Hi, my name is Nina Fatuzzo, and I work for the Dong lab at the University of Chicago. Today, I’ll be talking about my work with palladium/norbornene cooperative catalysis, and our use of this system to functionalize difficult-to-reach C-H bonds.

So, Marta Catellani really pioneered the use of palladium/norbornene cooperative catalysis. In 1997, she discovered something that we now call the Catellani reaction, and over the past few decades, the scope of this reaction has been expanded greatly. But in its traditional form, it features the coupling of an aryl iodide and several carbon-based substituents. So the reaction is catalyzed by palladium and this molecule, highlighted in yellow, called norbornene. So the first step of the reaction is that the palladium inserts into the C-I bond. The palladium is then at what we call the *ipso*, or the original, position on the ring. This chemistry was known at the time. The next step is where things get interesting. So this norbornene molecule then can insert into that C-Pd bond. And with that insertion, that step actually shifts the palladium over one position, placing it at the *ortho* position, and we see the formation of this aryl-norbornene palladacycle, or an ANP. And this is really the key step of the catalytic cycle. So once the palladium is at this ortho position, we’re able to add an R2 substituent to that position. I haven’t drawn this out explicitly, but basically what happens next is something called norbornene extrusion, where the norbornene leaves the ring, and palladium returns to its original position. At this point, the reaction can be quenched via a variety of different methods. What I’ve shown here is something called a Heck quench. This is the Heck reaction, and we’ll talk about it a little bit later. But the important thing to take away from this slide is that the use of norbornene as a co-catalyst allows us to activate positions that we wouldn’t normally have access to.

So shifting gears for a minute, we’re going to talk about how to functionalize alkenyl C-H bonds. So this is also a field that has been developed quite a bit in the last few decades. If you’ve ever taken organic chemistry you’re probably familiar with the Wittig reaction. This was kind of a first-generation way to form multi-substituted alkenes. So the Wittig reaction is a really interesting reaction. Unfortunately, it does have a pretty major limitation, which is that the isomer that you get out of this reaction depends entirely on the substrate. And so if you wanted, say, a *Z* isomer but you had a substrate that would give you the *E* isomer, there’s not really a way to access that *Z* isomer via this method.

So something of a second generation method is shown here: olefin cross-metathesis. Again, this has seen a lot of development in the last few decades, but again it has a fairly major limitation in some cases, which is that it can be difficult to determine which isomer will result from the reaction, and in some cases you end up with a mix of isomers. So that limitation is beginning to be addressed.

Then finally, we have sort of a third-generation method over here. This is called the directing group method. And so essentially this directing group here, DG as I’ve drawn it out, helps to place the metal catalyst on a specific C-H bond. And at that point, your substituent can insert into that position. So this method is really interesting because it does provide one specific isomer. You will always get this isomer, just due to the mechanism of the method. However, there is another limitation here. This position that I’ve highlighted in green is called the proximal C-H bond. It is closest to the directing group, and it is the bond that can be activated with this method. The distal bond is farther from the directing group, and it’s very difficult to activate using this method just because of the distance between this directing group and that distal C-H bond.

So with these limitations in mind, we envisioned a reaction that could place a substituent at this distal position here, and provide one specific isomer. And to do this, we turned to the Catellani reaction. So I’ve drawn the catalytic cycle of the mechanism that we developed. This first step here should look familiar to the directing group method that we just looked at. Our DG helps to place the palladium at that proximal C-H position. The next step is almost exactly what happens during the Catellani reaction. This norbornene will insert and that helps to shift that palladium over so that it’s now close to the distal C-H bond. And it can then insert into that bond. So once the palladium is at this position, we again see this ANP formation, which is again the key step in this catalytic cycle. And our substituent can insert into this C-Pd bond, placing our R1 substituent at this distal position.

Ok, so once we have an idea of what kind of mechanism we wanted to use, we turned to the optimization of the reaction. So our reaction couples an alkene, shown here, and an aryl iodide. So this aryl iodide is the substrate that we’ll be placing at this distal C-H position. So one of the key steps when optimizing a Catellani reaction is determining the type of norbornene that works best with your system. So norbornene can refer to a few different things. It can refer to this specific molecule here, **N1**, but it can also refer to a class of molecules that contain that norbornene motif and also a number of substituents, different types of substituents and at different places along the ring. And we’re not 100% sure as to why this is yet, but those substituents can vary the reactivity pretty dramatically. If you compare the yield for **N1** and **N2**, you’ll see that **N2** provides a 76% yield of product whereas **N1** provides only a 28% yield. So that’s a pretty massive difference. In our case, we found that the heavier norbornene tended to produce a higher reactivity. We think that’s just because the heavier norbornenes tend to be a bit more stable in solution, so they were more able to act as a catalyst for our system. Another key step was identifying what directing group would work best with this system. We tried a lot of different types of directing groups, but ultimately ended up with an oxime ether type. So **DG1**, **DG2**, and **DG3** are all oxime ether types, but again the substituents are varied a bit, and as you can see, that again plays a big role in reactivity. So ultimately **DG1** became our standard directing group.

We also ran a few control experiments. So with our standard conditions we see a 76% yield. That’s quite a high yield, and we’re happy with that. Without palladium, we see a 0% yield. That’s expected. Without palladium we don’t have any C-H activation at all. Without the pyridone ligand, which is this 3-CF3-pyridone up here, we only see a 16% yield. So that’s pretty low. The pyridone ligand is responsible for facilitating a couple of those key catalytic steps, so without that the reactivity of the cycle drops pretty considerably. Without our norbornene catalyst **N2**, we see a 0% yield. However, there’s a caveat. So I mentioned the Heck reaction earlier. Palladium can catalyze a number of different types of organic chemistry reactions, so it’s to be expected that there are some competing reactions present in this system, and one of them is the Heck reaction. The Heck reaction occurs whenever you have an alkene and a source of palladium, and in this reaction we have both. So ultimately the Heck reaction can result in coupling between the aryl iodide and the alkene, but it produces a different isomer. So if you look at **3a**, this is the Catellani product. You can see that the phenyl group and this carbon chain with the directing group off of it are *cis* to each other. If the Heck mechanism were to occur, the phenyl group and the aryl substituent would ultimately switch places, so that would put the phenyl group and the carbon chain *trans* to each other. So you’d end up with a completely different isomer. So that is something we had to look out for when we were optimizing our conditions. However, with norbornene present, you’ll see that the Catellani reaction is heavily favored.

So once we had our optimized conditions, we started looking at the scope of the reaction. Now, a lot of the reactions that are developed with catalytic systems end up as tools in total synthesis reactions. And so to ensure that we can produce a lot of different types of products and to increase the applicability of this reaction, we wanted to show that it can react with a variety of different substrates, tolerate a variety of different functional groups. So that’s what the scope is mostly here to do. So as you can see, our reaction is able to tolerate this CF3 group, the methoxy groups. We are able to tolerate cyclic alkenes versus linear alkenes, alkenes derived from secondary alcohols versus alkenes derived from primary alcohols. And you’ll notice that there is “*E* only” or an *E*:*Z* ratio shown. That’s referring to the Catellani to Heck ratio. So the Heck reaction will produce the *Z* isomer, and the Catellani reaction produces the *E* isomer. So when you see *E* only, that means that the Catellani reaction is the only reaction that we see. In the cases that we did see an *E*:*Z* ratio, it’s quite high, indicating that when norbornene is present in the system, the Catellani reaction really dominates over the Heck pathway.

So next we took a look at our aryl iodide scope. This is really where we see the most of our functional group tolerance. You can see that the reaction tolerates these ester groups, nitro groups, methoxy groups again, and even heterocycles, as shown in **3l** and **3p**. And again, the *E*:*Z* ratio is quite high. For most of these, we only see the *E* isomer. For **3p**, that ratio is a bit lower, but even so that *E* isomer is still the major product.

Finally, we wanted to show that our reaction could also tolerate an alkylation as well as an arylation. So again, placing an aryl group at that distal C-H bond is really exciting. It’s a new kind of mechanism for functionalizing alkenyl C-H bonds, but it does limit the scope of the reaction a bit. So we wanted to show that this reaction could also be applied to alkyl substrates. And so we were able to place a methyl group at that distal position with a 31% yield, and an alpha ester at the distal position with a 65% yield, which is quite high. You’ll notice here that the isomer is the Z isomer this time. That’s just a naming convention, this is still the Catellani product.

So with that I’d like to thank Dr. Guangbin Dong, my PI, and my mentor Zhao Wu for their invaluable support throughout this project. And I’d like to thank the Dong group as a whole. Thank you!