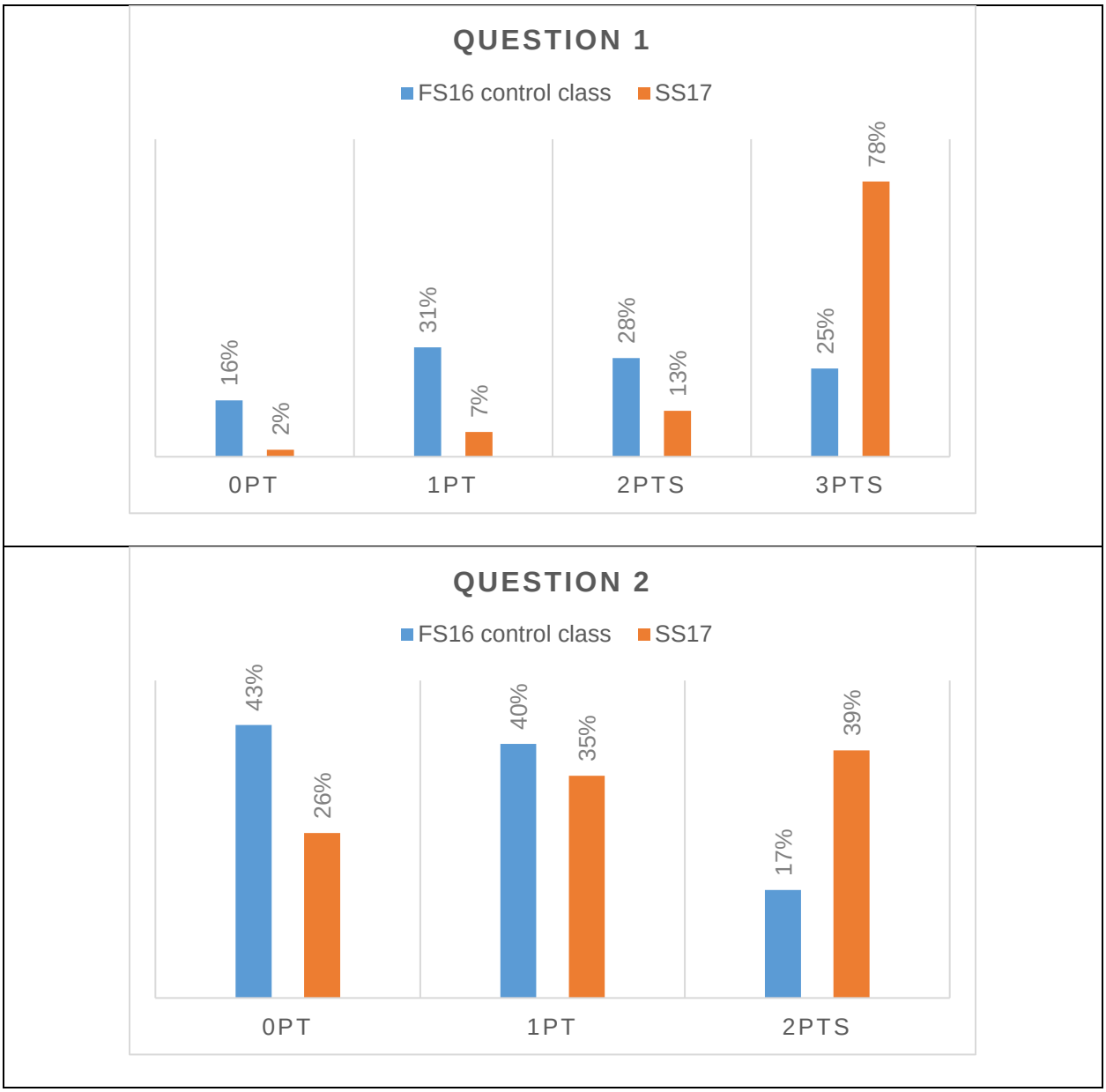


Figure 41. Points earned on assessment questions by the FS16 control class vs. SS17

We measured the percentage of students scoring 0 to 3 points respectively. As the data show students taught using the “WORDS” approach were 3 times as likely to earn full points on question 1 versus the FS16 control group. Similarly, the “WORDS” students were 8 times less likely to earn no points on question 1. The result from questions 2 were less dramatic, however improvements were still realized in terms of students earning full credit and those scoring no points. To be fair, our analysis of question 1 and

2 does not reveal what caused the difference in improvements observed between question 1 and 2. It may or may not be that students taught using the “WORDS” approach are better at identifying reagents need for functional group transformations versus products of such reactions.

6.8. The Aldol Question

Earlier in the Chapter, an aldol problem from FS16 was discussed (Figure 42.). As the case shown in student example 4, few of the written answers suggested some students were on the right track of solving the problem by their detailed arrow pushing. However, the answers were often still wrong.

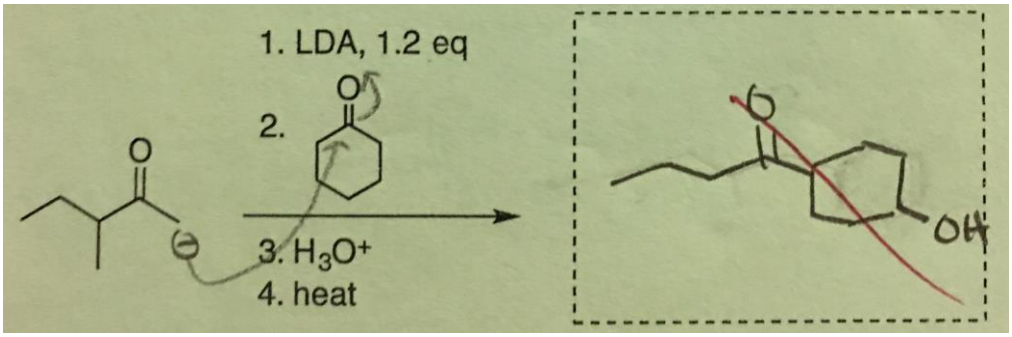
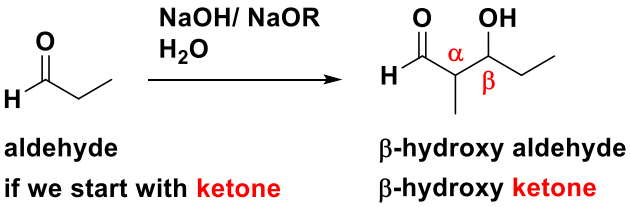


Figure 42. Example of a “correct mechanism” but a wrong answer.

This question also raises a potential failing of the “WORDS” approach. That is for reactions like the aldol condensation where multiple functional groups are produced, only memorize in words without understanding the bond construction that result in these functional groups will afford an incorrect answer.

In our class, we taught the aldol reaction emphasizing words to guide the students before introducing them the “art deco”/ the arrow pushing mechanism. We emphasized that aldehydes undergo a self-aldol to form a hydroxyl aldehyde, while ketones undergo a self-aldol to form a hydroxyl ketone. This was in keeping with the general thinking that students would better understanding of the purpose of arrow pushing mechanisms in

organic chemistry when introduced after students clearly know what new functional group generated.

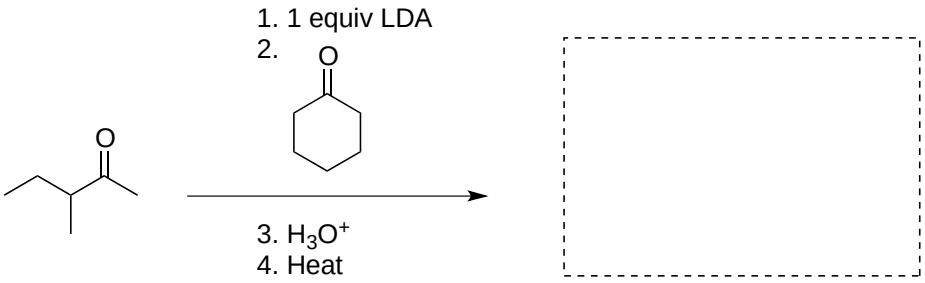


Scheme 24. aldol reaction

The potential failing here is if students do not take learn second step they can "know" which functional groups are produced, but not what compound is produced. In the case above, the student drew a hydroxyl carbonyl compound and aldol reactions do produce hydroxyl carbonyl compound.

To test for this possibility, on mid-term exam 3 students were presented with the same question, again taken from a FS16 final (Scheme 25). The correct answer was worth three points, with 2 points partial credit given for minor typos (e.g. and extra carbon in the chain or 1 point for mistakes like missing a methyl group. No points were given for seriously flawed structures such as that in Table 13.

Scheme 25. The aldol question



The raw data for the SS17 group is shown in Figure 43. This figure also provides an example of how we collected our data. For each question, the TA's would enter into a scantron sheet a specific answer (e.g. A–C in Figure 43) corresponding to the points

earned (1–3 respectively in Figure 43). No answer entered on the scantron sheet meant the student earned zero points. This method automated data collection for SS17 vs the manual collection of data from the FS16 control class.

In comparing the results of the two groups, the 19% of the FS16 controlled class received all 3 pts for the problem and the average points for this question was 0.59. Among the 194 students in total who took the exam, 107 students got the entire question right which means 55% got all 3 pts for the “WORDS” class. A 289% gain. The average for this question in the SS17 class is 1.8 pts, which is also 3 times higher compared to the controlled class.

White Exam

95 students

Q25

Response	Frequency	Percent
* ***A***	8	8.33
* ***B***	2	2.08
* ***C***	45	46.88
D	0	0.00
E	0	0.00
F	0	0.00
G	0	0.00
H	1	1.04
I	0	0.00
J	0	0.00
No Response	40	41.67

Yellow exam

99 students

Q25

Response	Frequency	Percent
* ***A***	4	4.04
* ***B***	3	3.03
* ***C***	62	62.63
D	0	0.00
E	0	0.00
F	0	0.00
G	0	0.00
H	0	0.00
I	0	0.00
J	0	0.00
No Response	30	30.30

Figure 43. The distribution and numbers of participants for this question in my class.

Though only as single example, these preliminary data suggest that students being taught with the “WORDS” approach are not simply memorizing the starting and ending functional groups any more than those taught traditionally. Furthermore, as the gains over the control group are similar for this aldol problem and the single functional group to single functional group transformations, the data suggest that the “WORDS” approach can remain effective as the reactions become more complex. More work would need to be done to validate these conclusions. Similarly, additional studies are needed to determine where students taught via either approach incorporate mechanistic thinking into their answers.

6.9. Are the initial results realized through this approach sustainable from semester to semester and from instructor to instructor?

Comparing instructors – "WORDS" vs. the Control: While the preliminary data indicate that this "WORDS" approach may improve student test scores, the inherent unevenness in teaching, including differences class size, class composition, semesters taught, quizzes, exams, amount of time dedicated to different topics, TA's, etc. make it difficult to ascribe any results to just one variable. Among these inconsistencies, the influence of different instructors of record is one that cannot be overlooked. Thus, it is a fair question to ask if differences between the control group instructor and myself influenced the observed results more so than the employed teaching methods. Quantifying any differences is a challenging task and the only ready quantitative measure of teaching are SIRS scores. Of course, numerous studies have shown SIRS scores to be poorly correlated with learning outcomes and even more problematic prone to gender and cultural biases.[7] Nonetheless, if for only anecdotal comparisons SIRS scores for me and the control instructor, also a woman, for SS17 were relatively similar. Moreover, what differences there were in our scores were small compared to the differences between our scores and the third CEM 252 instructor that semester, again also a woman. For purposes of review the SIRS scores of all three SS17 CEM 252 instructors are detailed in Table 14.

Table 14**.** SIRS scores for SS17 instructors and the control group instructor for FS16 (the scores in **bold** indicate the best SIRS score for that question among the SS17 instructors).

Question	"WORDS" instructor SS17 mean (responses)	Control instructor SS17 mean (responses)	Third instructor SS17 mean (responses)	Control Instructor FS16 mean (responses)
Objective	0.76 (243)	**0.49** (253)	0.82 (206)	0.54 (188)
Lecture	0.85 (243)	**0.60** (253)	1.34 (206)	0.61 (187)
Subject Matter	1.06 (243)	**0.71** (253)	1.32 (206)	0.65 (188)
Content	1.21 (242)	**1.19** (253)	1.35 (206)	1.22 (188)
Challenged	**0.38** (243)	0.43 (253)	0.63 (205)	0.34 (187)
Problem Assignments	1.26 (242)	**0.88** (253)	1.50 (205)	0.96 (187)
Text Helped	**1.17** (243)	1.39 (253)	1.33 (206)	1.37 (187)
Instructor enjoyed teaching	0.68 (242)	**0.57** (254)	1.34 (205)	0.60 (188)
Instructor showed concern	**0.36** (243)	0.83 (253)	1.67 (206)	0.81 (188)
Lectures well prepared	0.86 (243)	**0.43** (254)	1.07 (205)	0.44 (188)
Explanations helped	0.96 (243)	**0.65** (254)	1.52 (206)	0.62 (188)
Grading explained	0.61 (243)	**0.46** (253)	0.84 (206)	0.51 (187)
Exams were fair	**0.99** (243)	1.02 (254)	1.44 (206)	0.94 (187)
I rate this course	1.30 (243)	**1.21** (254)	1.88 (206)	1.35 (186)
I rate the instructor	0.88 (243)	**0.71** (254)	1.79 (206)	0.72 (187)

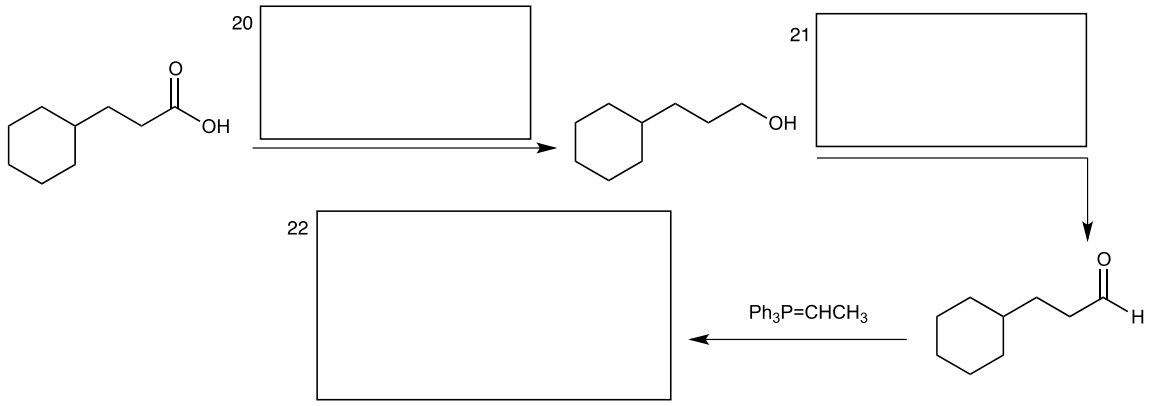
While the SIRS data for me and the control instructor are similar in nature, differences in the control group and my class are many. The control class was from FS16, which is the "off-semester" for Organic Chemistry II. The assessment problems were taken from an FS16 final exam and tested on my mid-term exams. This raises the question of whether

the length of time between when students are first taught a topic and when they are tested on the topic impacts their performance. In addition, the other variables mentioned existed, e.g. different TA's, amount of time dedicated to different topics, etc. It is noted that the same text, (David Klein, *Organic Chemistry*, 2nd Edition, Wiley, ISBN 9781118454312) was used in FS16 and SS17.

"WORDS" taught in a different semester (FS17) by a different instructor: The next question addressed was if the same teaching method used by a different instructor would produce the same or different results. To probe this question, a different instructor adopted the "WORDS" approach in FS17. As before assessment problems were draw from the final exam of the same FS16 control class. Similarly, the FS16 grading rubric was used by the FS17 TA's who again were unaware as to what problems were assessment questions. Other featured common to FS16 and FS17 include the text used, similar chapters covered, and it being the "off-semester". Relative to SS17, the FS17 instructor used many of the same i-Clicker questions that were designed to transitions students from words to structures. That said, the FS17 instructor chose different assessment problems than those used in SS17 and worked from a somewhat different set of lecture notes.

The first FS17 assessment occurred on exam 1, which covered Klein's chapters on Alcohols and Phenols (Chapter 13), Ethers and Epoxides (Chapter 14), and Aldehydes and Ketones (Chapter 20). Among these, Chapters 13 and 14 were only reviewed in class using the "WORDS" approach as those chapters were presumed to have been covered in CEM 251.

The problems chosen for assessment are shown in Scheme 28. The sequence of questions 20 to 22 asked students to provide the product for the conversion of a carboxylic acid to an alcohol (Q20), give the reagents enabling the oxidation of the intermediate alcohol to the aldehyde (Q21) and propose the product of a Wittig olefination with the resultant aldehyde (Q22). For each of these questions, students could earn 0–3 points. Those failing to provide the proper reagent (Q20 & Q21) or the correct functional group (Q22) earned zero points, while those with correct answers earned 3 points. For questions Q20 & Q21, students who gave a reductant (Q20) or an oxidant (Q21), but not a reductant or oxidant that would afford the product earned 2 points partial credit or 1 point if the structure of the reductant or oxidant was incorrect (only three students out of 314 earned 1 point for Q20 & Q21. Those who identified the correct functional group formed in Q22 but had other problems with their structure (e.g. gained or lost a carbon) earned 1 or more generally 2 points partial credit.

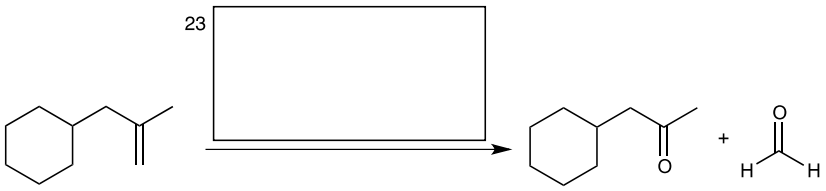


Scheme 26. Comparison questions 20-22

Question 23 asked for the conditions will break the carbon-carbon double bond of an alkene and to form two carbonyls where the carbon-oxygen double bonds are on each of the two carbons that originally composed the alkene. Partial credit (2 pts) could be

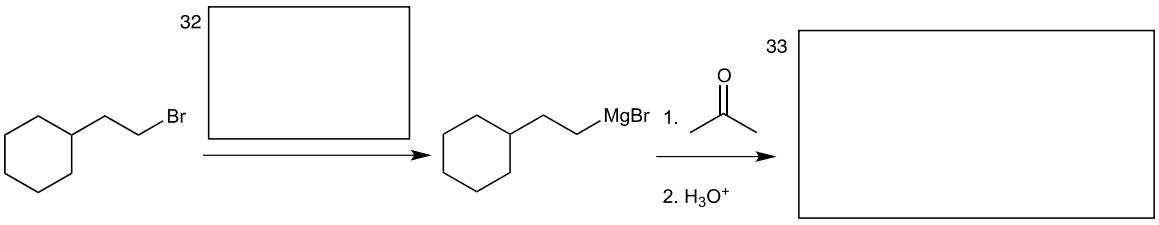
earned if the student indicated ozone as the reagent, but failed to include a reductant (e.g. DMS, Zn, or Ph_3P). One point, again rare, was earned if they recognized the reaction as being an oxidation of the carbon-carbon double bond.

Scheme 27. Comparison question 23



Questions 32 and 33 tested for conditions to provide a Grignard reagent from an alkyl halide and then to react that Grignard reagent with a ketone. Here, students lost a point if they did not indicate a dry solvent for Q32 or the need for a workup for Q33. For Q33, student would lose an additional point if they identified the correct functional group formed but had other problems with their structure.

Scheme 28. Comparison questions 22-33



Unfortunately, it was only realized after the exam that the control class only earned 2 points for questions 20 to 22. Therefore, the FS17 scores were prorated.

The FS17 class scored better than the FS16 class on four of the six assessment questions, although with the exception of question 23 (338% improvement) the gains on Q20, Q21, and Q33 were not as dramatic (48%, 23%, 40% respectively) as those observed in SS17. On problems Q22 and Q32, the FS17 class performed worse that

the FS16 students, seeing a respective 77% and 22% decrease in points earned. There was less of a pattern as to the ability of the two groups to recognize reagents vs. products. However, FS17 best out-performed FS16 on question 23, which asked for reagents of an ozonolysis, whereas FS16 most out-performed FS17 on question 22, which asked for the product of a Wittig olefination. Admittedly, this difference could simply be a function of one instructor stressing the cleavage of carbon–carbon double bonds while the other emphasized forming alkenes from carbonyls.

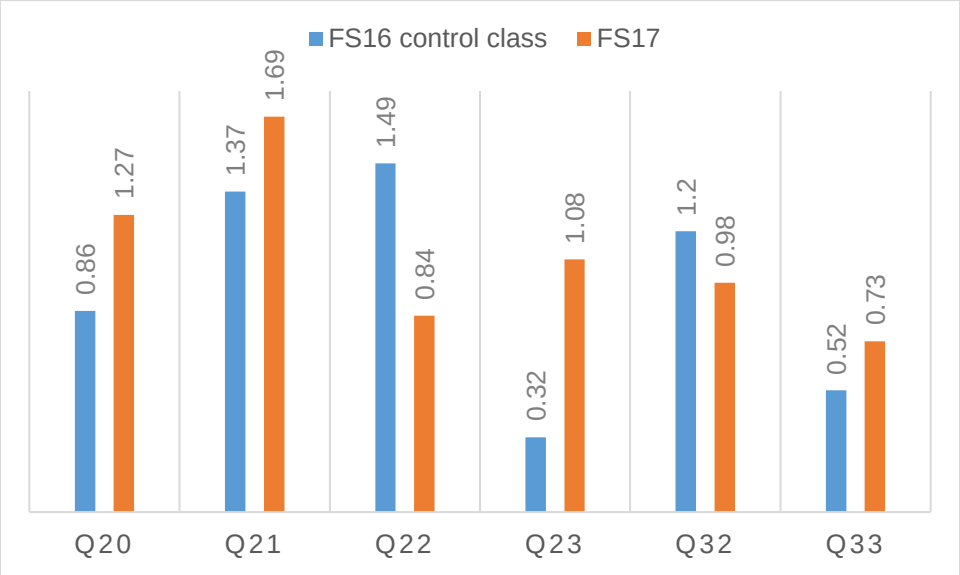
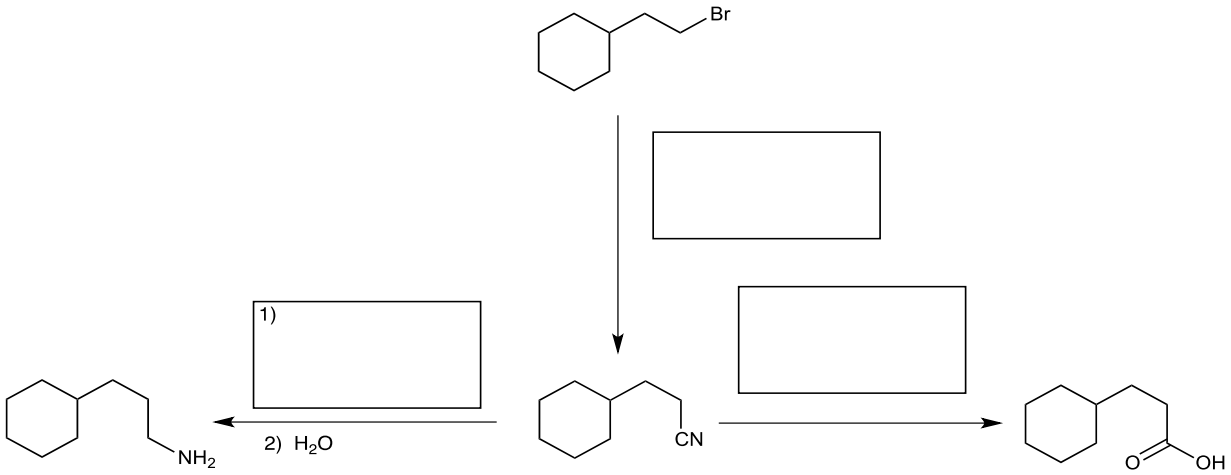


Figure 44**.** Comparison of assessment results “WORDS” FS17 vs. Control class FS16

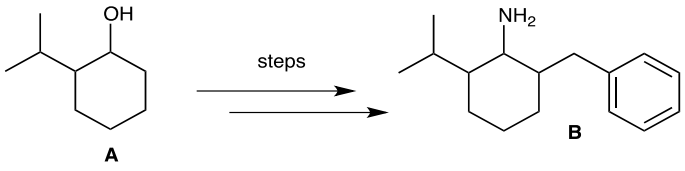
The second mid-term only assessed questions asking students to identify the reagents necessary to convert an alkyl bromide into a nitrile and then to take that nitrile onto an amine or carboxylic acid. Though students could earn partial credit, the 86% of the students earned three (13%), six (27%), or nine (46%) points by getting full credit on one, two, or three problems respectively. After prorating the FS17 scores, the FS17 class witnessed a 23% gain in points earned for this entire suite of questions.

Scheme 29. Comparison questions



For mid-term three, we decided to assess for the first time how a group of students taught using the “WORDS” approach would compare to the control group on a multi-step synthesis problem. That problem is shown above and was worth five points in FS17 and eight points in FS16. Partial credit was possible for both groups. The FS16 class clearly did better on this question, averaging 4.29 points or 241% better than the FS17 “WORDS” class who only averaged 1.78 points. Though only a single example points, these data may imply that the “WORDS” method may help students in recognizing functional group transformations, i.e. create “sentences”, but that more work needs to be done before they can do multi-step syntheses. i.e. write “paragraphs”.

Scheme 30. Synthesis question



As before, a variable that cannot be overlooked is the general effectiveness of the instructor. While, the SIRS scores for the SS17 and FS16 instructors were similar, the SIRS scores for the FS17 and FS16 instructors were quite different and not in favor of

the FS17 instructor. A side-by-side comparison of their SIRS scores is found in Table 15.

Table 15**.** SIRS scores for FS17 and SS17 “WORD” instructors and the control group instructor for FS16 (the scores in **bold** indicate the best SIRS score for that question among the three instructors).

Question	“WORDS” instructor FS17 mean (responses)	“WORDS” instructor SS17 mean (responses)	Control Instructor FS16 mean (responses)
Objective	1.90 (227)	0.76 (243)	**0.54** (188)
Lecture	2.28 (229)	0.85 (243)	**0.61** (187)
Subject Matter	2.35 (228)	1.06 (243)	**0.65** (188)
Content	2.03 (227)	**1.21** (242)	1.22 (188)
Challenged	083 (229)	**0.38** (243)	0.34 (187)
Problem Assignments	2.08 (227)	1.26 (242)	**0.96** (187)
Text Helped	1.72 (228)	**1.17** (243)	1.37 (187)
Instructor enjoyed teaching	1.71 (227)	0.68 (242)	**0.60** (188)
Instructor showed concern	2.43 (227)	**0.36** (243)	0.81 (188)
Lectures well prepared	1.89 (229)	0.86 (243)	**0.44** (188)
Explanations helped	2.39 (226)	0.96 (243)	**0.62** (188)
Grading explained	1.45 (229)	0.61 (243)	**0.51** (187)
Exams were fair	2.68 (228)	0.99 (243)	**0.94** (187)
I rate this course	2.91 (228)	**1.30** (243)	1.35 (186)
I rate the instructor	2.73 (228)	0.88 (243)	**0.72** (187)

With the admission that SIRS scores are questionable gages of teacher quality and learning outcomes, it is possible that the diminished/ mixed results in applying the “WORDS” approach in SS17 and FS17 could at least be partly due to the FS17 instructor being a generally less effective educator.

6.10. Conclusions

Though certainly a preliminary study, early evidence supports the “WORDS” approach as being effective at getting students to master functional group transformations. Gains were in student performance were relatively broad and could be achieved, albeit to different extents, in different semesters of CEM 252 being taught by different instructors. That said, instructor effectiveness may play a determining role in realizing any gains from the approach.

The method appears not to become problematic as the reactions and structures become more complex. However, the preliminary data point to data multi-step synthesis as an area where gains over traditional methods may not be realized.

Perhaps this approach, which unapologetically embraces some memorization, was at least partially successful in breaking students from trying to “copy & paste” pictures on an exam to the examples from lecture that they have in their mind. That said, truly validating our hypothesis that using “WORDS” to train students to identify and prioritize the functionally relevant elements of molecules that also bear other visually distracting features will require further study. Indeed, future work and additional study is needed to further validate the effectiveness and/or ineffectiveness of teaching organic chemistry in “WORDS”.

6.11. Final WORDS

Helping students understand and benefit from Organic Chemistry should be a universal goal for instructors. My thought is before pushing beginning students to think deeply about organic chemistry we should have them grow-familiar with this new world. Within the confines of a two-semester organic chemistry sequence only then will many, if not

the majority, of students be able to learn critical thinking that they can apply to future courses and situations where organic chemistry is central.

APPENDIX

APPENDIX

FS16 control class

TENTATIVE LECTURE AND EXAM SCHEDULE

Date	Topic	Reading Assignment
September 1	Conjugated π-systems	Chapters 17
September 6	" "	" "
September 8	" "	" "
September 13	Aromatics	Chapter 18/19
September 15	" "	" "
September 20	" "	" "
September 22	Alcohols, Phenols	Chapter 13
September 27	***1st Midterm***	***Chapters 17-19***
September 29	Alcohols, Phenols	Chapter 13
October 4	Ethers, Epoxides	Chapter 14
October 6	" "	" "
October 11	" "	" "
October 13	Aldehydes, Ketones	Chapter 20
October 18	" "	" "
October 20	" "	" "
October 25	***2nd Midterm***	***Chapters 13-14, 20***
October 27	Acids, Acid Derivatives	*Chapter 21*
November 1	" "	" "
November 3	" "	" "
November 8	" "	" "
November 10	Enols, Enolates	Chapter 22
November 15	" "	" "
November 17	" "	" "
November 22	***3rd Midterm***	***Chapters 20-22***
November 24	**THANKS GIVING**	--------
November 29	Amines	Chapter 23
December 1	" "	" "
December 6	Carbohydrates	Chapter 24
December 8	" "	" "

FINAL EXAM: MONDAY, DECEMBER 12, 7:45 – 9:45 AM, *COMPREHENSIVE.*

SS17

Planned Lecture/Reading/Exam Schedule:

CHAPTER	TOPIC	DATE COVERED
Chapter 15/16	Spectroscopy review and Course Intro	Jan. 9, 11, 13
Chapter 17	Conjugated Pi Systems	Jan. 18
Chapter 18	Aromatic Compounds	Jan. 20, 23
Chapter 19	Aromatic Substitution Reactions	Jan. 25, 27, 30, Feb. 1
Chapter 14	Ethers and Epoxides	Feb. 3
Chapter 13	Alcohols and Phenols	Feb. 6, 8, 10
EXAM 1	**Chapters 13, 14, 17, 18, 19**	**February 13th (Monday)**
Chapter 20	Aldehydes and Ketones	Feb. 15, 17, 20, 22
Chapter 21	Carboxylic Acid Derivatives	Feb. 24, 27; Mar. 1, 3, 13
Chapter 22	Alpha Carbon Chemistry	Mar. 15, 17
EXAM 2	**Chapters 20, 21, 22**	**March 20th (Monday)**
Chapter 22	Alpha Carbon Chemistry (Continued)	Mar. 22, 24, 27
Chapter 23	Amines	Mar. 29, 31; Apr. 3
Chapter 24	Carbohydrates	Apr. 5, 7, 10, 12
Chapter 26	Lipids	Apr. 14
EXAM 3	**Chapters 22, 23, 24, 26**	**April 17th (Monday)**
Chapter 25	Amino Acids and Peptides	Apr. 19, 21, 24, 26
Review	Chapters 13–26	Apr. 28
FINAL EXAM	**All Inclusive**	**May. 2 (Tuesday) 12:45– 2:45 P.M.**

FS17

Planned Lecture/Reading/Exam Schedule:

CHAPTER	TOPIC	DATE COVERED
Chapters 1–16	Course Intro and CEM 251 Review	Aug. 30
Ch 13, 14, 20–23	Survey of Functional Group Transformations	Sept. 6, & 11
Chapters 13	Alcohols and Phenols	Sept. 13
Chapter 20	Aldehydes and Ketones	Sept. 18, 20, & 25
EXAM 1	**Inclusive**	**September 27 (Wednesday)**
Chapter 21	Carboxylic Acid Derivatives	Oct. 2, 4, & 9
Chapter 22	Alpha Carbon Chemistry	Oct. 11 & 16
Chapter 23	Amines	Oct. 18
EXAM 2	**Inclusive**	**October 23 (Monday)**
Chapter 24	Carbohydrates	Oct. 25, 30, & Nov. 1
Chapter 18	Aromatic Compounds	Nov. 8
Chapter 19	Aromatic Substitution Reactions	Nov. 6 & 13
EXAM 3	**Inclusive**	**November 15 (Wednesday)**
Chapter 17	Conjugated Pi Systems	Nov. 20
Chapter 26	Lipids	Nov. 22
Chapter 25	Amino Acids, Peptides, and Proteins	Nov. 27 & 29
FINAL EXAM	**All Inclusive** **10:00 am – 12:00 pm** **C102 Wilson Hall**	**December 15 (Friday)**

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Chapter 7. Experimental details and characterization data

7.1. 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(□^{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.

7.2. 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) $\tilde{\nu}_{max}$: 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) $\tilde{\nu}_{max}$: 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; *Rf* = 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.

7.3. 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 C*H*$_3$ of Bpin), 1.38 (s, 12 H, 4 C*H*$_3$ 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. ^{1}H 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_2CH_3), 1.46 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.41 (s, 12 H, 4 CH_3 of Bpin), 1.41 (s, 12 H, 4 CH_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 CH_3 of Bpin), 1.38 (s, 12 H, 4 CH_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 rt 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 C*H*$_3$ of Bpin); 1.37 (s, 12 H, 4 C*H*$_3$ 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) $\tilde{n}_{max}$: 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 C*H*$_3$ of Boc), 1.39 (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 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 rt. 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 ^1H 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. ^1H 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. ^1H 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. ^1H 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 C*H*$_3$ of Bpin), 1.39 (s, 12 H, 4 C*H*$_3$ 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_2CH_3), 1.45 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.41 (s, 12 H, 4 CH_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 CH_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 rt. 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 rt 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) $\tilde{\nu}_{max}$: 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%

7.4. 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]

7.5. Experimental details for Chapter 5

To a solution of amino ester (1 mmol) in THF (10 ml) was added *N*-Boc amino acid (1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (2.2 mmol), HOBt (2.2 mmol), Et_3N (10 mmol) was added. The reaction was protected from light and stirred at room temperature for 24 h. The solution was washed with 1 N aqueous HCl and 1 N aqueous $NaHCO_3$ and extracted 3 times with EtOAc. The organic layer was washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (40% acetone in hexane).

Dipeptide 1: NBoc-Gly-Trp-OMe. The general procedure was applied to provide the dipeptide **1** (345.3 mg, 92%, mp 55-57 °C) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (br s, 1H, NH), 7.49 (d, 1H, *J* = 7.5, 1H), 7.31 (d, 1H, *J* = 7.5, 1 H), 7.12 (m, 2H), 6.94 (d, 1H, *J* = 2.2 Hz, 1 H), 6.79 (d, 1H, *J* = 7.4, NH), 5.26 (br s, 1H, NH), 4.90 (m, 1H), 3.71 (d, 2H, *J* = 4.4 Hz, 1H), 3.63 (s, 3H), 3.29 (d, 2H, *J* = 5.3, 1H), 1.42 (s, 9H). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 172.34, 169.47, 156.19, 136.23, 127.54, 123.32, 122.20, 119.64, 118.39, 111.55, 109.46, 80.30, 52.97, 52.56, 44.17, 28.37, 27.62.

Dipeptide 2: NBoc-Trp-Gly-OEt. The general procedure was applied to afford the dipeptide **2** (270.6 mg, 69%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (br, s, NH),7.57 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.15 – 7.08 (m, 1H), 7.08 – 7.01 (m, 1H), 4.52 (s, 1H), 4.03 (s, 1H), 3.84 (q, *J* = 3.5 Hz, 2H), 3.09 (d, *J* = 3.5 Hz, 2H), 1.41 (s, 9H), 1.23 (t, *J* = 4.5 Hz). ^{13}C NMR (125 Hz, $CDCl_3$) δ 172.34, 169.45, 155.57, 136.26, 127.51, 123.50, 121.77, 119.22, 118.54, 111.30, 109.90, 61.28, 55.06, 41.26, 30.81, 28.19, 13.97.

Dipeptide 3: NBoc-Trp-Phe-OMe. The general procedure was used to afford the dipeptide **3** (303.0 mg, 65%) as an oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.20-7.10 (m, 5H), 6.99 (s, 1H), 6.82 (d, *J* = 7.6 Hz, 2H), 6.30 (d, *J* = 6.5 Hz, 1H), 5.17 (s, 1H), 4.73 (s, 1H), 3.60 (s, 3H), 3.15 (dd, *J* = 14.5, 6.9 Hz, 1H), 2.94 (d, *J* = 5.8 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.41, 155.47, 136.40, 135.72, 129.22, 128.53, 127.56, 127.06, 123.47, 122.26, 119.76, 118.90, 111.36, 110.40, 80.16, 55.30, 53.32, 52.21, 37.95, 28.34.

Dipeptide 4: NBoc-Phe-Trp-OMe. The general procedure was used to afford the dipeptide **4** (299.1 mg, 64.2%, mp 165-166 °C) as white solid. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 10.78 (s, 1H), 8.15 (s, 1H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.30e7.23 (m, 5H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.90 (s, 1H), 6.38 (d, *J* = 5.5 Hz, 1H), 4.90 (m, 1H), 4.36 (m, 1H), 3.65 (s, 3H), 3.28 (m, 2H), 3.06-3.04 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.75, 170.77, 155.25, 136.59, 136.08, 129.43, 128.62, 127.53, 126.93, 122.26, 119.69, 118.49, 111.30, 109.79, 80.09, 55.68, 52.99, 52.31, 38.36, 28.21, 27.70.

Dipeptide 5: NBoc-Phe-His-OMe. The general procedure was used to afford the dipeptide **5** (123.0 mg, 29.5%) as an oil ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36 – 7.15 (m, 5H), 6.72 (s, 1H), 5.18 (d, *J* = 6.6 Hz, 1H), 4.84 – 4.67 (m, 1H), 4.28 (s, 1H), 3.78 (s, 3H), 3.29 – 2.91 (m, 5H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.27, 129.39, 128.80, 127.16, 52.98, 52.67, 28.43.

Dipeptide 6: NBoc-Trp-His-OMe. The general procedure was used to afford the dipeptide **4** (137.1 mg, 30.0%, 171-173 °C) as white solid. ^1H NMR (300 MHz, CD_3OD): δ 7.59 (s, 1H), 7.31 (m, 2H), 7.07 (m, 3H), 6.85 (s, 1H), 4.35 (t, 1H, *J* = 6.9 Hz), 3.77 (t, 1H, *J* = 7.1 Hz), 3.64 (s, 3H), 3.23 (m, 2H), 3.05 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD) δ 22.97, 27.69, 29.09, 51.68, 53.20, 56.36, 110.31, 111.69, 118.03, 119.19, 121.54, 124.11, 128.25, 134.88, 155.62, 172.14, 175.37.