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Palladium-Catalyzed Cross Coupling

Overview

This experiment will demonstrate the concept of a palladium-catalyzed cross coupling. The set-up of a typical Pd-catalyzed cross coupling reaction will be illustrated. Pd-catalyzed cross coupling reactions have had a profound effect on how synthetic chemists create molecules. These reactions have enabled chemists to construct bonds in new and more efficient ways. Such reactions have found widespread applications in the fine chemical and pharmaceutical industries. Pd-catalyzed cross coupling reactions add another tool to the chemist's toolbox for constructing carbon-carbon bonds, which are central to organic chemistry. The combination of the importance of making carbon-carbon bonds and the impact Pd-catalyzed cross coupling have had resulted in these reactions being the subject of the 2010 Nobel Prize in Chemistry. Ei-ichi Negishi, one of the recipients of the 2010 Nobel Prize in chemistry, explained in his Nobel lecture that one of his motivations for developing this chemistry was to develop "widely applicable straightforward Lego-like methods for hooking up two different organic groups".

Principles

Pd-catalyzed cross coupling reactions consist of an electrophile (typically an organohalide), a nucleophile (typically an organometallic compound or an alkene), and a palladium catalyst. Regardless of the electrophile or nucleophile used, all Pd-catalyzed cross couplings rely on the Pd-catalyst to activate and combine both partners. Generally speaking, a Pd(0) species reacts with the organohalide via an oxidative addition to form an organopalladium species (RPdX). This organopalladium species then reacts with the nucleophilic partner to generate a new organopalladium species and ultimately construct a new carbon-carbon bond. Depending of the nucleophilic partner, the Pd-catalyzed cross coupling is given a specific name (see Table below).

Nucleophile	Reaction name
Organoboron	Suzuki
Organostannane	Stille
Organozinc	Negishi
Organomagnesium (Grignard reagent)	Kumada
Organosilane	Hiyama
Olefin/alkene	Heck
Alkyne	Sonogashira

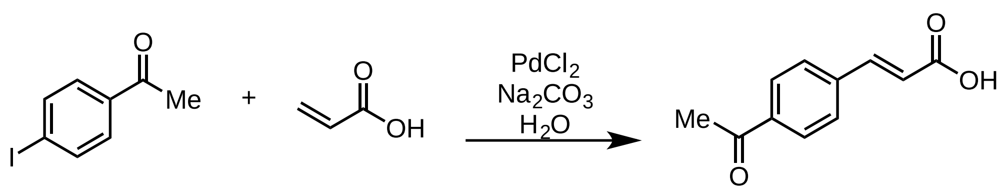
There are two general mechanisms associated with these Pd-catalyst cross couplings. One for the Heck reaction, and one for the other cross coupling reactions. Overall, the Heck reaction couples an alkene with an organohalide to generate a now more substituted olefin (Figure 1). The first step of a Heck reaction is the same as all other Pd-catalyzed cross couplings. To begin, oxidative addition occurs between the Pd(0)-catalyst and the organohalide to generate an organopalladium(II) species. Next, the olefin coordinates to this newly formed organopalladium(II) species. After olefin coordination, carbopalladation occurs to generate a new carbon-carbon and carbon-palladium bond. Next, beta-hydride elimination occurs to generate a Pd(II)-hydride species and the olefin product. Finally, reductive elimination of HX regenerates our Pd(0)-catalyst which can continue to coupling another molecule of organohalide and olefin.

(insert figure 1)

For the remaining cross coupling reactions, the mechanism is as follows (Figure 2). Oxidative addition between the organohalide and Pd(0) catalyst results in the formation of an organopalladium(II) species. This organopalladium(II) species reacts with the nucleophilic organometallic compound in a step called transmetalation to generate an organopalladium(II) species with two carbon-palladium bonds. Finally reductive elimination occurs to create a new carbon-carbon bond and regenerate the Pd(0) catalyst.

(insert figure 2)

Procedure



1. Add 4-iodoacetophenone (246 mg, 1 equivalent, 1 mmol), acrylic acid (100 µL, 1.5 equivalents, 1.5 mmol), sodium carbonate (Na_2CO_3, 318 mg, 3 equivalents, 3 mmol), $PdCl_2$ (2 mg, 0.01 equivalents, 0.01 mmol), and water (5 mL, 0.2 M) to a round bottom flask (~20 mL) equipped with a magnetic stir bar.
2. Heat the reaction to approximately 100 °C and stir until complete consumption of 4-iodoacetophenone (approx. 1 hour).
   2.1. The reaction can be monitored by TLC.
3. Cool the reaction mixture to room temperature after completion.
4. Acidify the reaction mixture with 1 M aqueous HCl to ~pH of 1.
   4.1. The pH of the reaction mixture can be checked with litmus paper.
   4.2. A solid should precipitate
5. Collect the solid *via* filtration.
6. Purify the crude material by recrystallization using a 1:1 mixture of methanol/water.

Representative Results

The product should be a solid with the follow ^{1}H NMR spectrum: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.60 (s, 3H), 6.67 (d, J =16.0 Hz, 1H), 7.65 (d, J =16.0 Hz, 1H). 7.83 (d, J =8.4 Hz, 2H). 7.97 (d, J =8.4 Hz, 2H).

Summary

This experiment has demonstrated how to set up a typical Pd-catalyzed cross coupling reaction. The basic concepts and techniques presented are applicable to other transition metal catalyzed reactions, in addition to classical Pd-catalyzed cross couplings.

Applications

These Pd-catalyzed cross coupling reactions have changed the way molecules are synthesized in academic and industrial settings. The impact of this technology can be seen in how chemists construct complex structures for pharmaceuticals, agriculture chemicals, and materials. Beyond Pd-catalyzed cross couplings, transition metal catalysis has and is continuing to change the way synthetic chemists prepare molecules that can have an impact on society through their potential therapeutic use.

Many molecules of interest for treating diseases have linkages connecting aromatic or heteroaromatic rings. Palladium cross coupling reaction, like the Suzuki reaction have found widespread use in the pharmaceutical industry for making these types of structures. For example, Crizotinib (Xalkori), an anti-cancer drug for the treatment of non-small cell lung carcinoma, is synthesized on a several kilo-scale using a Suzuki coupling.

(insert figure 3)

Palladium cross couplings have also been applied towards the synthesis Taxol (an anticancer drug), Varenicline (an anti-smoking drug), and precursors for high performance electronic resins.

(insert figure 4)

Legend

Figure 1: the Heck reaction couples an alkene with an organohalide to generate a now more substituted olefin.

Figure 2: mechanism for the remaining cross coupling reactions.

Figure 3: Crizotinib (Xalkori), an anti-cancer drug

Figure 4: Taxol (an anticancer drug), Varenicline (an anti-smoking drug), and precursors for high performance electronic resins.

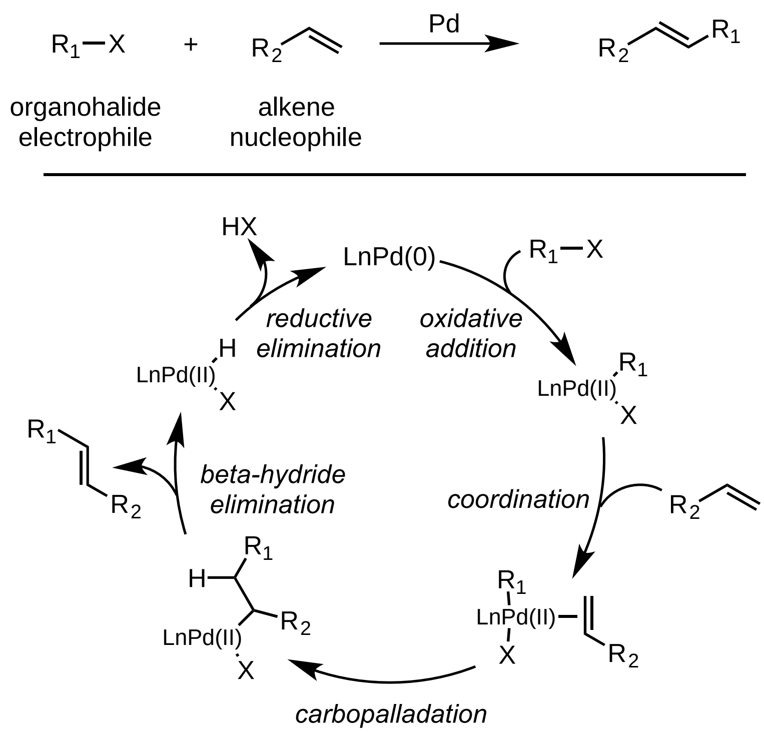


Figure 1

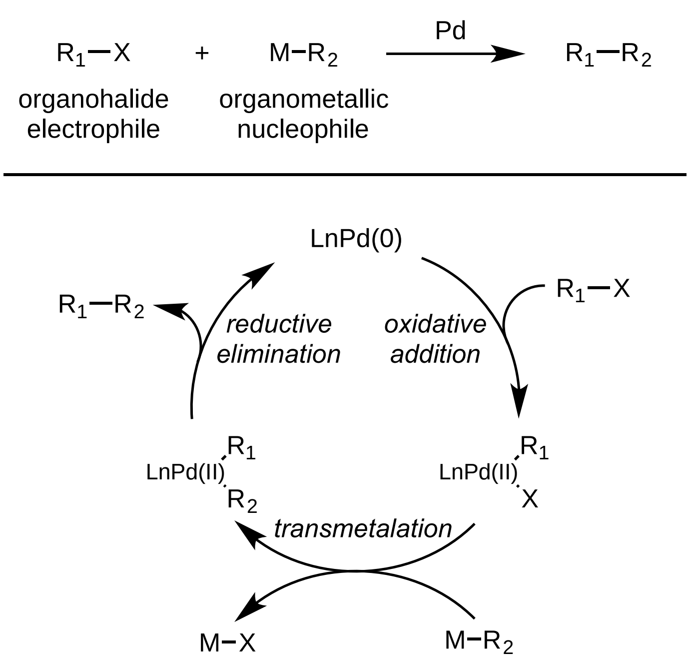


Figure 2

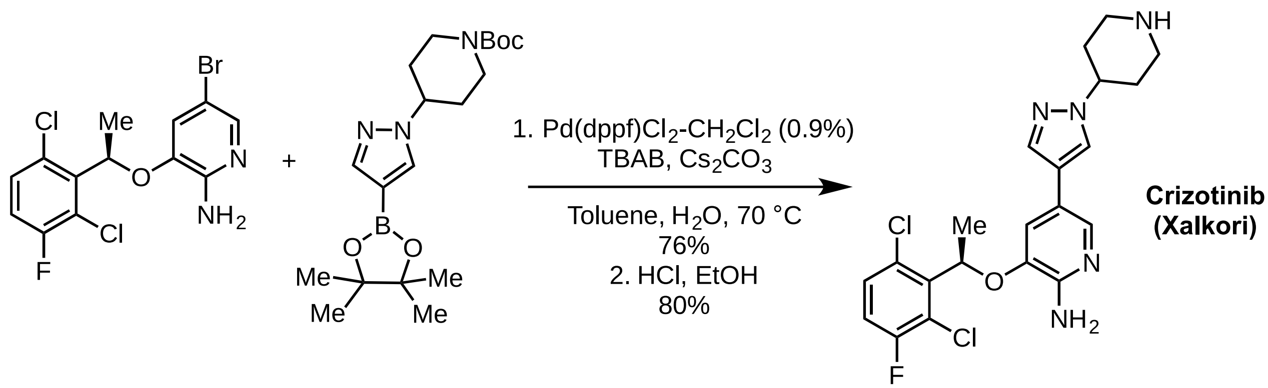


Figure 3

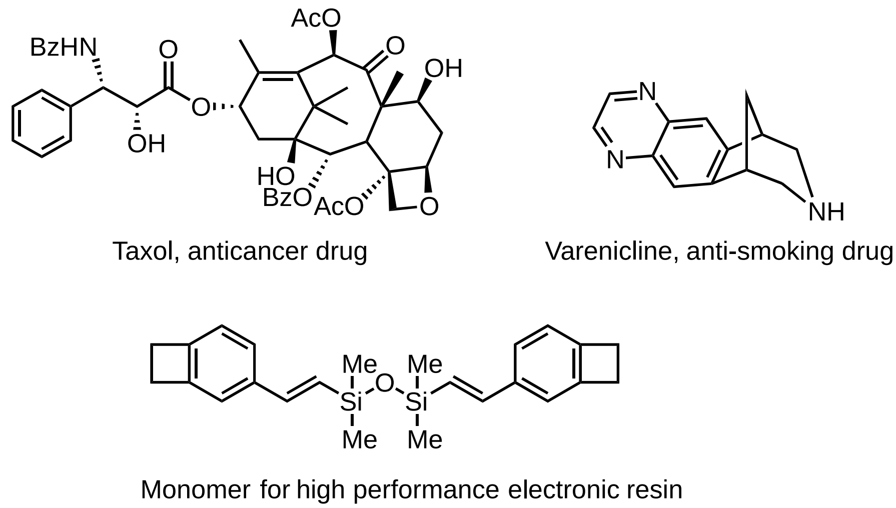


Figure 4