4.9: Oxidative Addition of Polar Reagents

Organometallic chemistry has vastly expanded the practicing organic chemist's notion of what makes a good nucleophile or electrophile. Pre-cross-coupling, for example, using unactivated aryl halides as electrophiles was largely a pipe dream (or possible only under certain specific circumstances). Enter the oxidative addition of polarized bonds: all of a sudden, compounds like bromobenzene started looking a *lot* more attractive as starting materials. **Cross-coupling reactions** involving sp^2– and sp-hybridized C–X bonds beautifully complement the "classical" substitution reactions at sp^3 electrophilic carbons. Oxidative addition of the C–X bond is the step that kicks off the magic of these methods. In this post, we'll explore the mechanisms and favorability trends of oxidative additions of polar reagents. The landscape of mechanistic possibilities for polarized bonds is much more rich than in the non-polar case—concerted, ionic, and radical mechanisms have all been observed.

Concerted Mechanisms

Oxidative additions of aryl and alkenyl C_{sp^2}–X bonds, where X is a halogen or sulfonate, proceed through **concerted** mechanisms analogous to oxidative additions of dihydrogen. Reactions of N–H and O–H bonds in amines, alcohols, and water also appear to be concerted. A π complex involving η^2-coordination is an intermediate in the mechanism of insertion into aryl halides at least, and probably vinyl halides too. As two open coordination sites are necessary for concerted oxidative addition, loss of a ligand from a saturated metal complex commonly precedes the actual oxidative addition event.
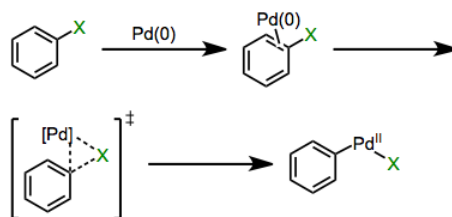

Figure *[Math Processing Error]*: Concerted oxidative addition of aryl halides and sulfonates. (Copyright; author via source)

Trends in the reactivity of alkyl and aryl (pseudo)halides toward oxidative addition are some of the most famous in organometallic chemistry. Aryl iodides are most reactive, followed by bromides, tosylates, and chlorides. To counter the lower electrophilicity of aryl chlorides, electron-rich alkyl phosphine ligands may be used to accelerate reactions of aryl chlorides. These "hot" ligands increase electron density at the metal center, facilitating oxidative addition. Because they tend to be bulkier than aryl phosphines, though, complexes of alkyl phosphines sometimes operate through slightly different mechanisms than aryl phosphine complexes. Although the exact species undergoing oxidative addition may differ (see below), all of the actual oxidative addition events are thought to be concerted.
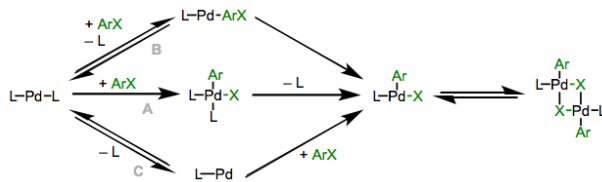

Figure *[Math Processing Error]*: Mechanisms of oxidative addition to palladium(0) phosphine complexes. Much depends on the nature of L. (Copyright; author via source)

Here, as we've seen before, electron-rich organohalides react more slowly than electron-poor compounds. Oxidative addition depletes electron density from the metal center and increases electron density in the organic ligands, so this trend makes sense!

S$_N$2 and Ionic Mechanisms

Very electrophilic halides often react through ionic mechanisms in which oxidative addition *per se* takes place over multiple steps. As strange as it may be to imagine a metal center as a nucleophile, this exact reactivity is central to the S$_N$2 and ionic mechanisms of oxidative addition. In a slow step, the metal center attacks the electrophilic atom, displacing halide. Rapid recombination of the positively charged metal complex and negative halide ion yields the product of oxidative addition. In essence, this mechanism involves oxidative ligation followed by association of oppositely charged ions. Loss of a dative ligand is sometimes necessary as an intermediate step, if the metal complex is saturated after the S$_N$2 step.
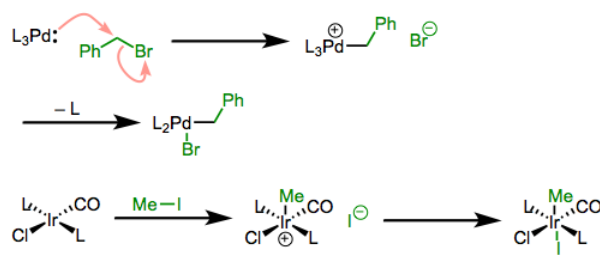
Figure *[Math Processing Error]*: SN2 mechanisms of oxidative addition: oxidative ligation followed by ligand substitution or simple coordination. (Copyright; author via source)

An extremely solid analogy can be drawn between these reactions and classical S_N2 reactions from "sophomore organic" chemistry. Primary halides react most quickly, followed by secondary and tertiary halides. Inversion at carbon is observable in these reactions, and entropy of activation is negative (suggesting an associated transition state). Negatively charged metal complexes kick butt in these reactions, and as electron-withdrawing ligands are added to the metal center, reactivity decreases. Added halide anions can actually accelerate S_N2 oxidative additions—the anion coordinates to the metal center, making it negative and increasing its electron-donating power.

A nice analogy can also be drawn between S_N2-type oxidative additions and oxidative additions of strong acids, which occur basically through the same mechanism (with replacement of hydrogen for carbon). During these so-called "ionic mechanisms," protonation of the metal center usually occurs first, followed by ligand substitution or simple coordination of the conjugate base. In rarer circumstances and for less nucleophilic metal complexes, coordination of the conjugate base can actually occur first, followed by protonation!

Radical Mechanisms

Radicals are sometimes thought of as the bucking broncos of the chemistry world, and as such, radical mechanisms for oxidative additions are more difficult to control and less appealing. For example, one must be careful to use solvents that don't react with the intermediate radicals. Still, a considerable amount of effort has been directed at "taming the wild beast." In some ways, radical reactions offer complementary selectivity to ionic and concerted mechanisms.

Non-chain radical mechanisms involve single-electron transfer from the metal complex to the organohalide, followed by recomination of the resulting radicals. The metallic and organic radicals, when stable, can even be isolated from the reaction as products.

$PtL_2 + RX \rightarrow PtL_2X^{\cdot} + R^{\cdot} +$

$PtL_2X^{\cdot} + R^{\cdot} \rightarrow PtL_2XR$
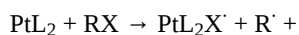
Reactivity trends here depend on the stability of the intermediate radical species. Tertiary halides react most rapidly, followed by secondary and primary halides. More electron-rich metal centers react more rapidly (are you sick of this trend yet?), since they can more easily donate an electron to the organohalide.

Chain radical mechanisms involve reactions between radical intermediates and even-electron starting materials, resulting in the continuous regeneration of radicals as products form. I like to imagine the radical intermediates as Tom Hanks in *Cast Away*, floating in an ocean of even-electron starting material. A nice example of this reactivity was explored by Hill and Puddephatt in the mid-1980s.
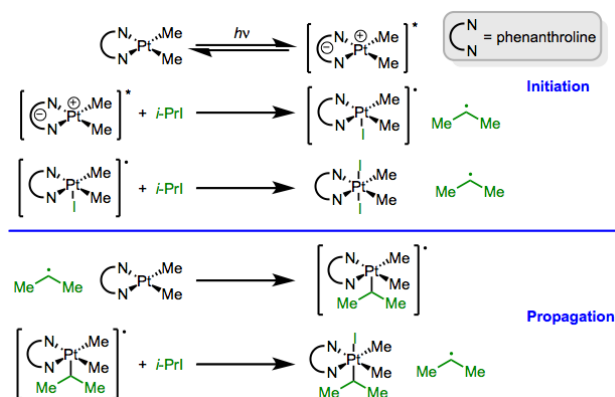
Figure *[Math Processing Error]*: Organometallic complexes can carry out radical chain mechanisms too! Here, isopropyl radical is the propagating radical. (Copyright; author via source)

Excitation of the Pt(II) complex yields a charge-transfer complex that can abstract iodine from isopropyl iodide. A second abstraction event completes the initiation phase. During propagation, isopropyl radical couples with the (unexcited) Pt(II) complex, and the resulting organometallic radical abstracts iodine from the starting organohalide. Free radical scavengers kill the reaction, but interestingly, only the isopropyl radical reacts with radical traps.

Lastly, I'll just mention briefly that **binuclear oxidative additions**, which involve two metal centers "tugging" on the organohalide in concert, often involve radicals and/or one-electron transfers. Here's one example involving chromium, and here's a somewhat more famous example involving cobalt (by Budzelaar!).

Summing up, oxidative additions of polar reagents are critical steps in many organometallic reactions. We've only just barely scratched the surface of this important class of reactions, but a few powerful trends have emerged. In general, more electron-rich OM complexes and more electron-poor polar organics react more rapidly in oxidative additions. Steric hindrance in the metal complex can also play an interesting role, either by changing the actual species that undergoes oxidative addition or by discouraging oxidative addition altogether. Next up, we'll take a brief look at the microscopic reverse of oxidative addition, **reductive elimination**. Most of the trends and mechanisms associated with reductive elimination are simply the opposite of those for oxidative addition, so our discussions of reductive elimination will be fairly short.

This page titled 4.9: Oxidative Addition of Polar Reagents is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Michael Evans.