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Hello everyone, my name is Sriya and I am a senior here at UIUC majoring in chemistry and conducting research in organic chemistry in the Burke Lab. Today I am going to discuss some exciting results I've obtained while developing a generalized method of making small molecules.

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Building block based construction has been enabling to creating the objects we use in our daily lives. These objects range from cars to buildings and complex structures using Legos

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However, only recently has building block construction transitioned to the microscopic scale. For common biopolymers such as polypeptides, oligonucleotides and oligosaccharides, their building block based syntheses have been achieved by viewing these molecules as smaller subunits or building blocks and then using one reaction to connect these subunits together. For example, in polypeptides, these subunits consist of amines which are stitched together using a reaction called amide bond formation.

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Natural products and small molecules have often been an inspiration for drug molecules. However, simplifying their synthesis by using a similar building block based approach as seen in biopolymers is challenging because subunits and linkages in small molecules are a lot less apparent. Often times when these molecules are used for drug molecules, they require multiple modifications to be made. Sometimes these modifications are as simple as one reaction. But often times, they are a lot more complex than one reaction. If we could figure out a way to make these small molecules in a building block-based fashion, it could be transformative to our ability for drug discovery as we could easily switch out blocks to make derivatives that could be tested for biological activity. Although making small molecules in a building block based way may seem challenging, nature has already shown us how various complex small molecules can be made from just a very small pool of building blocks.

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Embarking upon this challenge, the Burke group has demonstrated how small molecules can be made in a generalizable fashion through the method: Iterative cross coupling. This method takes inspiration from iterative peptide coupling that attenuates the reactivity of a nitrogen in order to selectively make amide bonds between amines. Similarly, iterative cross coupling attenuates the reactivity of a boron to make carbon-carbon bonds between various subunits in a small molecule. In iterative cross coupling, first we start off with a bifunctional building block containing a halogen and a protective boron. In this case, we use a MIDA ligand to protect our boron. Once we selectively react a halogen with a boronic acid, a reactive boron, we form a carbon-carbon bond after which the MIDA can easily be cleaved to reveal a new reactive terminus that can further couple with more bifunctional building blocks in order to construct a small molecule.

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For example, a boronic acid can selectively react with a halogen to form a new carbon-carbon bond. And once this is done, the protective MIDA group can be cleaved off with some base to reveal a new reactive

boron terminus which is in this case a boronic acid. And which can then participate in further couplings while selectively making a new carbon-carbon bond. In this way, after two more building blocks and one reaction, the synthesis of ratahnine can be completed in a completely building block based fashion.

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This methodology has not only been used by the Burke group in order to make small molecule but also by many labs across the world in order to construct a large variety of small molecules. However, a major limitation to this method is, in order to make a carbon-carbon bond between various subunits, unsaturation must be present. Both coupling partners must be unsaturated in nature for the reaction work. However, after realizing that most small molecules that advance into clinical development contain many elements of three dimensionality, we decided we needed to expand this method to making sp3-sp3 carbon carbon bonds.

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If we were to use our current iterative cross coupling method to make three dimensionally enriched small molecules, we are faced with several limitations. Although there has been lots of progress in making the boron coupling partner three dimensional in nature, a major rate limiting step in the catalytic cycle prevents us from utilizing a building block of this nature in order to make sp3-sp3 carbon carbon bonds. Hence, we looked at other methods that also use boron to install carbon-carbons bonds and we found the 1,2 metallate rearrangement.

Slide 9: In this method, a species containing a nucleophile and leaving group reacts with a boron to form a boronate complex. Then a migration takes place that kicks the leaving out to install a new bond between boron and the nucleophile. Both the stereochemistry of the migrating group is conserved and there is inversion at the migratory terminus.

The Aggarwal group at the University of Bristol has even shown how these nucleophilic- leaving group species can be made chiral, through their synthesis of lithiated carbenoids. These carbenoids can very effectively react with a boron to install Csp3-Csp3 bonds in high selectivity.

Recent developments in their group have led to bench stable precursors of these chiral carbenoids.

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So we hypothesized that we could combine iterative cross coupling with the Aggarwal homologation method in order to make both the unsaturated and and saturated portions of small molecules. So in our new cycle, we would have a new bifunctional building block containing a masked carbenoid and MIDA boronate, which is analogous to what was known before. A reaction can then take place selectively between the carbenoid and the reactive boron which is in this case a pinacol ester. Once the new Csp3-Csp3 bond is installed, MIDA can be cleaved to reveal a new terminus.

Our new coupling platform could give us access to a wide variety of chemical space that was previously inaccessible with iterative cross coupling. As you can imagine, we could start making various saturated motifs as well as unsaturated motifs present in small molecules.

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In order to test our hypothesis, We first synthesized a bifunctional building block containing a MIDA protected boron and a reactive pinacol boronic ester. We then subjected it to this masked carbenoid, however, observed no reaction. We assumed this was because our carbenoid was getting protonated by the MIDA backbone.

However, recent developments in the Burke Group have led to a second generation protecting group, called TIDA, that contains four gem dimethyl groups in the place of protons. So we synthesized a new bifunctional building block containing a TIDA boronate and a reactive pinacol ester, and subjected it to same conditions and obtained a high yield of the desired product. After obtaining these exciting positive results, we decided to explore the scope of this new reaction to other various motifs such as aryl, heteroaryl and saturated bifunctional building blocks.

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In order to demonstrate that this method was iteratable, it was very important that we performed an experiment that would distinguish between the newly formed boron versus the boron that would engage in the next coupling reaction. So we conducted an experiment that would allow us to access the selectivity of coupling between an unhindered, primary reactive pinacol ester and a hindered secondary pinacol ester. So after conducting this experiment, we still observed high selectivities for the unhindered boron, which told us that we could very easily differentiate between the two borons.

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Next we needed to develop reaction conditions that would allow us to easily deprotect our TIDA boronate to a reactive pinacol ester. We were also able to accomplish that and observed high yields for these reactions.

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Lastly, we needed to ensure we could make bifunctional building blocks that containing the sulfoxide and the TIDA boronate. We were also able to accomplish this and further showed that we could couple these blocks to form new sp3-sp3 carbon-carbon bonds.

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After demonstrating a new methodology can make saturated carbon-carbon bonds in high selectivities in an iterative fashion, we wanted to demonstrate its use through the total synthesis of two natural products. We are currently working on synthesizing this antifungal macrolide from just three building blocks and a few modifications to demonstrate how we can make the saturated portions of small moelcules in a building block based fashion. We are also working on the synthesis of samroiyotmycin A, a potential anti malarial. With this synthesis, we hope to demonstrate how we can interchange between both parts of our iterative cross coupling cycle to make both the saturated carbon-carbon bonds and the unsaturated carbon-carbon bonds in small molecules.

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With that, I'd like to thank Professor Burke, my postdoctoral mentor, Dr. Daniel Blair, my two undergraduate coworkers David and Vikram, all the funding agencies that have generously supported this work, and lastly, all of you for your attention.