

Lecture 11

Inorganic chemistry

Hydroformylation (Oxo-process)
Carbonylation of methanol: Monsanto Process
Cativa Process

Homogeneous catalysis: Pd catalyzed C–C bond formation
reactions for organic synthesis

Homogeneous catalysis: Pd catalyzed C–C bond formation reactions for organic synthesis



Richard F. Heck



Ei-ichi Negishi



Akira Suzuki

**Chemistry 2010 Nobel Prize
awarded jointly to 3 chemists!**

Carbon based chemistry (Organic) is the basic foundation through which.....

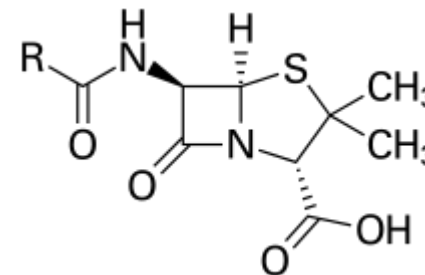
Life displaying mind-boggling phenomena

Colours in flower

Poisons in snake

Bacteria killing substances-penicillin

etc



Penicillin core structure, where
"R" is the variable group



Through the greatest art in a test tube.....Chemists creating sophisticated chemicals; ...carbon based molecules.....

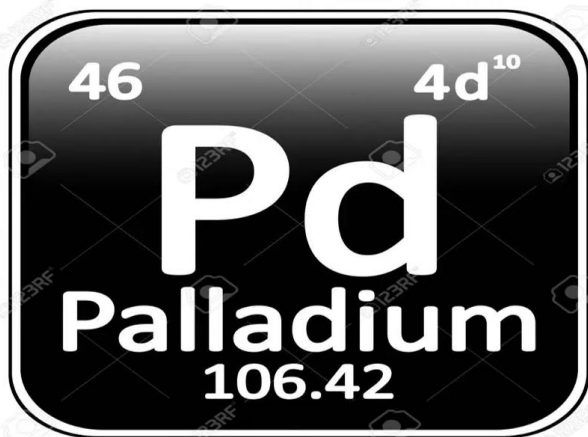
By the process, chemists mimicking in test-tube the silent complex chemistry running within nature
Resulting new medicines and revolutionary materials etc!!!

In order to achieve that.....

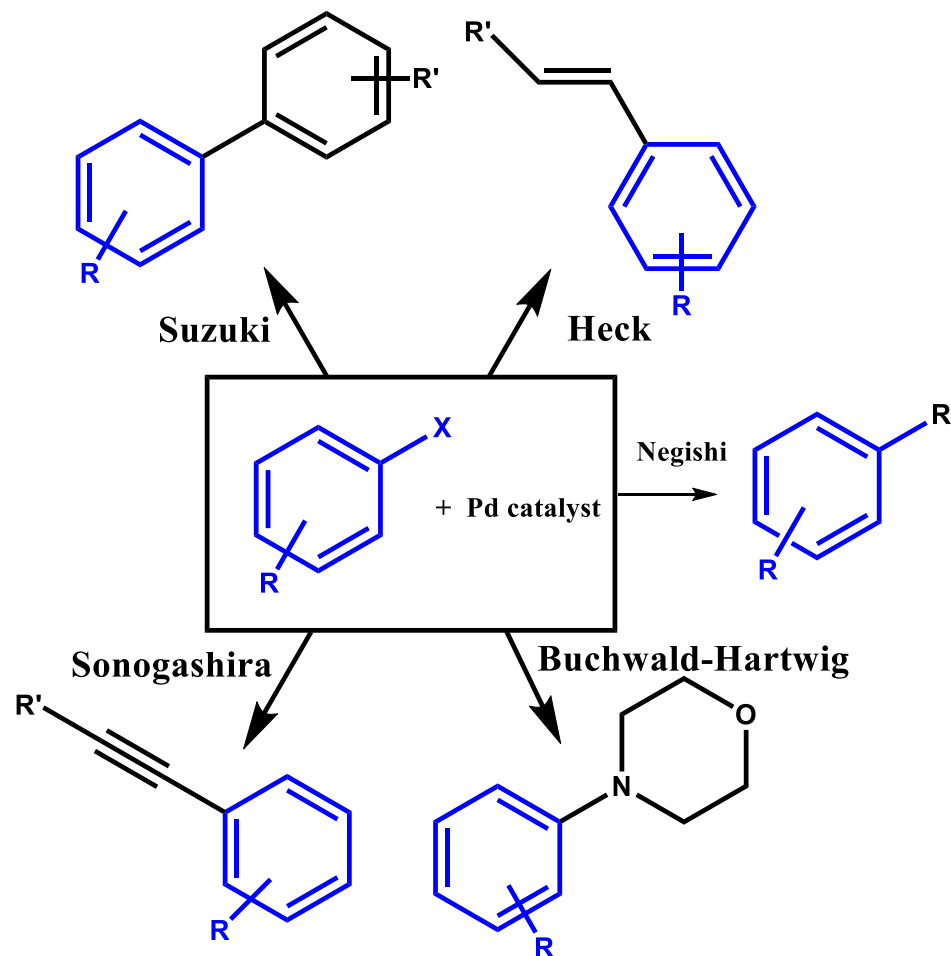
one need to join carbon atoms together for creating these complex molecules

For synthesizing complex molecules chemists ended up with too many by-products in the test-tube

**Palladium-catalyzed cross coupling
solved that problem and...**

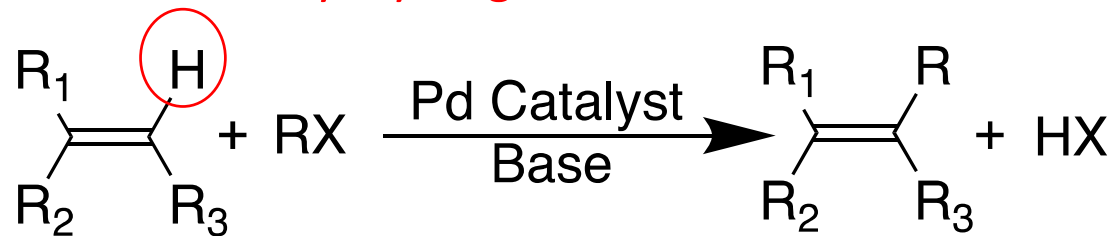


**provided chemists with a more
precise and efficient tool to handle.**



Heck Coupling

Alkene with vinyl hydrogen



R = aryl, vinyl, heterocyclic

X = I, Br, OTf, COCl, etc.

Base: 2° or 3° amine, NaOAc, KOAc, etc.

Pd Catalysts

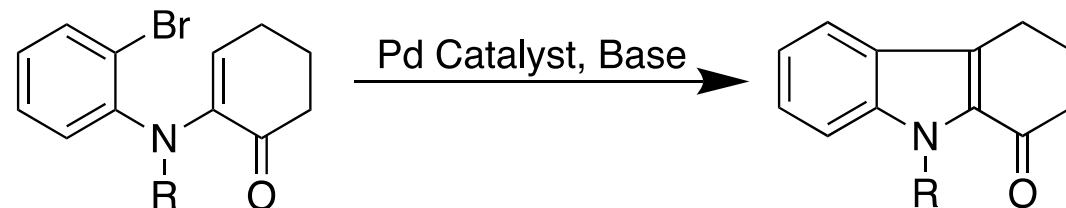
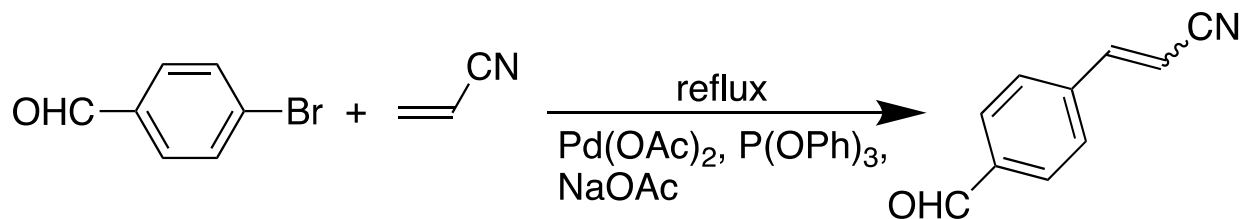
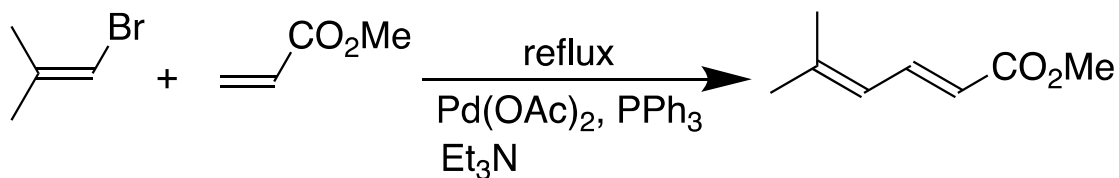
Pd(OAc)₂, Pd(PPh₃)₂Cl₂, Pd(PPh₃)₂(CH₃CN)₂

Pd(PPh₃)₄, Pd₂(dba)₃

The Heck reaction is a cross-coupling reaction of an organohalide with an alkene to make a substituted alkene using palladium as a catalyst and a base.

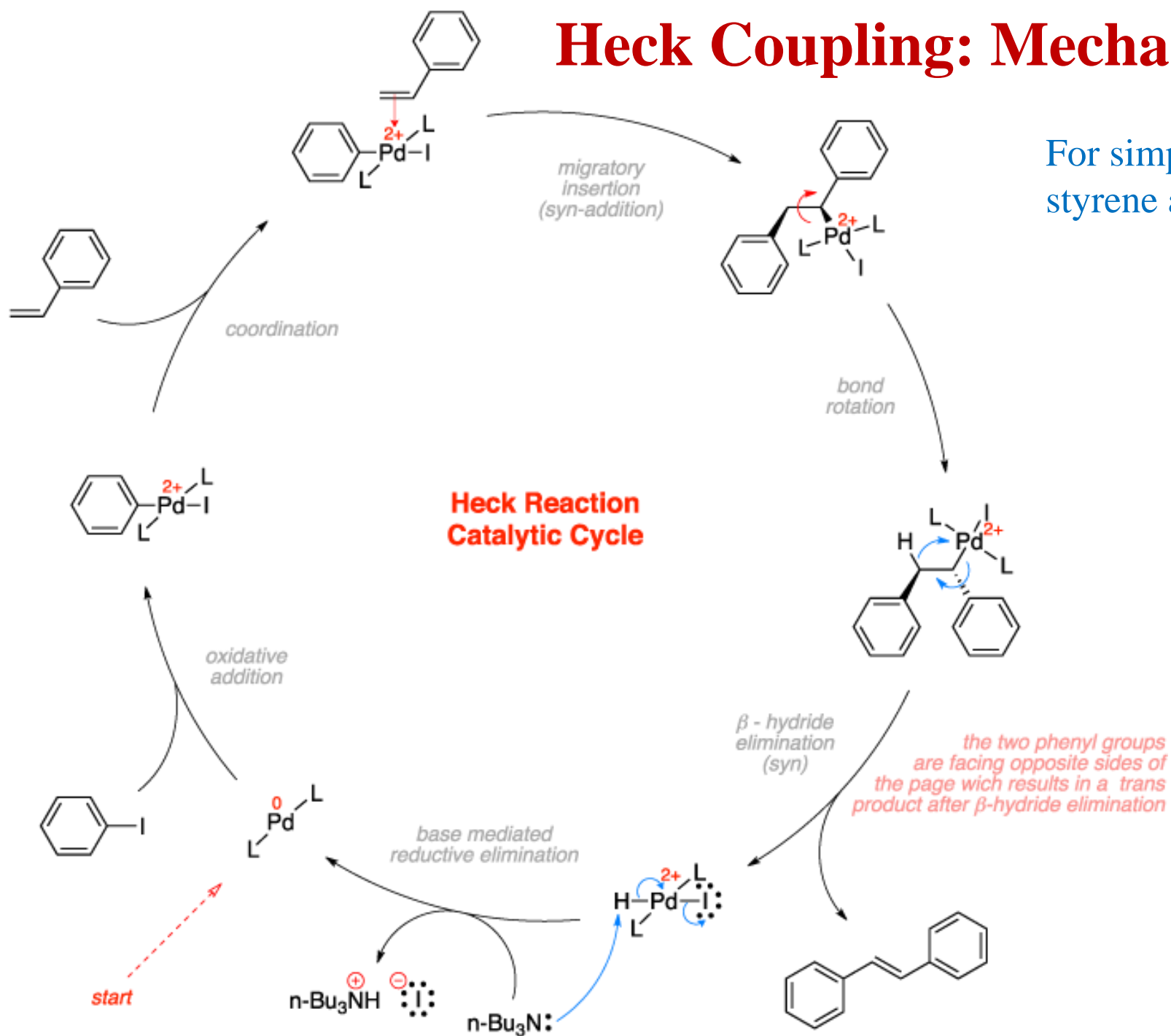
- This reaction, independently developed by *Mizoroki* (1971) and *Heck* (1972), a vinylic hydrogen atom is replaced by a vinyl, benzyl, or aryl group.

Examples: The reaction is selective for the preparation of trans olefin.



Heck Coupling: Mechanism

For simplicity, in this mechanism PhI, styrene and R_3N is used

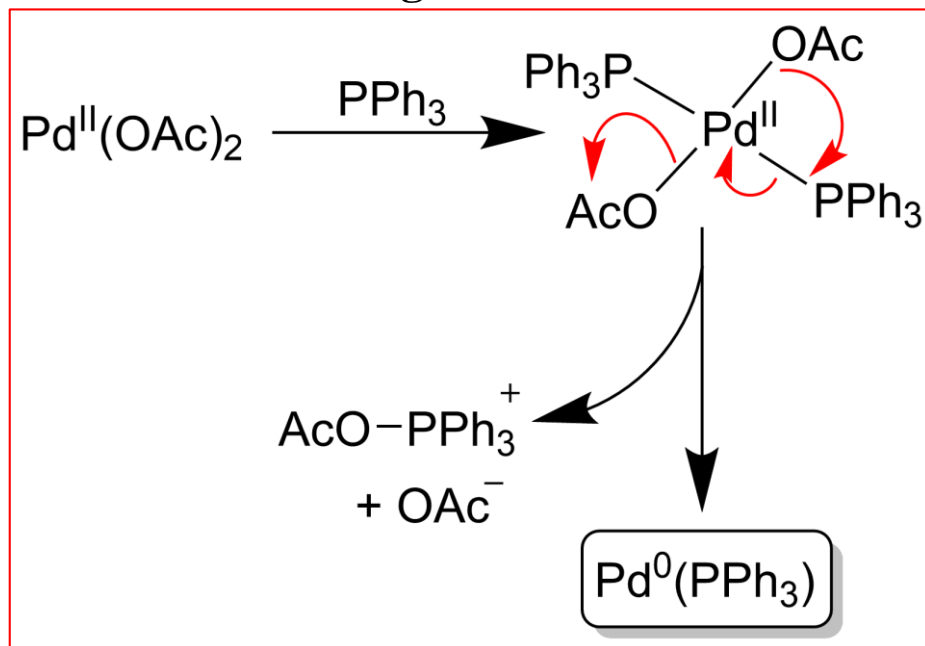


What are the fundamental requirements of a redox cycle catalyst?

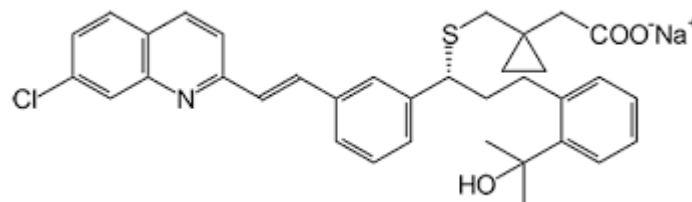
Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, 37, 2320–2322.

Heck Coupling: Mechanism

Mechanism for the generation of Pd⁰ from Pd^{II}



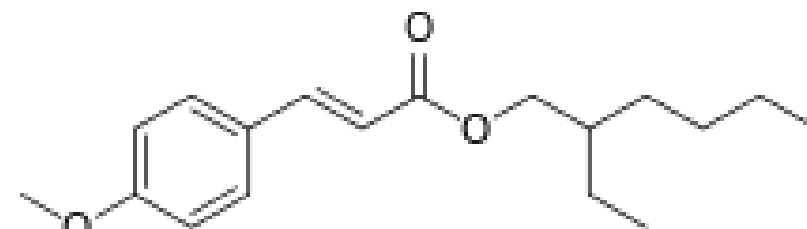
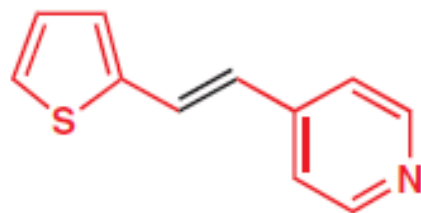
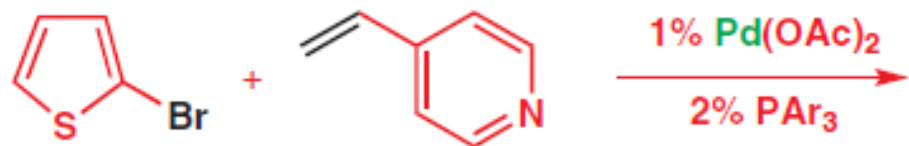
Remember Pd(0) is the active catalyst for most of the time. Pd(II) presumably gets reduced to Pd(0) by amines, phosphines, organometallic reagents such as butyl lithium also by alkenes.



Used in the maintenance treatment of asthma



Here is the Heck reaction at work coupling two heterocyclic substrates. Easy chemistry to do, but impossible without a Pd catalyst.



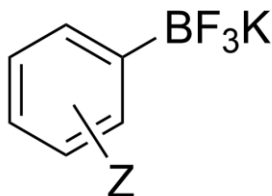
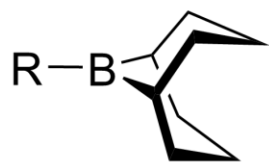
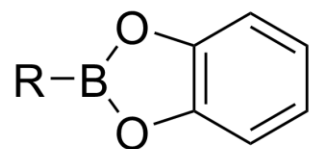
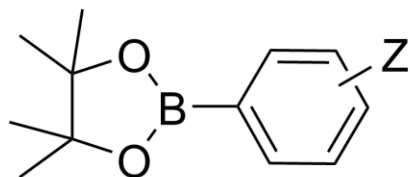
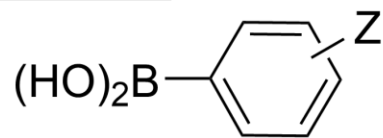
is an ingredient in some sunscreens and lip balms

Suzuki–Miyaura Coupling

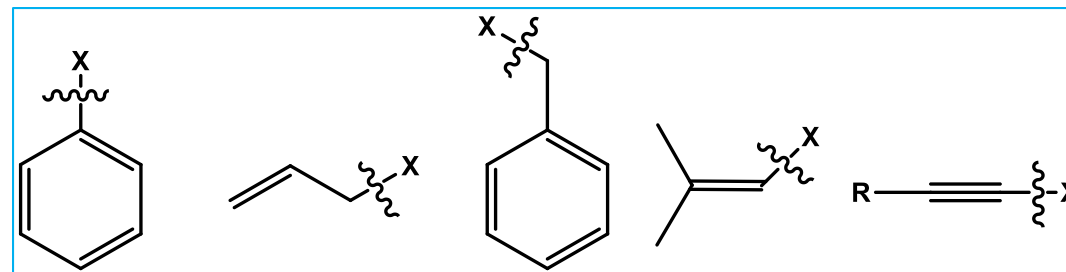
The Suzuki coupling of a boronic acid or ester with a vinyl or aryl halide or triflate is probably the most commonly used of all cross-coupling reactions.



R-BY₂



R¹ = aryl, allyl, benzyl, alkenyl, alkynyl



R = aryl, alkyl, alkenyl

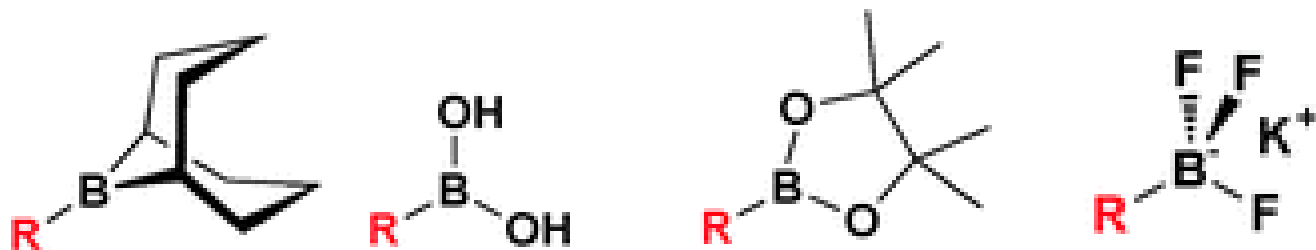
Z = aromatic substitution at *o*, *m* or *p* positions

Base = NaOH, NaOEt, Na₂CO₃, Na₃PO₄, Bu₄NF, Cs₂CO₃, etc.

Common Pd Catalysts:

- Pd⁰(PPh₃)₄
- Pd^{II}(OAc)₂ + PPh₃
- Pd⁰₂(dba)₃
- Pd^{II}(PPh₃)₂Cl₂

How easy to synthesis boron derivatives for Suzuki–Miyaura Coupling?

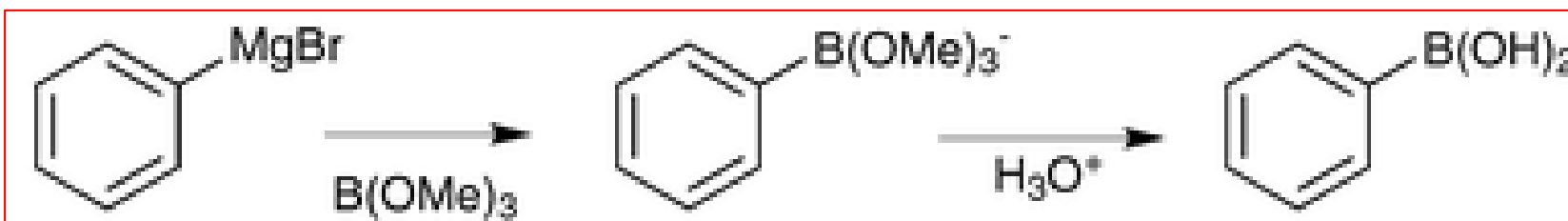
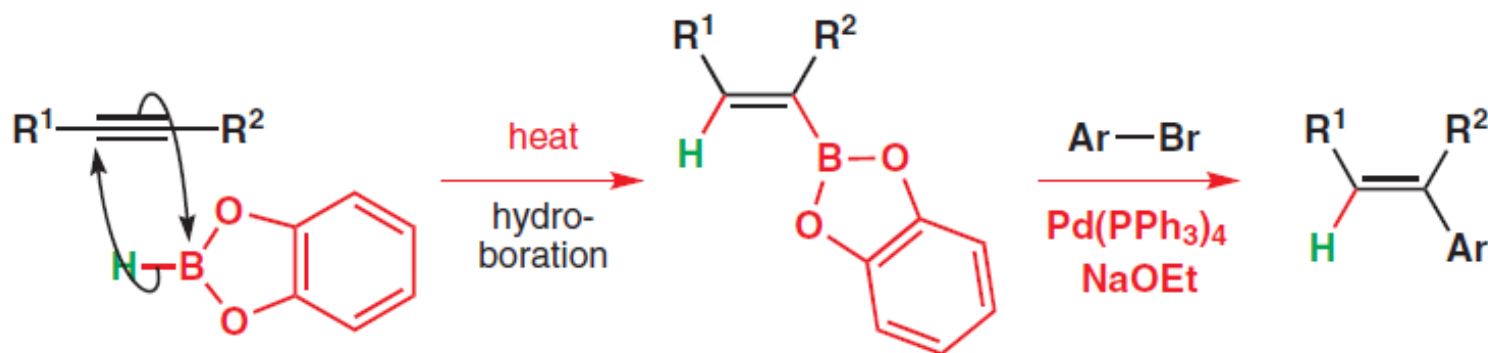


Are they commercially available?

How stable they are to store longer time?

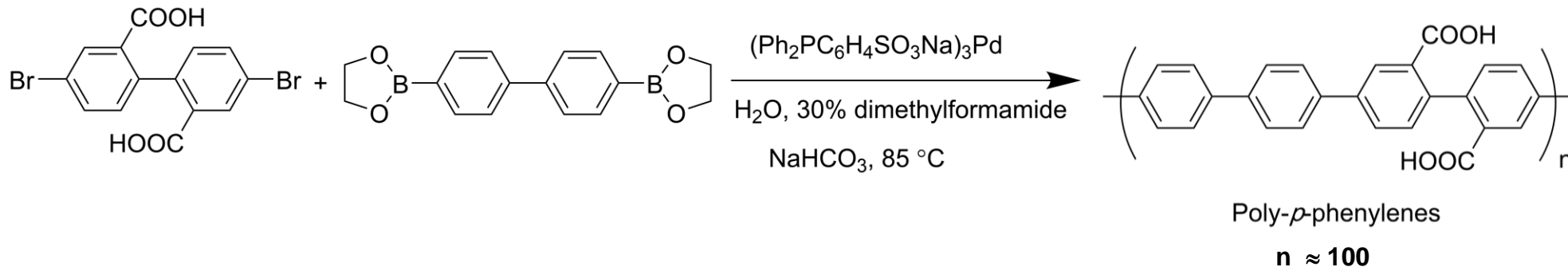
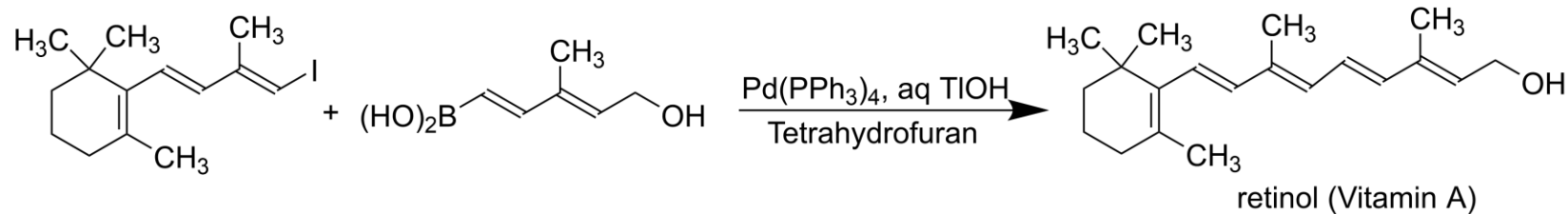
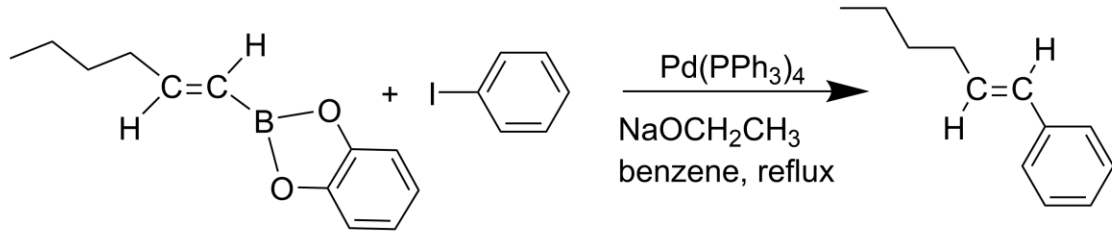
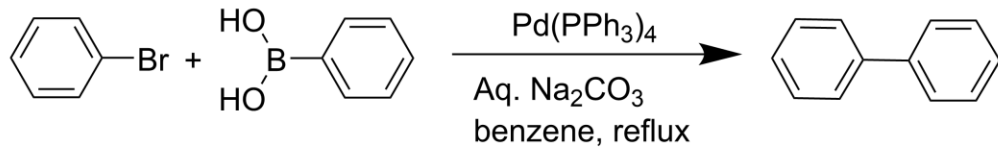
Are they non-toxic and cheap?

General synthetic routes for the synthesis of boron reagents



Suzuki–Miyaura Coupling: Examples

the geometry of both unsaturated components is preserved during the coupling so this is an excellent method for the stereo-selective synthesis of dienes.



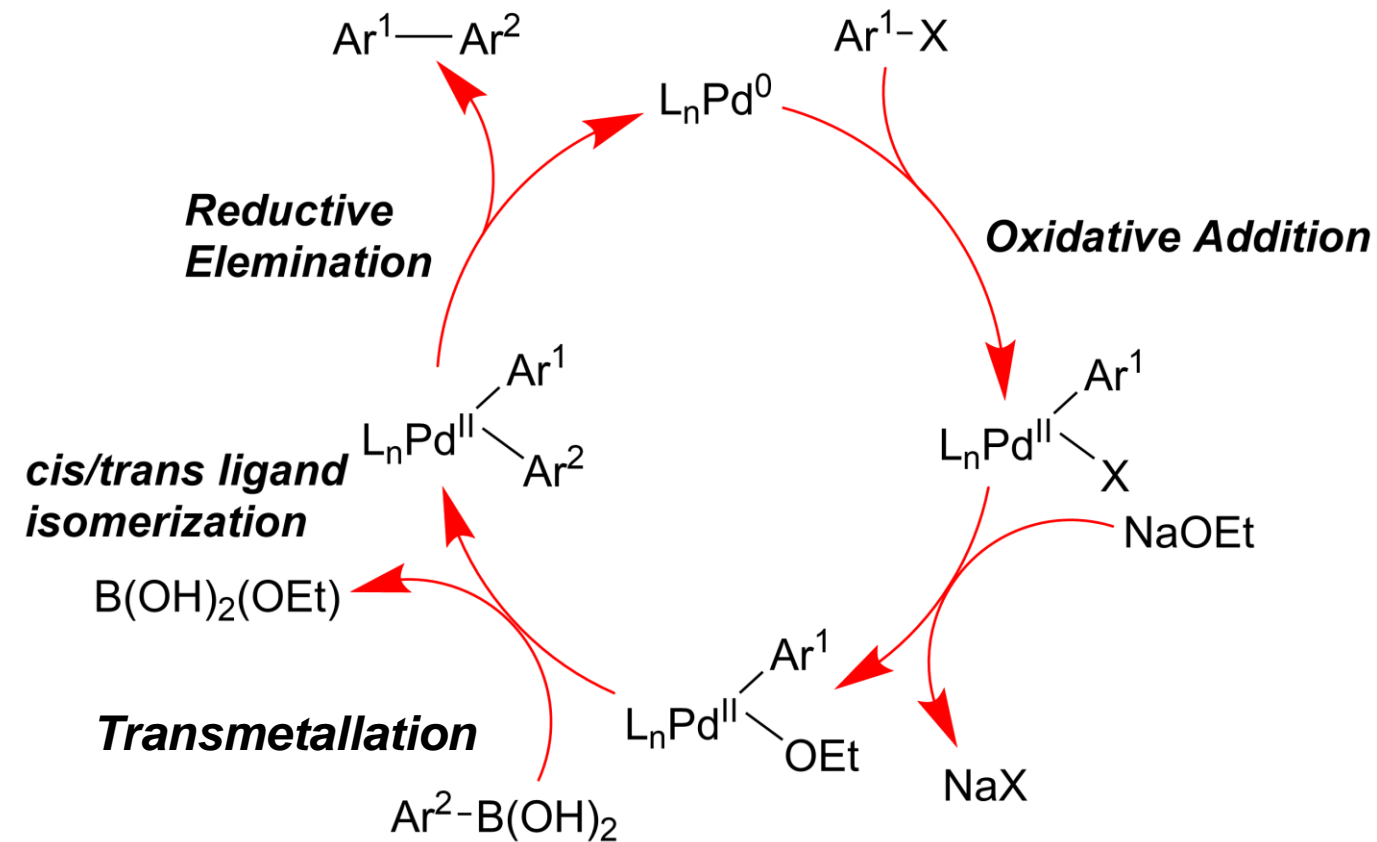
Poly-*p*-phenylenes

$n \approx 100$

(LED material)

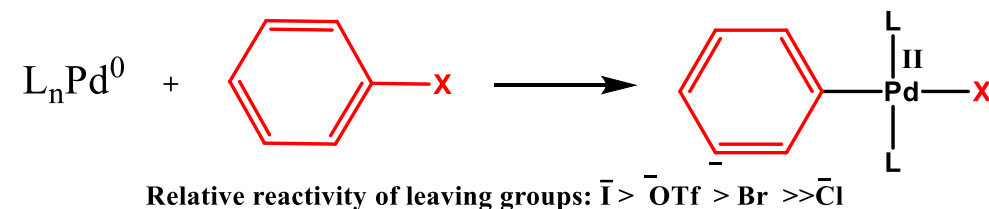
Suzuki–Miyaura Coupling: Mechanism

Mechanism

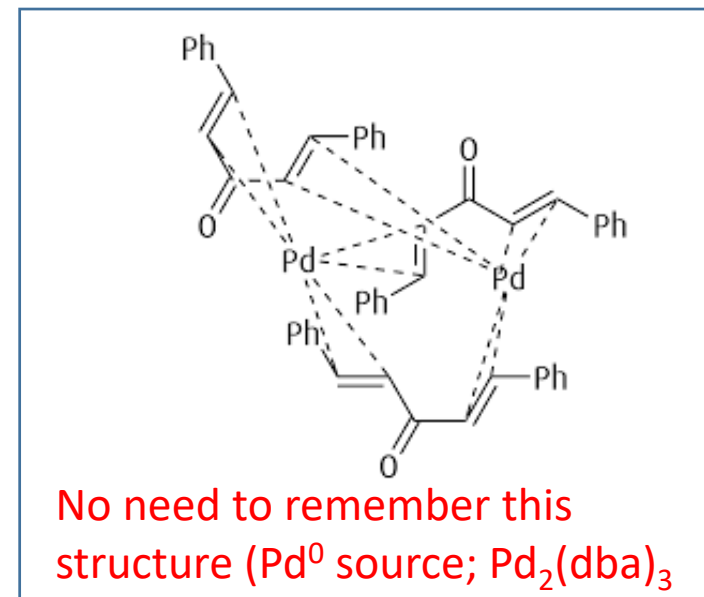
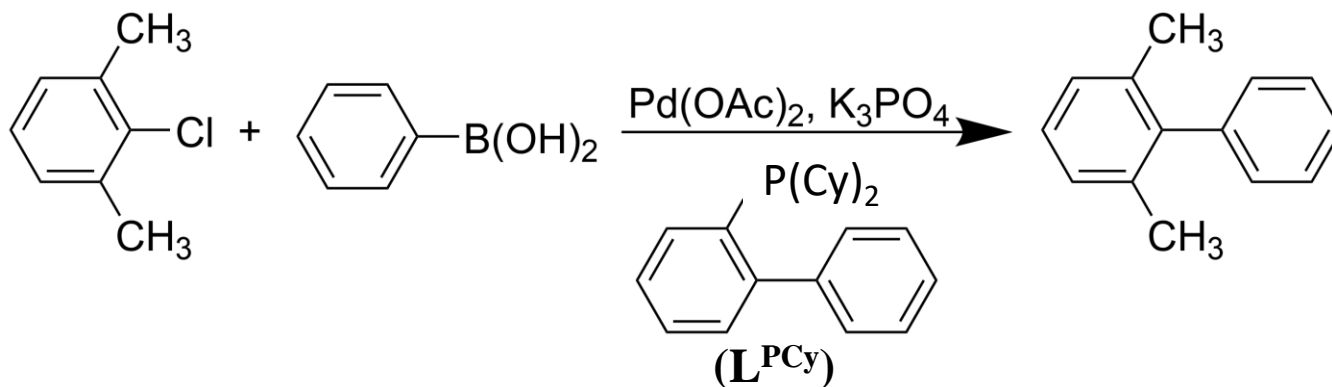
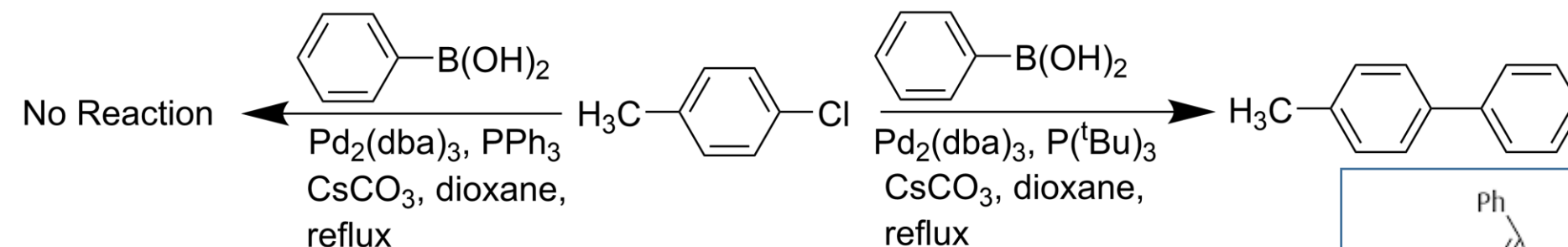


Electronic effects of Oxidative Addition

- The order of reactivity is in good agreement with substituent effect in the oxidative addition of aryl halides to the palladium(0) complex

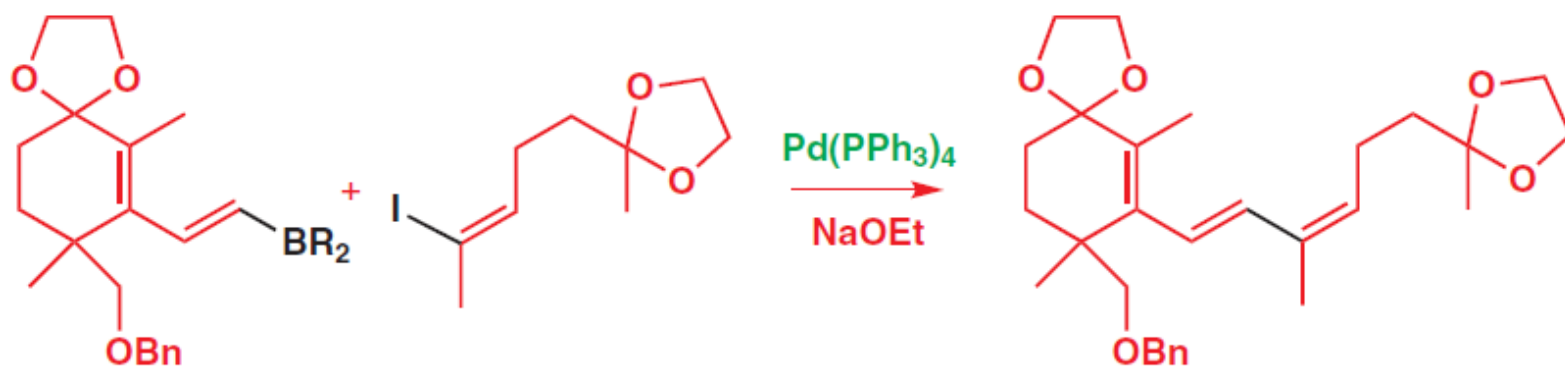


Suzuki–Miyaura Coupling: Mechanism

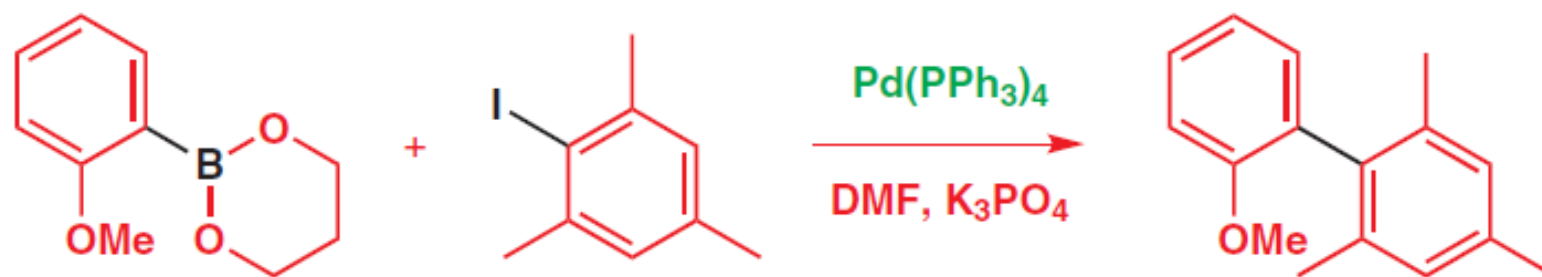


- Bulky phosphine ligands (e.g. tBu_3P) lead to a monoligated palladium species which is highly reactive to oxidative addition.
- *ortho*-phenyl moiety in L^{PCy} may provide a stabilizing interaction between the aromatic π -system and one of the metal d -orbitals, and increases the steric bulk around the metal, which promotes reductive elimination and favors monophosphine palladium species.

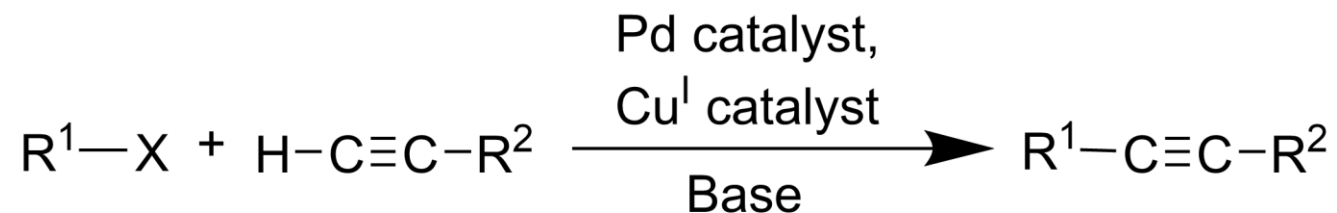
Suzuki coupling has been used in the synthesis of the unsaturated units of a range of natural products,



Sterically demanding substrates are tolerated well and Suzuki coupling is often used for aryl–aryl cross-couplings.



Sonogashira Coupling



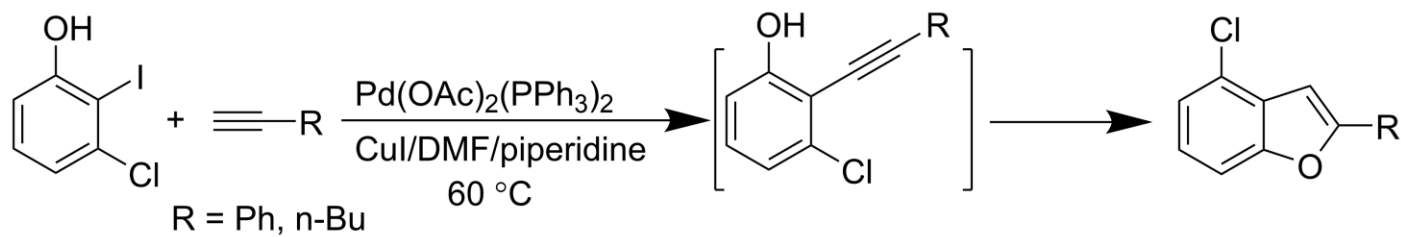
R^1 = aryl, hetaryl, vinyl

R^2 = aryl, hetaryl, alkenyl, alkyl, SiR_3

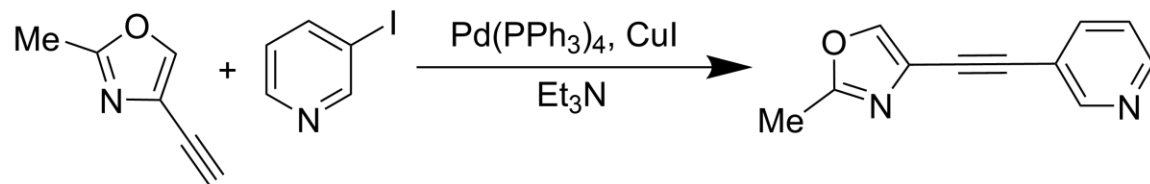
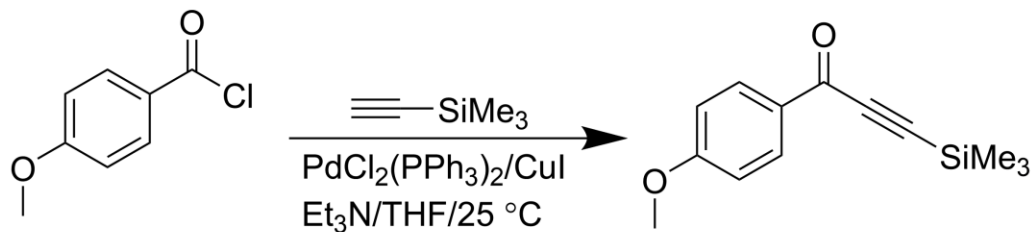
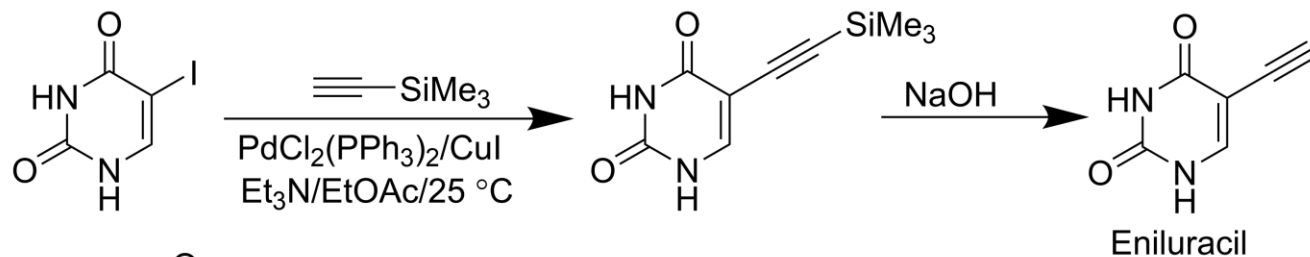
X = I, Br, Cl, OTf

- One of the most straightforward methods for the preparation of arylalkynes and conjugated enynes is the palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl halides which was described for the first time by Sonogashira et al. in 1975.
- Usually, the Sonogashira coupling is carried out in the presence of catalytic amounts of a palladium(II) complex as well as copper(I) iodide in an amine as solvent.

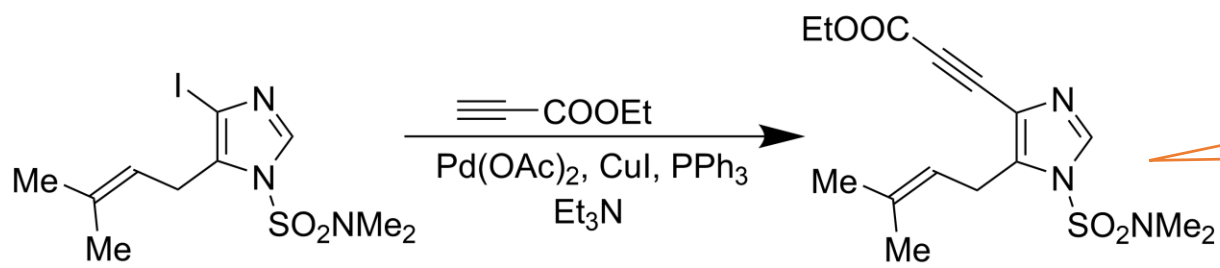
Sonogashira Coupling: Examples



Sonogashira cross-coupling is key to the synthesis on an industrial scale of eniluracil, an anticancer drug used to treat breast and colorectal cancers



The compound is an antagonist for use in the treatment of drug abuse.



Potentially useful drug for the treatment of rheumatoid arthritis

Sonogashira Coupling: Mechanism

The copper-cocatalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles as shown here.

