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Tuning Reactivity in C(sp^3)–C(sp^2) Cross-Electrophile Coupling

by

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Chapter 1: An Introduction to Cross-Electrophile Coupling

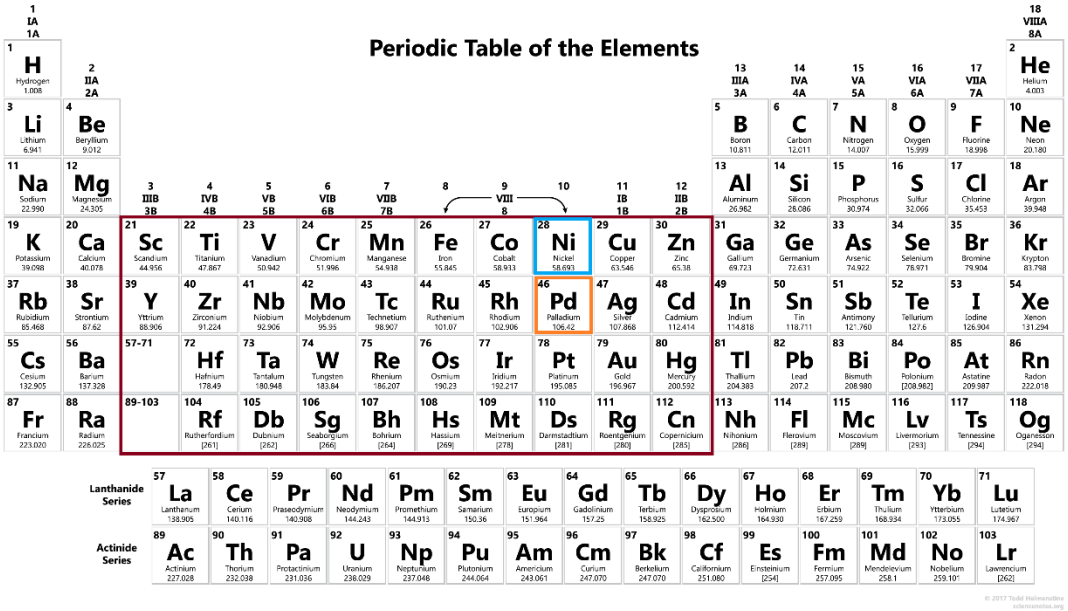
The sheer amount of jargon in chemistry can make chemistry research inaccessible to a general audience. I wrote this chapter to contextualize and share my doctoral research to my friends, family, and anyone else who wants to read it! I've had a lot of fun writing this, and I implore anyone in a specialized field to give this kind of writing a go. I would like to thank the Wisconsin Initiative for Science Literacy (WISL) at UW-Madison for providing this platform, and for sponsoring and supporting the creation of this chapter. I am especially grateful to Professor Bassam Shakhashiri, Elizabeth Reynolds, and Cayce Osborne for their help in making this chapter as clear as possible.

Organic chemistry is the study of carbon-based (organic) molecules. Some organic molecules are the building blocks that keep people alive. The sugars, fats, and proteins that we eat get broken down in our body into smaller building blocks that the body can use to create energy, make hormones that regulate bodily functions, and generally keep our bodies chugging along. Other organic molecules may not be used to keep us alive but still have important applications in everyday life. We can use dyes to make beautifully colored fabrics, plastics to make containers and toys, and drugs to treat diseases. Some of these organic molecules can be extracted from plants and other natural sources, but others need to be made in a lab using chemical reactions. Because organic molecules are primarily made of carbon atoms, reactions that form bonds between carbon atoms are especially powerful for building complex molecules that we can't find in nature.

Cross-coupling reactions are reactions that are commonly used to form carbon-carbon bonds in the synthesis of drugs and pesticides, allowing chemists to stitch two organic

fragments together to make a new, larger molecule. Cross-coupling reactions typically require a transition metal catalyst, a molecule that lowers the energetic barrier to a reaction by unlocking different mechanistic pathways, to form the desired carbon-carbon bond. Transition metals are any of the elements highlighted in the red box on the periodic table in **Figure 1**, with the most commonly used metal being Palladium (Pd). Transition metals make useful catalysts because they are stable at different oxidation states, meaning they can easily give up and take back electrons. These transition metal catalysts are made up of two distinct things: a transition metal and a ligand. Ligands are organic molecules that bind to transition metals and change how that metal reacts with other molecules. Palladium catalyzed cross-coupling reactions are so useful that Richard Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the Nobel Prize in 2010 for their research in this area.

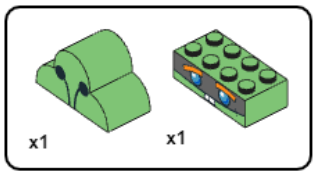
Figure 1.1: The Periodic Table of the Elements with transition metals highlighted by the red box, palladium is highlighted by the orange box, and nickel is highlighted by the blue box.



I like to think about a transition metal as a person, a ligand as a set of tools, and a chemical reaction as a task that needs to get done. You want to pick the right person with the right tools to get a job done. Some tasks can be done by most people and don't require specific tools: Most people can go pick up some milk, whether they walk, bike, take the bus, or drive to the store. Some tools can bridge a person's skill gap for some tasks. This thesis would be practically illegible if I wrote it all by hand, but a word processor lets me write this clearly. Certain tasks can only be done by masters of a craft and with specialized tools. You wouldn't want a chef to use a baseball bat to perform your open-heart surgery, just like a sports team would never pay a surgeon to hit baseballs with a chef's knife, and you would never ask a baseball star to prepare you a salad using a scalpel. Similarly, the task of forming the desired carbon-carbon bond can only be accomplished by using the right combination of transition metal and ligand.

A catalyzed reaction is like a frozen pizza factory, with reactants being the raw ingredients and the product being the pizza. Our jobs as people who develop new reactions is to make sure all the machines work together to make pizza and to make the manufacturing process more efficient. Every step needs to happen in the right order and at the right rate to make your pizza dreams come true. Some problems in the factory have simple solutions. If the pizzas aren't getting cold enough, you can just leave them in the freezer longer. Other problems in the factory have more flexible solutions. If cheese is being dispensed too quickly, you'll end up with some very cheesy pizzas and, once you run out of cheese, cheeseless pizzas. For this you could slow down the cheese machine, speed up every other machine, fill the cheese machine with more cheese at the start, or even market cheeseless pizzas as a great meal for lactose intolerant people.

Figure 1.2 LEGO analogy for conventional cross coupling. The two LEGO bricks can only combine in one way.



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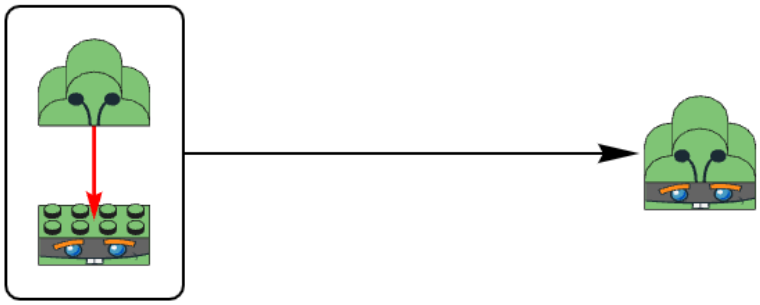


Conventional cross-coupling reactions use a palladium catalyst to form carbon-carbon bonds between nucleophiles (organic molecules that donate a pair of electrons) and electrophiles (organic molecules that accept pairs of electrons). The correct carbon-carbon bond is formed during the reaction because of how nucleophiles and electrophiles react together, like how two LEGO blocks just snap into place because of their complementary studs and anti-studs. Researchers have spent decades studying and improving palladium catalyzed cross-coupling reactions. However, there are still challenges, specifically centered around the use of palladium catalysts and the use of nucleophiles.

Palladium catalysts are highly efficient and useful, but palladium is expensive (~$1,400 per ounce) and not abundant (palladium makes up 0.0000015% of the earth's crust and is the 70th most abundant element) making it not ideal to use palladium for the synthesis of molecules on large scale. The price and scarcity of palladium has sparked a lot of interest in finding

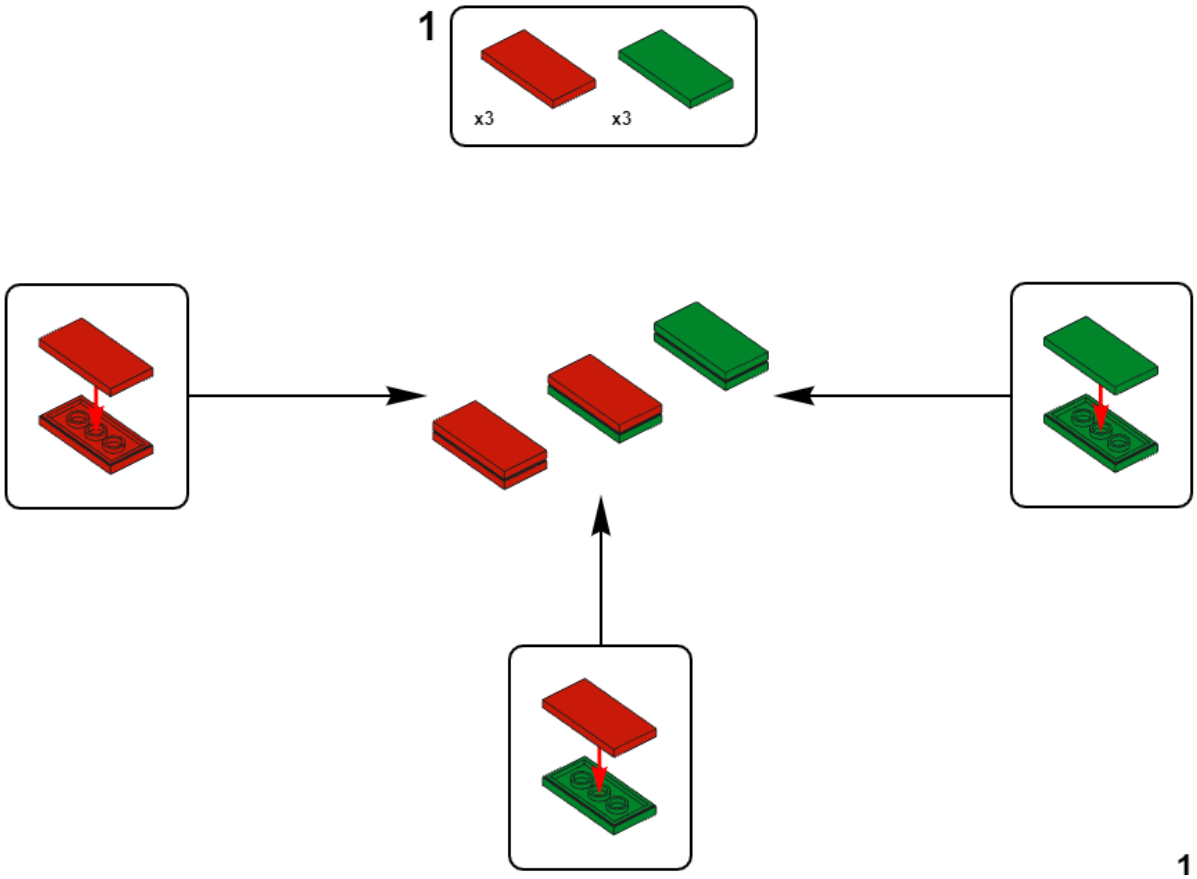
alternative metals that can catalyze cross-coupling reactions. Nickel (Ni) is in the same group of the periodic table as palladium, so the two metals react similarly in some cases, but nickel is significantly cheaper (~$0.80 per ounce) and more abundant than palladium (nickel makes up 0.0084% of the earth's crust and is the 23rd most abundant element). 0.0084% may not seem like much, but that means there is 5600 times more nickel than palladium on earth.

The types of nucleophiles that are used in cross-coupling reactions are known as organometallic reagents, organic compounds that contain a carbon-metal bond. Organometallic reagents come with their own unique set of challenges. Organometallic reagents are highly sensitive to moisture; even humid air can be wet enough to decompose organometallic reagents, so researchers need to take extra precaution when storing or handling organometallic reagents. This means that, more often than not, if you want to use an organometallic reagent in a reaction you would have to make it and use it right away. These organometallic reagents are typically made by reacting an electrophile with a metal. You can buy thousands of times more electrophiles than nucleophiles because you don't have to take care to store electrophiles away from air and water. The abundance and stability of electrophiles has motivated researchers to spend the last several decades finding creative, useful reactions that rely on electrophiles.

You can avoid making organometallic reagents by cross-coupling two different electrophiles together: this is called cross-electrophile coupling. Reacting two electrophiles together is like trying to put two LEGO bricks together end to end. Normally this would be an impossible LEGO building technique, but with enough glue you can make the impossible possible. Nickel based catalysts are used a lot in cross-electrophile coupling reactions because they are good at telling the difference between two different electrophiles. If nickel is like your hands that are putting the LEGO bricks together, ligands are like your eyes. If you have a pile

of red and green LEGO bricks and pick two at random, you'll end up making a mixture of red-red, red-green, and green-green LEGO bricks stuck together. If you only want red and green LEGO bricks stuck together, you need to be able to see the difference between them.

Figure 1.3: LEGO analogy for Cross-Electrophile Coupling. Each tile only has anti-studs so putting the correct two pieces together requires you to be able to see color



An important step of cross coupling involves the metal activating the electrophile, Nickel is capable of activating different types of electrophiles in different ways, functionally allowing it to tell the difference between electrophiles. Nickel based catalysts are really good at interacting with both polar molecules (molecules with a pair of reactive electrons) and radicals (molecules with only one reactive electron). The cross-electrophile coupling reactions

I have studied have been reactions between electrophiles that react through polar (two-electron) mechanisms and electrophiles that react through radical (one-electron) mechanisms.

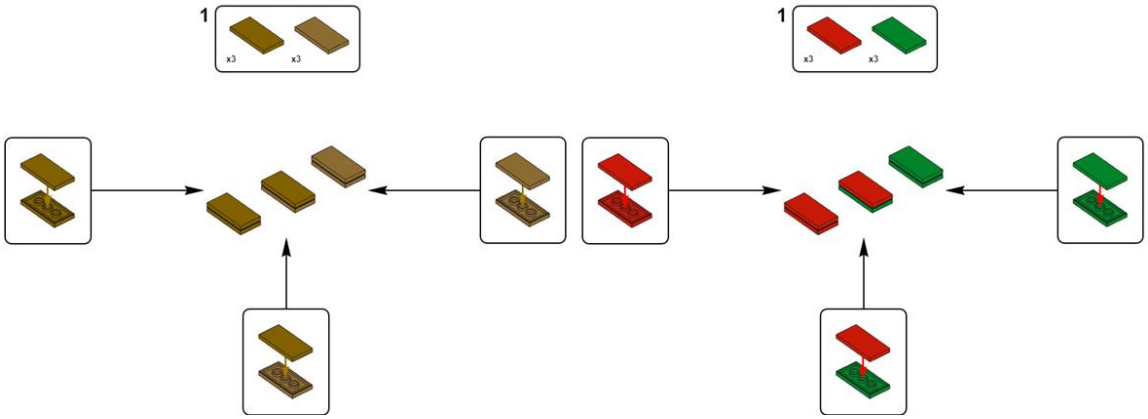
In graduate school the molecules I was most interested in were ones that contained strained rings, cyclic molecules where the ring is only made up of three or four atoms. Strained rings can be made entirely of carbon atoms, or they could have either a nitrogen atom or an oxygen atom in the ring. These small rings can have big effects on how a drug behaves in your body: they can make it easier for your body to absorb a drug from your stomach, they can slow down how long it takes your body to metabolize so it can be effective in your body even longer, and they can even make a drug more potent so you don't need to take as large of a dose. Although strained rings can be a really useful part of drugs, we never know what type of ring is going to be a part of the best drug until we test each of them out, and to test each of them out you have to make every single variation. Usually, you would have to make each ring, building the molecule from the ground up. It would be nice if we could use our LEGO approach to trying each different strained ring. Cross-electrophile coupling reactions are really good at stitching together two organic molecules to make one larger molecule, so I thought it would be useful to have a cross-electrophile coupling reaction that could work with strained rings, making it easy to swap out one ring for another. I searched databases of molecules I could buy, and I found that you can buy most strained ring molecules with a carboxylic acid functional group attached to them. A functional group is a reactive part of a molecule. Normally carboxylic acids don't play nice with catalysts that are good at promoting cross-electrophile coupling reactions, but you can easily turn carboxylic acids into redox-active esters. Redox is a portmanteau of the words "**red**uction" and "**ox**idation", and the word redox is used to describe a reaction that involves one molecule giving an electron to another molecule, so when a molecule is "redox-active" that means it can participate in a redox reaction. Once redox-active

esters get reduced they form a radical, which is exactly what we need for a cross-electrophile coupling reaction.

Getting this reaction to work wasn't as simple as "throw in a redox-active ester and call it a day". The main problem I had to solve was that the two electrophiles were mismatched in how quickly they reacted. I used two different strategies to control the relative rates of different steps in the reactions. 1) The ligand on the catalyst has a big effect on how quickly the catalyst reacts with each electrophile, so I researched different ligands and even made a brand new one. 2) Electrophiles have their own innate reactivity, so I studied how changing things like the structure of the electrophile or the solvent the reaction is run in changes an electrophile's reactivity.

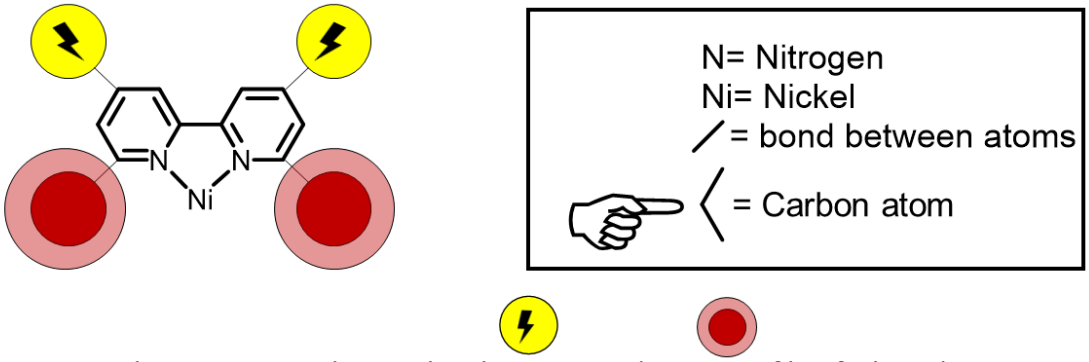
Let's start with the ligand. I mentioned before that ligands are like your eyes when you're trying to tell the difference between red and green LEGO bricks. Some people will have no problem distinguishing the two, but people that have certain colorblindness will struggle to tell the difference between red and green, and people who are completely blind won't be able to tell the difference at all. We might not be able to swap out our eyes very easily, but as chemists we can certainly change what ligand we put into a reaction. With so many different steps in a reaction, a ligand could be great for one step but terrible for the rest of them. When you're trying to find the right ligand for a new reaction you typically start by trying out ligands that have been used in similar reactions, bipyridine ligands are commonly used in cross-electrophile coupling reactions so they're a great place to start. Sometimes it's a great start and all you need to do is make minor changes to the structure of the ligand just to tweak its reactivity. The reactivity of bipyridine ligands is easy to tweak by adding different substituents to them. These substituents can change things like how tightly the ligand binds to nickel or how much space it takes up around the nickel atom.

Figure 1.4: Illustration of the importance of finding the right ligand for a reaction. (Left) LEGO **Figure 1.3** image with a deuteranopia filter applied. (Right) Copy of **Figure 1.3**.



Sometimes making small tweaks to a ligand isn't enough and you need to explore different types of ligands. One way we categorize ligands is by their denticity. Denticity refers to how atoms on a ligand can stick to a metal, with monodentate meaning one sticky atom, bidentate meaning two sticky atoms, and so on. When I started studying this reaction, I tried out bipyridine ligands and other, similar, bidentate ligands to try and find the best one. These all worked pretty well, but the reactions were not totally selective for the desired product over side reactions. I then tried a bunch of other ligands, and eventually found one that made the desired product with the best selectivity and in the highest yield. And it had never been used before! Since this ligand was brand new, I wanted to study what made it different, so I made enough to use for two papers. Ben, a graduate student that was working with me, took some of the ligand and made one of the reaction intermediates. He grew a crystal of this intermediate and we got a molecular picture using X-rays.

Figure 1.5 Ligand structure can change how a catalyst reacts.

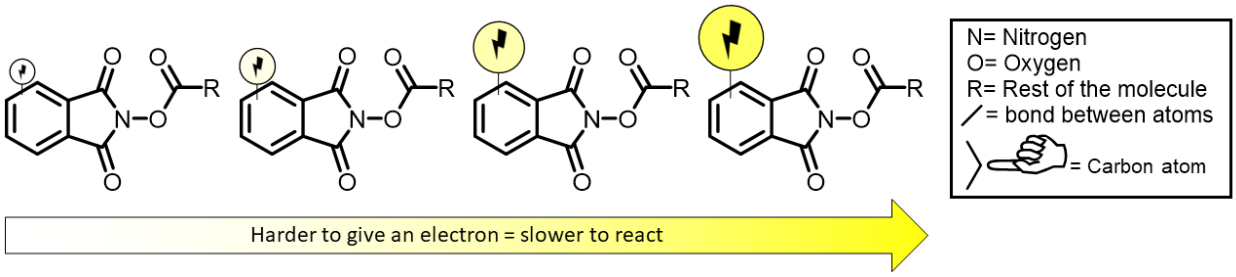


Substituents can change the electronic and steric profile of a ligand, ultimately changing how a catalyst behaves

One of the challenges I faced in my research was that redox-active esters react too quickly. If a molecule is too reactive it's like when the cheese machine in a pizza factory is too fast: it uses up the cheese before we can make all of the cheese pizzas we want. In my reaction, the redox-active ester was being used up faster than the other electrophile could react so I had to figure out a way to slow down how quickly the redox-active ester was being consumed. You can figure out how reactive a redox-active molecule is by measuring the molecule's reduction potential. The reduction potential tells you how easy it is to give an electron to a molecule. I had the hypothesis that if a redox-active esters was harder to reduce it would react more slowly. First, I made several different redox-active esters and measured their reduction potentials. I made some that were easier to reduce and some that were harder to reduce. Then, I studied the reaction between these new redox-active esters and a reductant, taking samples from the reactions at different times to measure how quickly they reacted. I found that the redox-active ester that was the hardest to reduce was also the slowest to react. Lastly, I took each of the redox-active esters I had made and tried them out in a bunch of different cross-electrophile coupling reactions. I found a good correlation between the reduction potential of the redox-active esters and the yield of the reaction product, with the most reactive redox-active esters

giving the lowest yield of the product and the least reactive redox-active esters giving the highest yield of the product.

Figure 1.6 Redox-active esters which are harder to give an electron to are slower to react.



Once I had a grasp of what controls the selectivity of the reaction and what knobs I could turn to tweak reaction outcomes, I looked at what sorts of molecules I could make. I was able to make small, proof-of concept molecules, as well as larger complex molecules that have been studied for their medicinal properties. With the help of my collaborators, I showed that this reaction could be done in different types of reactors, which would be helpful for doing both large- and small-scale reactions. Since we published a paper on this work last year, a chemical supplier has already begun selling the new ligand I used for this work, and chemists at several different companies have started using this reaction to help with the discovery of potential drugs.