A. Student laboratory manual chapter

Suzuki-Miyaura Coupling Reaction

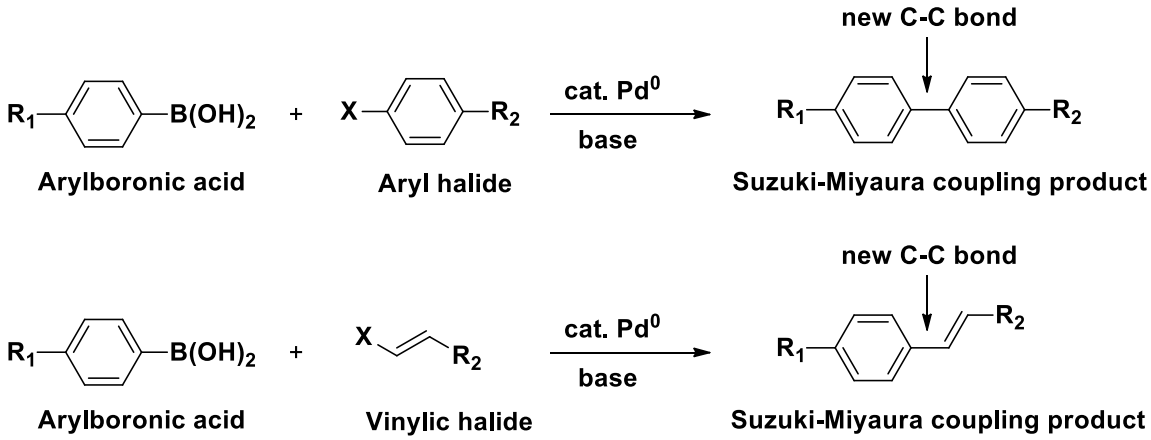
1. Introduction

The study and use of compounds featuring carbon-metal bonds (**organometallic chemistry**) is a major area of synthetic chemistry. Organometallic compounds that you may be familiar with include organomagnesium halides, (RMgBr, Grignard reagents), organolithium reagents (RLi) and lithium diorganocuprates (R_2CuLi, Gilman reagents). Recall that metal atoms are less electronegative than carbon and so the polarity of a C-M bond is reversed in comparison to typical "organic" bonds such as C-H, C-X (X= halogen), C-N etc. *i.e.* the carbon atom in an organometallic compound is nucleophilic rather than electrophilic. This reversal of typical bond polarity allows organometallic compounds to exhibit some unusual reactivity patterns. Organometallic compounds are often used to enable transformations that are difficult or impossible to accomplish with classical organic reagents.

The Grignard reagent is an example of an organometallic compound featuring an **s-block** metal. Such reagents are typically used in **stoichiometric** amounts (*i.e.* in at least a 1:1 ratio with other starting materials) and are consumed as the reaction proceeds. There are, however, a large number of organometallic compounds featuring **transition metals**. Many important industrial processes use transition-metal organometallic compounds as **catalysts**. Recall that a catalyst is an additive used in a sub-stoichiometric amount that increases the rate of a chemical reaction without itself being consumed or undergoing a net chemical change. In other words, a catalyst lowers the activation energy of a chemical process by lowering the energy (strictly, ΔG) of the transition state for conversion of reactants to products. The catalyst does not alter the energy of the reactants or products.

Examples of process that use transition-metal catalysts include catalytic hydrogenation (Ni, Pd, Pt, Rh compounds), hydroformylation (Co), alkene polymerization (Ti, Zr), alkene metathesis (Mo, Ru), and coupling reactions (Pd, Ni). The **Suzuki-Miyaura coupling reaction** is an example of the latter process (the reaction is often referred to as a Suzuki coupling).

In a typical Suzuki coupling reaction, an arylboronic acid is combined (*coupled*) with an aryl or vinylic halide under basic conditions in the presence of a Pd-based catalyst to form a **single bond between two sp^2-hybridized carbon atoms**. If the two organiccomponents are not identical, the process is termed a **cross-coupling** reaction (Scheme 1).



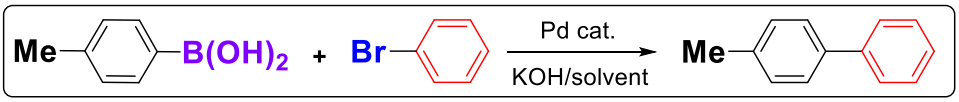
Scheme 1 Suzuki-Miyaura coupling reactions.

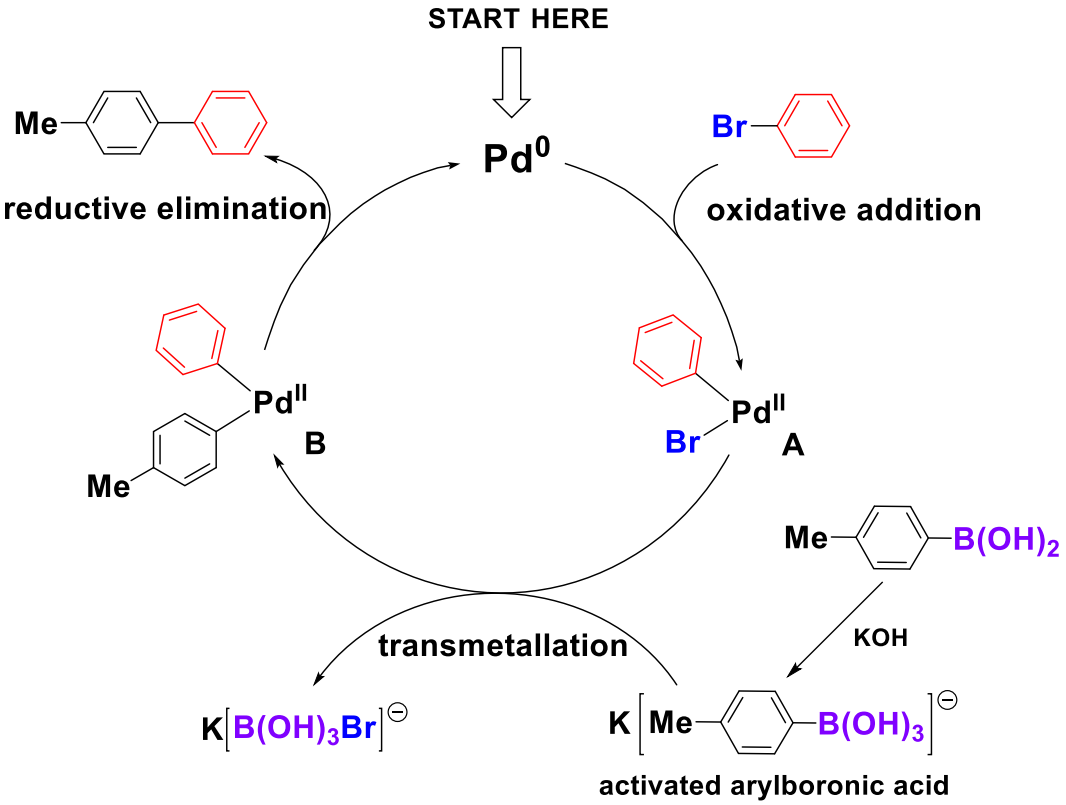
Akira Suzuki shared the 2010 Nobel Prize in Chemistry with Richard Heck and Ei-ichi Negishi for the development of Pd-catalyzed cross-coupling reactions. The Heck and Negishi reactions, along with many other "named" Pd-catalyzed coupling reactions (such as the Sonogashira, Stille, Kumada and Buchwald-Hartwig reactions) are used widely in synthetic, pharmaceutical, and industrial chemistry.

2. The catalytic cycle

It is common and logical to show the mechanism of a stoichiometric organic reaction as a linear, step-wise process. An alternate representation that is highly effective for discussing catalytic organometallic processes is a **catalytic cycle**. The cycle highlights the key steps in the process and shows how the catalytically active species is regenerated.

The important steps in a catalytic organometallic process occur primarily on the metal atom, and so it is logical to draw a catalytic cycle showing how the metal atom is involved in each step and, ultimately, how the metal catalyst is regenerated. A generalized catalytic cycle for a Pd-catalyzed Suzuki cross-coupling reaction is displayed in Scheme 2. The stoichiometric coupling partners are 4-methylphenylboronic acid and bromobenzene, and KOH is the added base.





Scheme 2 Simplified catalytic cycle for a Suzuki-Miyaura cross-coupling reaction.

The above catalytic cycle features important steps common to many Pd-catalyzed cross-coupling reactions. Before describing each step, however, we should recognize that:

- the Suzuki coupling does not proceed in the absence of a base (KOH in this case);

- the boron atom of the arylboronic acid is electrophilic and so, under basic conditions, $ArB(OH)_2$ does not exist as a neutral compound but rather as an "activated" arylboronic acid $[K][ArB(OH)_3]$.

The key steps of the catalytic cycle are:

1) Insertion of the initial Pd^0 species into the C-Br bond of the aryl bromide. This process is termed **oxidative addition** because Pd^0 is oxidized to Pd^{II} to generate species **A**. Oxidative addition is often the rate-determining step in this type of catalytic cycle. The insertion of Mg^0 into the C-X bond of an aryl halide during formation of a Grignard reagent could also be viewed as an oxidative addition, although the exact mechanisms of the two processes are quite different.

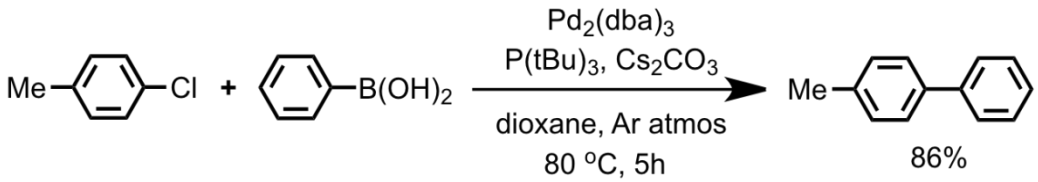
2) The Pd^{II} species **A** then reacts with the activated arylboronic acid in a step termed **transmetallation**. This process involves transfer of the aryl group from the activated arylboronic acid to the palladium atom to form the corresponding Pd^{II} species **B**. This step is crucial to the entire coupling process because it sets up the two aryl groups to be coupled in close proximity on the Pd atom. The by-product borate salt $[K][B(OH)_3Br]$ is soluble in water.

3) The final step of the catalytic cycle involves the formation of a new C-C σ-bond between the two aryl groups bonded to the Pd^{II} atom of **B**. The process of **reductive elimination** to give the coupling product can be viewed as the reverse of the oxidative addition step. In addition to generating the product, the reductive elimination step also regenerates the initial Pd^0 species, allowing the catalytic cycle to begin again.

It is worth noting that the C-Pd bonds of the species involved in the above steps are not strongly polarized (in contrast to the highly polarized C-Mg bond in a Grignard reagent or the C-Li bond in organolithium reagents) and so **the Suzuki-Miyaura coupling reaction can be performed in aqueous solution and in the presence of a wide range of organic functional groups**. In addition, the arylboronic acid starting materials are non-toxic, air- and moisture-stable, and accessible from simple starting materials (for example, by the reaction of an alkyl borate $B(OR)_3$ with a Grignard reagent). Both of these features (among others) make the Suzuki-Miyaura coupling a common reaction.

If you are doing the corresponding wet lab exercise, a substituted aryl halide ArX (X = halide) will undergo a Suzuki coupling reaction with *p*-tolylboronic acid (4-methylphenylboronic acid) in the presence of aq. KOH solution to produce the corresponding biaryl compound. The Pd-catalyst is in the form of an aqueous 1000 mg/L (1000 ppm) standard solution.

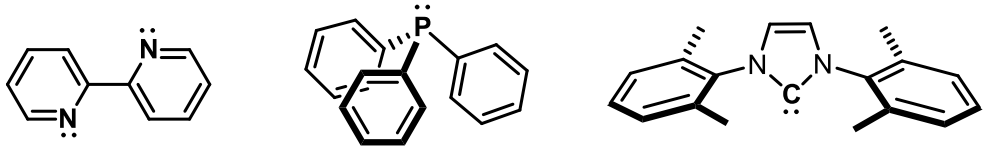
There are many different procedures for performing Suzuki-Miyaura reactions, the exact conditions being dependent upon the nature of the coupling partners. For example, it would be desirable to be able to perform coupling reactions using aryl chlorides because they are typically cheaper and less toxic than the corresponding bromides and iodides. Unfortunately, aryl chlorides are much less reactive in Suzuki-type reactions than the corresponding bromides and iodides. One way of addressing this problem is shown in Scheme 3.



Fu *et al*, *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

Scheme 3 Suzuki-Miyaura cross-coupling reaction using 1-chloro-4-methylbenzene.

The above coupling reaction proceeds in high yield using 4-chlorotoluene as a substrate. Note, however, that the reaction also requires heating (80 °C) for an extended time (5 h) with a relatively expensive and heavy base (Cs_2CO_3) in a toxic solvent (dioxane) under an atmosphere of dry argon gas. The process also requires an added **ligand**, in this case tri(*tert*-butyl)phosphine, P(*t*Bu)$_3$. A ligand is a molecule that uses one or more Lewis-basic donor atoms such as O, N, P, or, in some cases, C to bond to a metal center (a Lewis acid) (Scheme 4). Ligands allow the metal complex to be soluble in organic solvents, and enable the active site of a catalytically active species to be tuned both sterically (size and shape of groups on the ligand) and electronically (how strongly the ligand binds to the metal atom). The design and synthesis of ligands is an important sub-area of organometallic chemistry.



Bipyridine **Triphenyl phosphine** **N-Heterocyclic carbene**

Scheme 4 A selection of common ligands.

The reaction shown in Scheme 3 represents interesting and important chemistry, but we need to be aware of the wider environmental picture when selecting a route for the synthesis of a molecule. One could argue that the advantage of using an aryl chloride as the substrate is outweighed by the requirement for reflux conditions in a toxic solvent using an air-sensitive ligand. In contrast, the reaction that you will perform in the lab proceeds rapidly at room temperature in a benign solvent without the need for a ligand or an inert atmosphere, but requires an aryl bromide as the starting material, uses a halogenated solvent in the work-up, and requires the use of non-recyclable drying agent.