Loudon Chapter 18 Review: Vinyl/Aryl Reactivity
Jacquie Richardson, CU Boulder – Last updated 2/7/2020

Chapter 18 covers leaving groups that are directly attached to double-bonded sp^2 carbons. These molecules don't do most of the regular alkyl halide chemistry from Ch. 9 (S_N1/S_N2/E1), but they can do E2 under the right circumstances.

Really bad at S_N1/S_N2/E1
Okay at E2 sometimes

Aryl iodide   Vinyl bromide
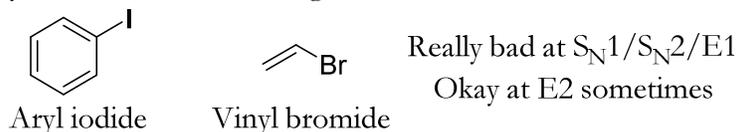
(This is in strong contrast to Ch. 17. There, we saw that leaving groups that were one atom away from an sp^2 carbon – either allylic or benzylic – were generally really good at alkyl halide reactions, due to resonance stabilization of the intermediates or transition states.)

Really good at S_N1/S_N2/E1
(E2 works better if the halogen is one carbon further away)

Benzyl iodide   Allyl bromide
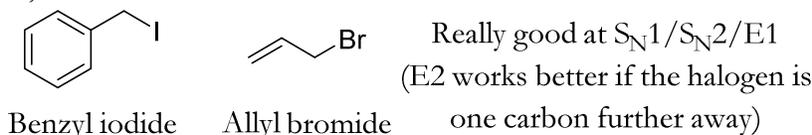
So let's go through the four reactions and look at why vinyl/aryl halides are so bad at them.

S_N2 on Aryl/Vinyl Halides
This reaction is so slow that it's basically considered no reaction. (For vinyl halides you will eventually get S_N2 product if you leave the reagents together long enough, but it's not occurring on a useful timescale).

Why is this? We already know that when S_N2 happens on a regular alkyl halide, the carbon goes from sp^3 to sp^2 during the transition state.

sp^3 carbon sp^2 carbon
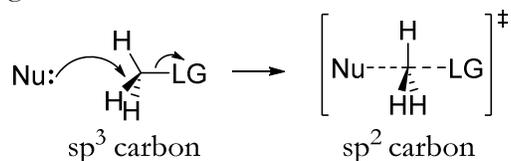
If a vinyl or aryl halide does this, then it would have to go from sp^2 to sp.

sp^2 carbon sp carbon
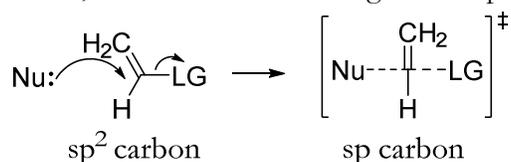
Going sp^2 to sp costs a lot more energy than going sp^3 to sp^2. In fact, it costs about 5 kcal/mol more, which means that at room temperature the rate will be slower by about 4 orders of magnitude.

On top of this, there are geometric problems too. To perform backside attack on a vinyl halide, you have to attack from within the plane of the molecule, which causes steric issues with the other carbon of the double bond. This isn't too bad when the carbon is just a CH_2 group, but if it has anything larger attached then the reaction is very sterically hindered.
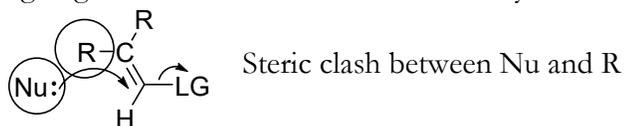
Steric clash between Nu and R

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This problem is even worse for backside attack on an aryl halide, since you would have to attack from inside the ring, and the nucleophile would be stuck inside the ring afterwards.

That's just silly
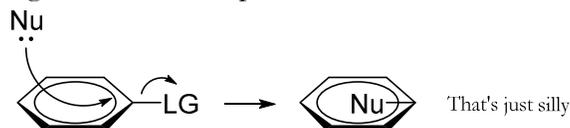
E2 on Aryl/Vinyl Halides

This is the only one of the four reactions that works somewhat okay. In fact, we've already seen E2 being performed on a vinyl halide when we made alkynes in Ch. 14.
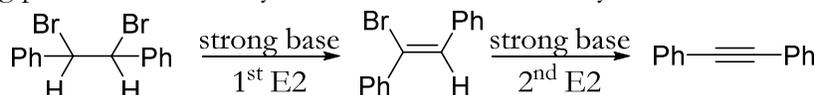
Interestingly, since the H and the leaving group are locked into the same plane no matter what, you don't have to get the leaving group and the H antiperiplanar (pointing in opposite directions) like in regular E2. Synperiplanar (pointing the same direction) works too.

Br and H antiperiplanar
E2 works fine

Br and H synperiplanar
E2 works fine
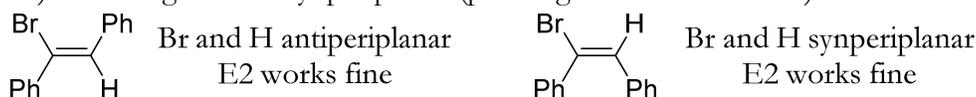
However, this is still going sp^2 to sp, so it still costs a large amount of energy and you need harsh conditions or a strong base to make it happen.

What about E2 on aryl halides? It turns out this is a little more complicated and not covered in Loudon.

S$_N$1/E1 on Aryl/Vinyl Halides

This doesn't work either. Remember that both of these mechanisms start by losing the leaving group and forming a carbocation:
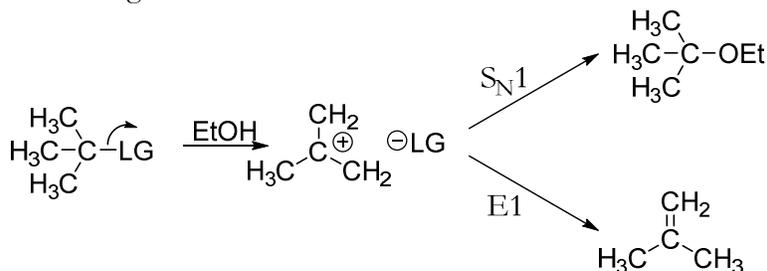
Aryl and vinyl carbocations are heavily disfavored, both because of the high cost of going sp^2 to sp and because there's no resonance stabilization like there would be in allylic/benzylic carbocations. The empty p orbital can't become conjugated with the double bond because it's perpendicular.

p orbitals of double bond

Empty p orbital
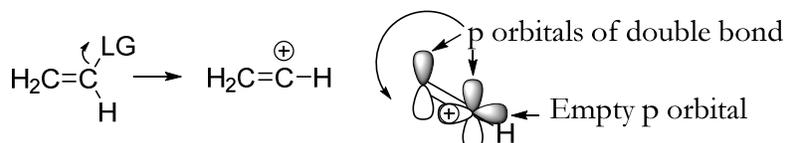
This problem is even worse for aryl halides, because when a carbon in the ring goes to sp, it wants to hold a linear geometry that distorts the ring too much to be allowed.
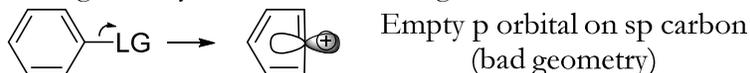
Empty p orbital on sp carbon
(bad geometry)

Instead, the carbon is forced to stay sp^2 hybridized (or sort of – it's in a hybridization state somewhere between sp and sp^2), which is not as bad as forcing a linear atom into a ring, but it still comes with an enormous energy cost.

 Empty sp^2-ish orbital on sp^2-ish carbon
(okay geometry but high cost in hybridization)
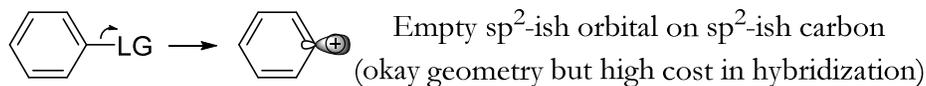
To top this all off, it's not that easy to detach the leaving group in the first place. The bond strength between the leaving group and the sp^2 carbon is higher than it would be between a leaving group and an sp^3 carbon. This is because there's more p character in an sp^2 atom's bond, so the bonds are shorter and therefore stronger.

 sp^2 carbon: Bond is shorter and harder to break

 sp^3 carbon: Bond is longer and easier to break

Nucleophilic Aromatic Substitution (S_NAr)

Although S_N1 & S_N2 don't work for aryl halides, there's one reaction that does: nucleophilic aromatic substitution. This can be contrasted with electrophilic aromatic substitution:

- EAS: make/add electrophile, put + charge on ring, EDGs are activating because they stabilize + charge, get rid of + by removing H^+ from carbon with new group
- S_NAr: make/add nucleophile, put - charge on ring, EWGs are activating because they stabilize - charge, get rid of - by removing X^- from carbon with new group

This starts with a nucleophile attacking an aromatic ring, which breaks aromaticity and puts a negative charge onto one of the ring atoms. The charge can move around by resonance – note that in one case, it can move out onto the NO_2 group. The negatively-charged intermediate is called a Meisenheimer Complex and is often brightly colored.
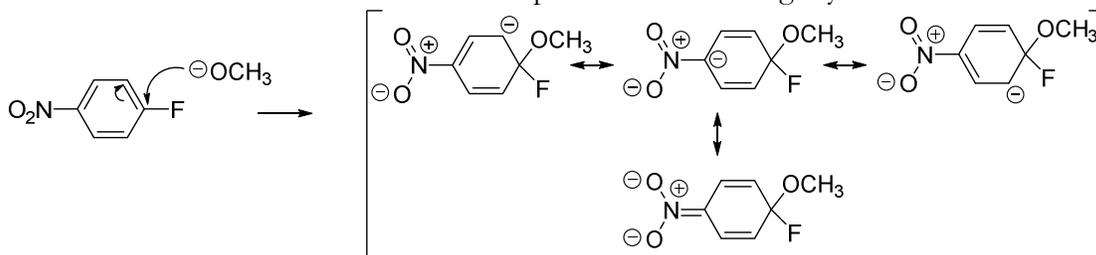
All of these are resonance states of the Meisenheimer Complex intermediate

To finish the reaction, the ring has to kick out the leaving group and reestablish aromaticity.
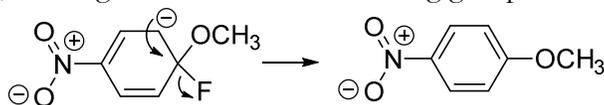
Since the rate-determining step involves forming an anionic species, anything that can help stabilize the negative charge will speed up the reaction. The more electron-withdrawing groups you have, the faster it will go. EWGs help stabilize the charge when they're ortho or para to the leaving group, but not meta.
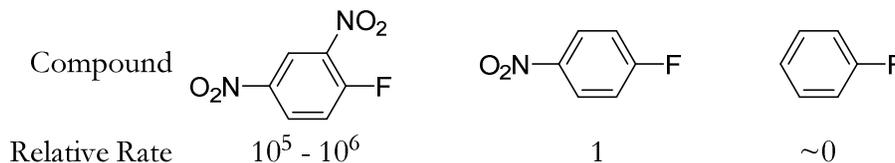
Compound			
Relative Rate	$10^5 - 10^6$	1	~0

Note that this is the opposite of the trend for electrophilic aromatic substitution from Ch. 16. Here, EWGs stabilize the negative charge, so they're activating and speed up the reaction. In Ch. 16, EWGs destabilized the positive charge, so they were deactivating and slowed down the reaction.

This also means that the more electron-withdrawing the halogen is, the more it will stabilize the negative charge and speed up the reaction. For this reason, F is the best halogen for S_NAr. Even though it's the worst leaving group, that doesn't matter because the rate-determining step doesn't involve it leaving. Aryl fluorides will usually do this reaction 10^2-10^3 times faster than aryl chlorides, bromides or iodides.

Transition Metals

There's another category of reactions that can occur on aryl/vinyl halides, but these are all catalyzed by transition metals. Before we look at these reactions, we need to look at the electronic structures of transition metals.

The transition metals are all of the elements located in the d-block of the periodic table (the region where any new electrons are being added to the d orbitals of the atom). This part of the periodic table is shown below, along with the total number of valence electrons in s and d orbitals on each atom.

Valence Electrons→	3	4	5	6	7	8	9	10	11	12
Period 4	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
Period 5	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
Period 6	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg

Bonding to transition metals is a little different than covalent or ionic bonds. All groups that bond to the transition metal are called ligands, and they all bond to the metal by donating electron pairs to form complexes. There are two types of ligands:

1. **L-type ligands** become neutral molecules when they dissociate from the metal. L-type ligands' bonds to the metal atom are often (but not always) shown as arrows instead of covalent line bonds. These are called **dative bonds**, and both electrons in this bond belong officially to the ligand. If a dative bond breaks, the metal's charge doesn't change.
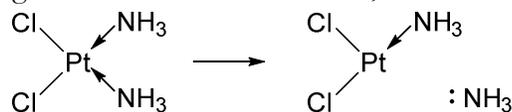
Examples are NH_3, H_2O, R_3P, CO, alkenes, and benzene rings. The first four of these donate lone pairs, and the last two donate π electrons. Benzene rings can donate from all three of their π bonds at once, making them "L_3" ligands.
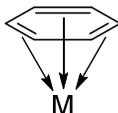
2. **X-type ligands** become anions when they dissociate from the metal. If a bond to an X-type ligand breaks, the ligand takes a negative charge and so the metal must take a positive charge. Examples are Br^-, I^-, H^-, and R^-.
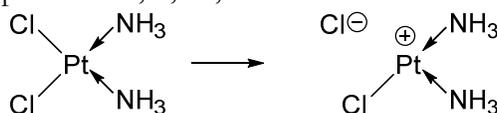
Some ligands can act as multiple L-type ligands at once (4 or 6 electron donors like benzene), or like L-type and X-type at the same time. Cyclopentadienyl, shown below, is an L_2X ligand.

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Cyclopentadienyl (cp)
(aromatic ring)

2L + 1X ligand
6 electrons donated

We can also look at multiple ways to count electrons around the transition metal, similar to methods that we've seen in the past for non-d-block atoms (see Ch. 1 notes).

1. **Oxidation state:** This is almost the same as formal charges from before. Bonds to X-type ligands are treating the same as covalent bonds: one electron is assigned to the metal and one to the X-type ligand. Bonds to L-type ligands count as having both electrons belong to the L-type ligand. Since we know that each X-type ligand puts an additional positive charge on the metal:

   Oxidation state of metal atom = # of X-type ligands + charge on metal

   The oxidation state of the metal is usually given in parentheses after it – for example, iron with an oxidation state of zero is Fe(0).

2. **Unshared electrons:** This is given by d^n **notation**. For example, a metal with five lone pairs (ten unshared electrons) would be a d^{10} atom. This is calculated from the default number of valence electrons in the neutral metal (from the periodic table) and the oxidation state.

   n = # of lone pair electrons = valence electrons in neutral metal – oxidation state

3. **Electron count:** this is equivalent to counting an octet for non-d-block atoms, but since we're using s+p+d orbitals, we can actually fit up to 18 valence electrons around a transition metal instead of just 8. This is called the **18-electron rule**. Most transition-metal complexes are most stable with a total count of 18 electrons around the metal, but plenty of electron-deficient complexes exist, often with 16 electrons. For the total electron count, you add up the number of unshared electrons (the d^n number), plus two electrons for every ligand, regardless of its type. We can combine this with the two equations above to get:

Electron count = # of valence electrons in neutral metal – charge on metal + # of X-type ligands + 2•(# of L-type ligands)

Now we can use this to look at some examples:
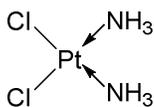
# of valence e⁻ for Pt = 10
Charge on Pt = 0
# of L-type ligands = 2
# of X-type ligands = 2

Oxidation state = 2+0 = +2
Unshared electrons = 10-2 = 8 or d^8
Electron count = 10-0+2+2(2) = 16
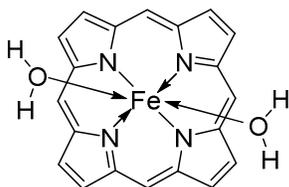
# of valence e⁻ for Fe = 8
Charge on Fe = 0
# of L-type ligands = 4
# of X-type ligands = 2

Oxidation state = 2+0 = +2
Unshared electrons = 8-2 = 6 or d^6
Electron count = 8-0+2+2(4) = 18

Reaction Steps on Transition Metals
The types of reaction step that can happen on transition metals are surprisingly limited. They fall into only a few categories:

1. Ligand Dissociation/Association/Substitution: These processes are all very similar to each other. A ligand detaches from the metal, subtracting two from the electron count

(this is dissociation). Or the reverse process: a new ligand can attach, adding two to the electron count (this is association). Or one ligand dissociates and a different one associates (this is ligand substitution) - this can be a one-step or two-step process. Usually X-type ligands only exchange for X-type, and L-type ligands exchange for L-type.

18 electrons   16 electrons   18 electrons

Overall:
Ligand substitution
(L-type replaced by
L-type)
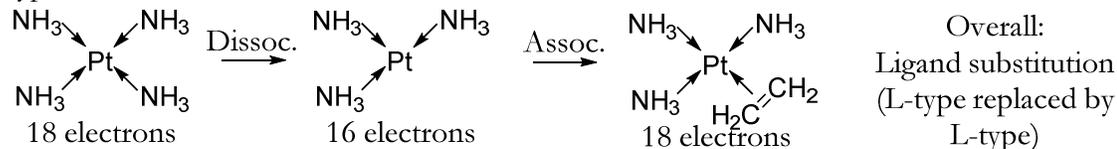
2. Oxidative Addition/Reductive Elimination: These processes are the reverse of each other. The metal inserts itself into the middle of a bond between two other atoms, adding two X-type ligands and increasing its oxidation number by 2 (this is oxidative addition). Or it does this in reverse, kicking out two X-type ligands that end up bonded to each other and decreasing its oxidation number by 2 (this is reductive elimination).

14 electrons; Pt is +0   16 electrons; Pt is +2
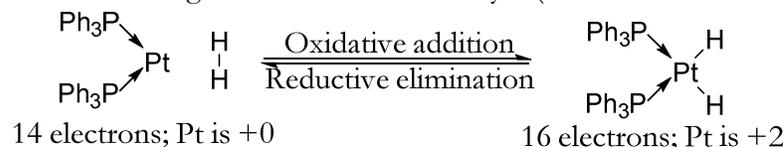
We've already seen this for Grignard formation: the magnesium inserts into a C-Br bond.
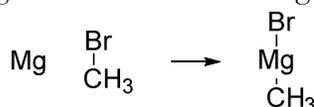
Both of these processes occur with retention of stereochemistry – if either ligand is chiral or cis/trans, it will retain the same stereochemistry after addition/elimination.

3. Ligand Insertion/β-elimination: These processes are also the reverse of each other. An L-type ligand inserts itself into the bond between the metal and an X-type ligand, forming a new X-type ligand (this is ligand insertion). Or an X-type ligand can split into a new L-type and a new X-type.

16 electrons; Pt is +2   14 electrons; Pt is +2
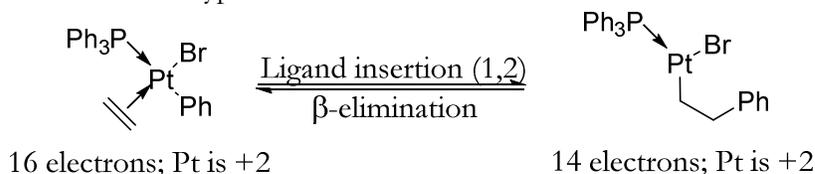
This is extremely useful for synthesis, since it can create new carbon-carbon bonds. Most useful insertions are 1,2-insertion, similar to 1,2-addition to dienes. The metal and the other ligand are added to adjacent atoms, as shown above. It can also be 1,1-insertion, where they are added to the same atom – this is very common when CO is a ligand.

Palladium-Catalyzed Couplings

Palladium-catalyzed coupling reactions are a cornerstone of modern organic synthesis. These powerful, versatile reactions allow the formation of carbon-carbon bonds to aromatic or vinylic systems; in fact, this is one of the few methods available to create these types of bonds. The 2010 Nobel Prize in chemistry was awarded for these reactions. We'll cover two reactions from this category: Heck and Suzuki reactions.

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The Heck Reaction

The Heck reaction creates a bond between an aryl or vinyl halide, and an alkene. (A similar reaction, the Sonogashira reaction, uses an alkyne instead of an alkene.)

$X = I, Br, Cl, or OTf$
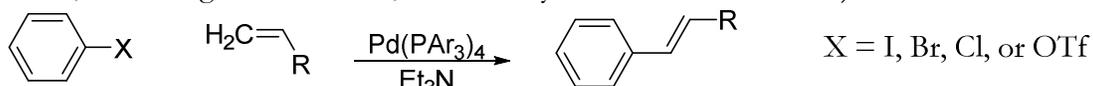
The catalyst normally used for the Heck reaction is a Pd(0) catalyst with four triarylphosphine (Ar₃P) ligands. (The aryl group can vary.) Since this puts it at an electron count of 18, it must lose some ligands before it has room to add any of the actual reagents. The reaction starts with two of the ligands dissociating to make the active species, still Pd(0).
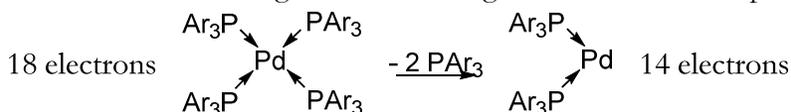
The active palladium species then enters into a catalytic cycle. This is usually shown as a closed loop, emphasizing the fact that the catalyst is regenerated at the end of each cycle (you should start reading the cycle from the part that says "Start here"). The remaining Ar₃P ligands are shown as "L". The driving force for this reaction is the fact that HBr is created, which can go on to react irreversibly with Et₃N, preventing the backwards reaction.
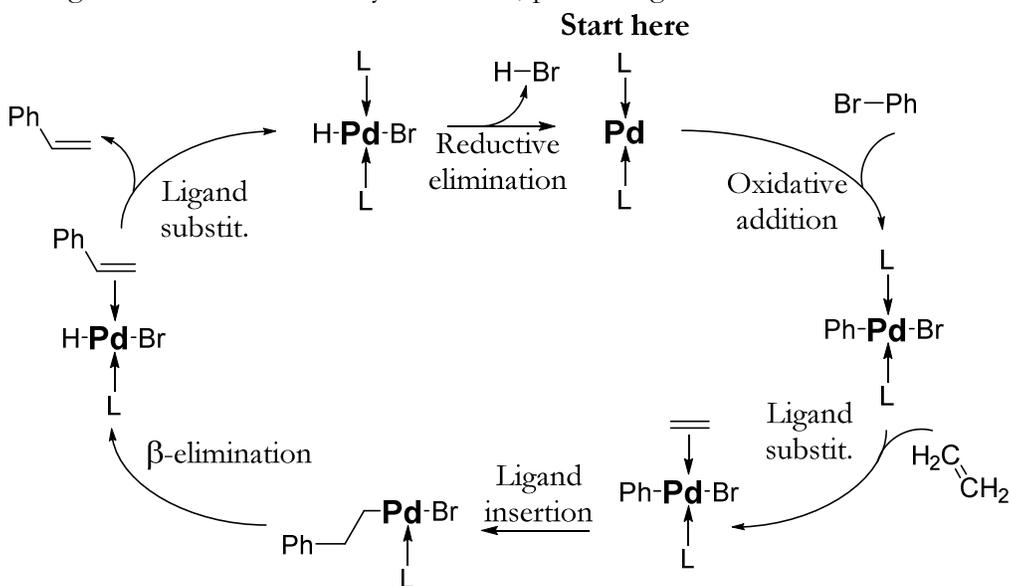
One downside of this reaction is its lack of control over regiochemistry: if the alkene is not symmetrical, the new bond can be formed to either end of the alkene.
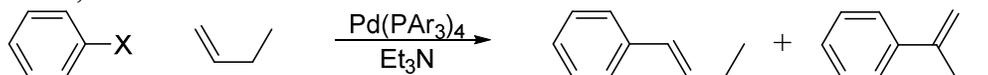
Another thing worth pointing out about this reaction: if the alkene is part of a ring, the new alkene does not form in the same location as the old alkene during β-elimination. Instead, it forms one carbon further away. This is because of the geometry of the elimination – in a ring, there is no proton at the correct location that is pointing towards the metal, so a different proton is removed instead.
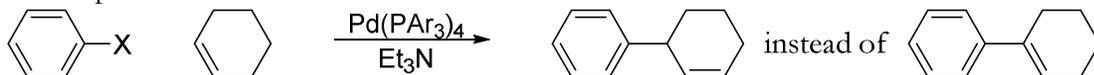
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The Suzuki Reaction
The Suzuki reaction creates a bond between an aryl or vinyl halide, and an arylboronic acid.
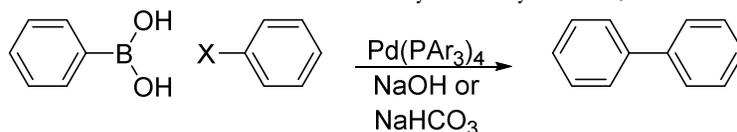
(Two other similar reactions are Stille and Negishi couplings, which use $-SnR_3$ or $-ZnBr$ instead of $-B(OH)_2$.)
The catalyst and the first steps for this reaction are the same as for Heck: two ligands must dissociate to give a 14-electron Pd(0) species. From there, the catalyst enters into a loop again. Most of these steps are fundamental transition-metal steps, but there is a new step: the $B(OH)_2$ forms a bond to the OH, forming a new ligand which can then perform a ligand substitution on itself (an intramolecular ligand substitution) and kick out $B(OH)_3$.
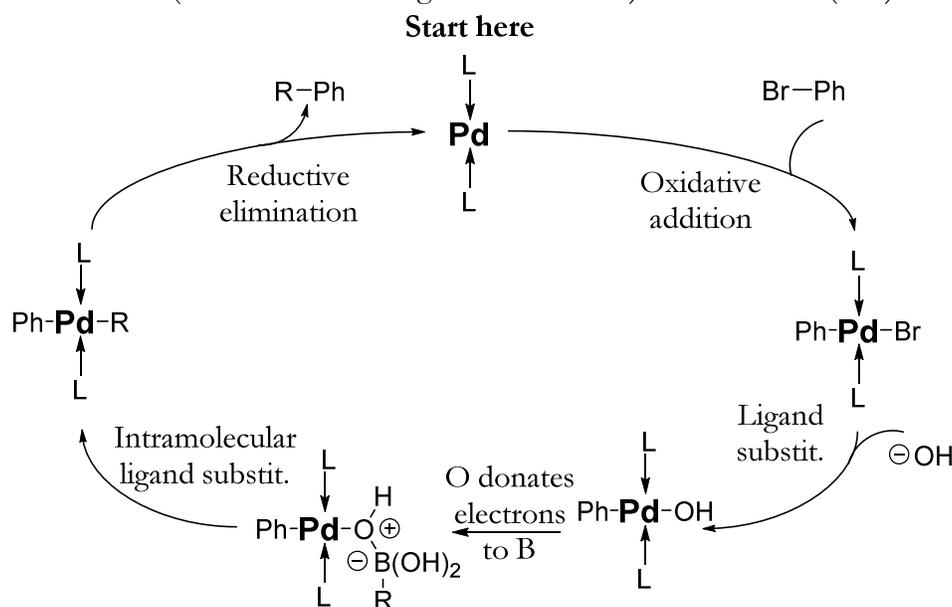
Alkene Metathesis
Alkene metathesis is an extremely useful tool for the synthesis of any molecule with an alkene. In this reaction, two alkenes are cut in half across the double bond. The four carbons that used to be part of these alkenes form new alkenes with each other, rearranging which groups are double-bonded to which.

Although there are only two products shown here, multiple different outcomes are possible. For instance, you could create a molecule with A + D groups, or B + C, or A + A, or B + B, or so on. The best way to minimize the number of products is to have at least some of the groups be identical, or to have one side product that can easily be removed (maybe if A & C are both Hs, then one product is just ethylene, which can be removed from the reaction as a gas). There is also the issue of cis alkenes vs. trans alkenes. Generally, the trans alkene will be favored due to steric issues, but there are some cases where this is not true.
There are several catalysts capable of performing this reaction, but the most widely-used are those designed by Robert Grubbs. Several generations of the Grubbs catalyst have been

created, but all follow the pattern of a ruthenium atom with a double bond to carbon. There are several other groups attached to the ruthenium which can alter the catalyst's stability and reactivity. For example, the second-generation Grubbs catalyst, G2, is shown below.

Grubbs Catalyst,
2nd Generation
(G2)
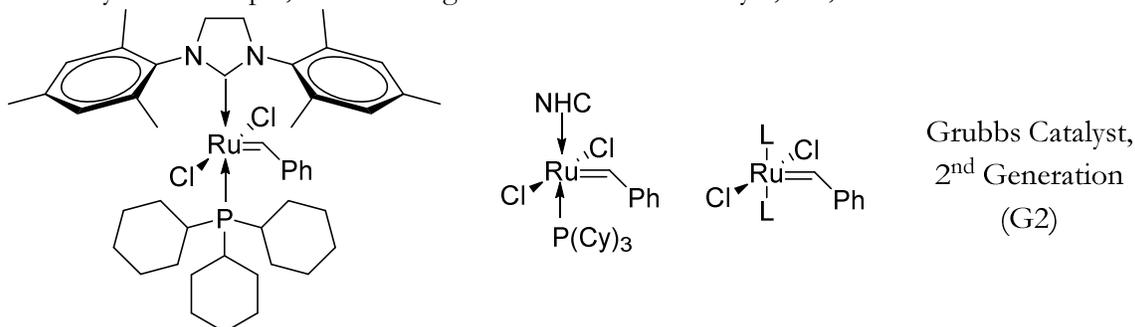
In addition to the two chloride ligands, which are X-type, and tricyclohexylphosphine or P(Cy)$_3$, which is L-type, the ruthenium atom also has an L-type ligand labeled as NHC. This stands for Nitrogen Heterocycle-Stabilized Carbene. Overall the ruthenium atom has 16 e$^-$. The mechanism for this reaction begins with dissociation of the P(Cy)$_3$ ligand, which drops the ruthenium atom down to 14 electrons. This allows the alkene reagent to associate with it.
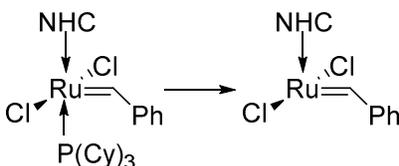
From this point on, the catalyst enters a catalytic cycle that involves the successive formation (cycloaddition) and breakup (cycloreversion) of four-membered rings containing the ruthenium. Each cycloaddition step is actually two fundamental steps occurring at the metal: association of a new alkene molecule, followed by ligand insertion. Each cycloreversion step is also two fundamental steps occurring at the metal: β-elimination of the new bond to the ring, followed by ligand dissociation. Every ring-opening step produces a molecule of alkene. Again, any possible combination of R-groups is possible, even though only two possible products are shown here. Also note that the first time it goes through the catalytic cycle, the ruthenium will have a double bond to a carbon with a Ph group, instead of a B group.
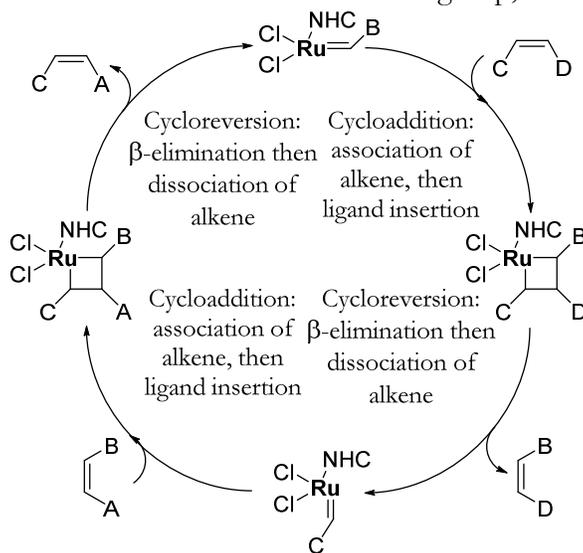
Ch. 18 Synthesis Practice
Here's a synthesis problem that puts a lot of this into practice.
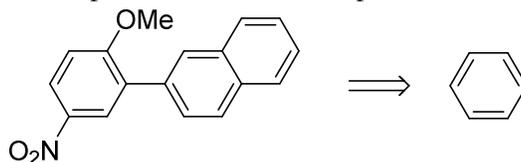
Since we're making a bond between two aromatic rings, the immediate suspect is Suzuki. Let's try this as the immediate precursor to the product and see where we can go from there. We have to put the Br on one side of the disconnect and the $B(OH)_2$ on the other. Since we know how to add a Br to a ring, let's put that on the ring that's in the starting material.
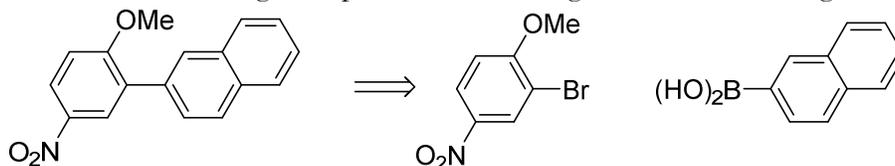
Now we have several groups on this ring, one of which (the OMe) can only be attached by S_NAr. Let's try that as the next precursor. Note that this step only works well at the Br that's para to the nitro group. Also note that we could use Cl in place of either/both Brs – there's not that much difference in reactivity between them for S_NAr. Sadly, we can't use F since we don't know how to get it on the ring.
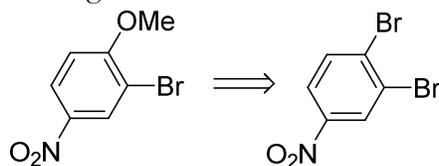
This is looking like just an EAS problem from here, so probably best to add the NO_2 group as the last of the three since it's deactivating. Adding 2 Brs to the ring is a little difficult, since the first Br added will be slightly deactivating, but we can still force it with long reaction times and higher temperature. (We'll also get the para-dibromo product, but that can be discarded.)

Putting it all together: