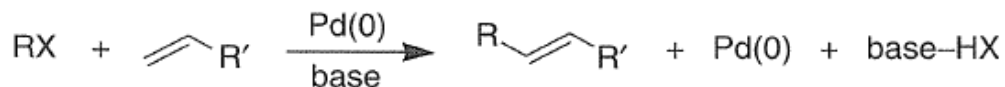


Heck reaction (Palladium(0)-Catalyzed Olefin Insertion reaction)

The Heck reaction involves coupling of alkenyl or aryl halides with alkenes in the presence of a catalytic amount of a Pd(0) complex and a base to furnish alkenyl- and aryl-substituted alkenes.

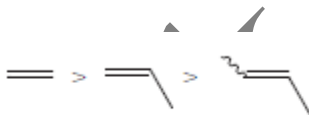


R: Allyl, Alkenyl, Aryl, Alkynyl, Benzyl R': Alkyl, Alkenyl, Aryl, CO, R, OR

Base: 2^o or 3^o amine, NaOAc, K₂CO₃, KHCO₃, KOAc.

The base may serve a dual purpose: reducing the Pd(II) precatalyst to Pd(0) and promoting reductive elimination of the PdH(X) intermediate by shifting the equilibrium towards Pd(0).

Alkene: Increasing the db substitution dramatically decreases the rate of intermolecular Heck reactions:



Catalyst:

Pd(II) sources often used: Pd(OAc)₂, PdCl₂PR₃, PdCl₂(CH₃CN)

Pd(0) sources: Pd(PPh₃)₄, Pd(dba)₂+ PR₃

Mechanism:

The mechanism of Heck reaction occurs through a cyclic mechanism. The catalytic cycle of Heck reaction is shown and included following steps.

Step1: Oxidative addition

The reaction is initiated by oxidative addition of an alkenyl halide or an aryl halide to a coordinatively unsaturated 14-electron Pd(0) complex, generating a 16-electron o-alkenyl- or o-aryl palladium(II)-complex (A).

Step2: Carbopalladation

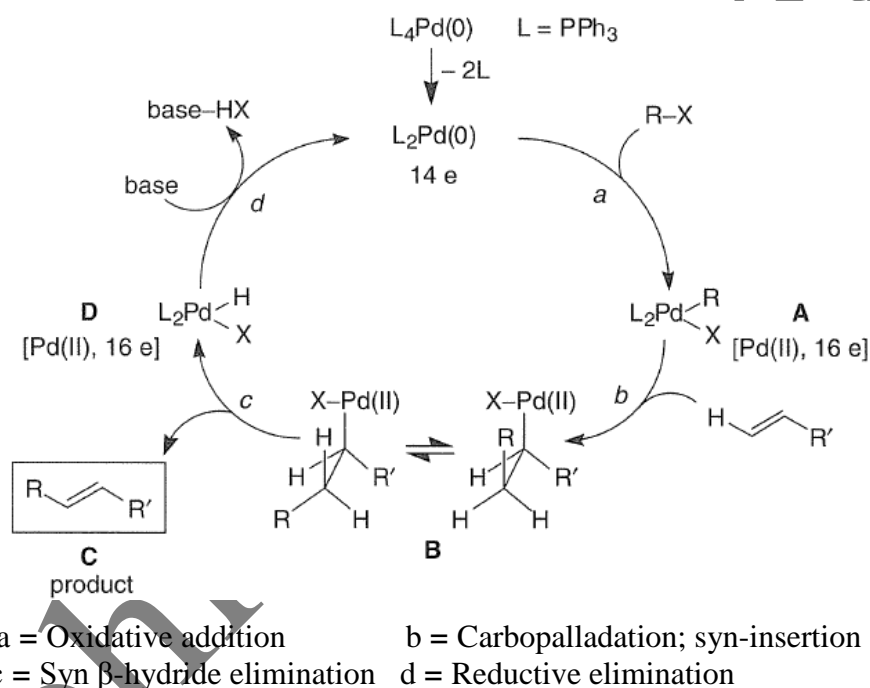
The alkene, in the reaction mixture leads to its coordination with A. Subsequent syn insertion of the alkene double bond into the o-alkenyl- (or the o-aryl) Pd-C bond via a four-centered transition state produces intermediate (B).

Step3: Syn β -hydride elimination

The unsaturated ligand R of the palladium complex A becomes attached to the less hindered carbon of the alkene. Rotation of the newly formed carbon-carbon bond in B aligns a β -hydrogen with the palladium atom for a syn β -hydride elimination which leads to the coupling product C and the hydrido palladium complex (D).

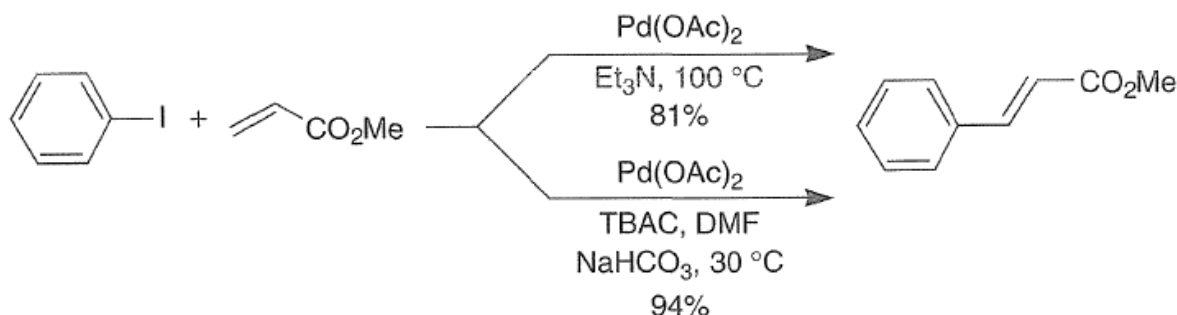
Step3: Reductive elimination

Reductive elimination of HX from D by the added base regenerates the Pd(0) catalyst. For steric reasons (anti-periplanar arrangement of R and R'), the Heck reaction with terminal alkenes generally yields (E)-alkenes.



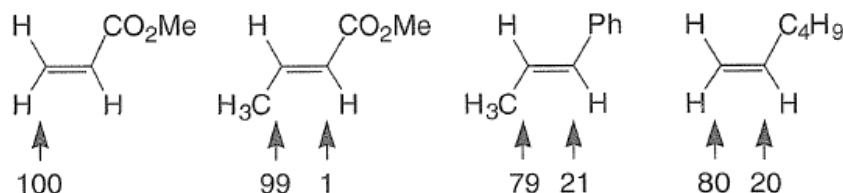
A disadvantage of Heck-type reactions with organic halides is the relatively high temperature (-100 °C) required for the coupling reaction. Many modifications and improvements of the palladium catalyst have been reported since the original work of Heck.

Example: Addition of tetrabutylammonium chloride (TBAC) as a phase transfer agent markedly improves the reactivity of the catalyst.



Stereochemistry:

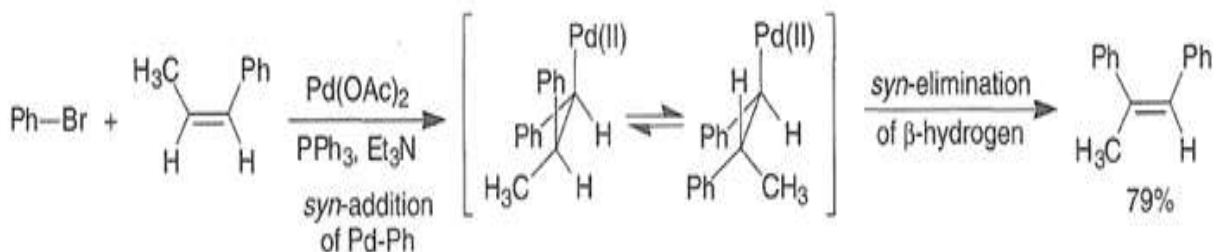
The regiochemistry of addition of the organopalladium intermediate to the olefins is dominated by steric effects, in that the organic group prefers the less substituted carbon of the double bond regardless of the substituents on either reactant. However, electronic effects play a significant role in the case of some olefins. Thus, electron releasing groups on the double bond lead to increased addition to the most electron deficient carbon of the double bond.



(Regioselectivity in the addition of RX)

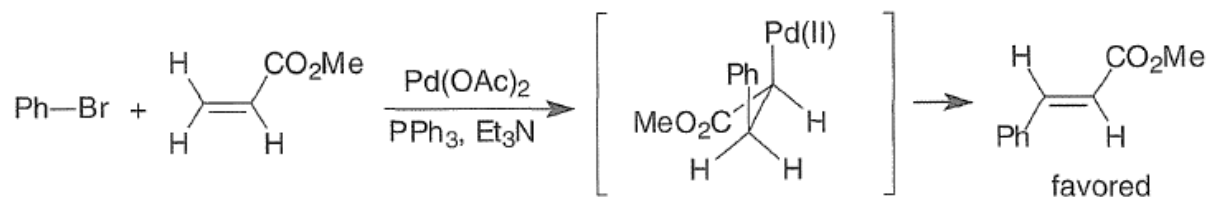
Reaction is stereoselective for the *E* olefin because the corresponding TS leading to the *cis* olefin involves energetically unfavorable R'/R eclipsing interactions.

The stereochemistry of the desired product alkene is the result of a *syn*-addition of the organopalladium followed by a *syn*-elimination of palladium hydride.

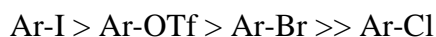


If the organopalladium intermediate contains two β -hydrogens, *syn*-elimination can yield a mixture of (*E*)- and (*Z*)-alkenes. However, the thermodynamically more stable alkene is formed

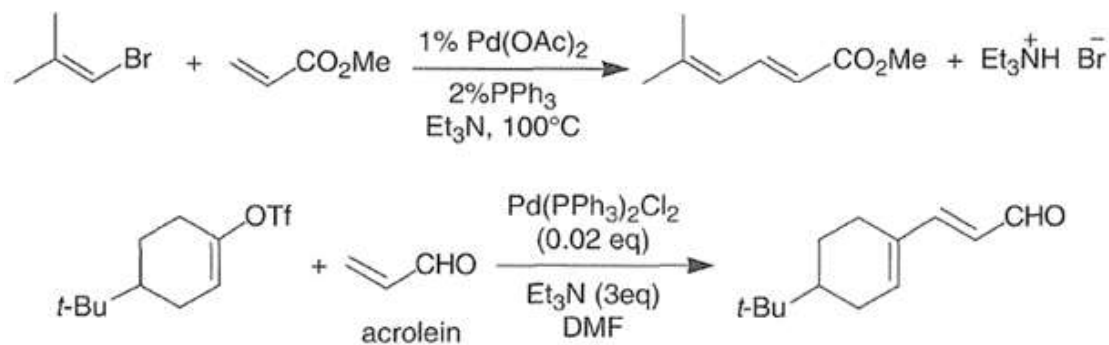
preferentially. Aryl substituents such as -Cl, -CN, -COOR, -CHO and -NMe₂ do not interfere with the coupling reaction.



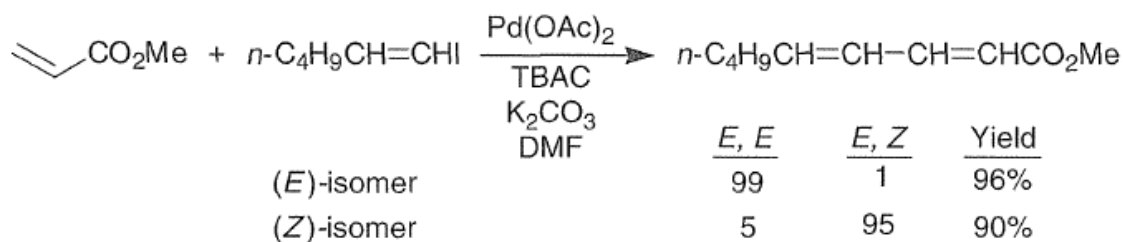
The reactivity order of aryl halides in oxidative additions is as follows:



Vinylation of alkenes with vinyl halides or vinyl triflates furnishes conjugated dienes. Vinyl triflates are especially attractive in coupling reactions since they can be prepared regio- and stereoselectively from enolizable ketones by treatment with a hindered base and trapping the enolate oxygen with triflating agents such as triflic anhydride Or or N-phenyltrifluoromethanesulfonimide (PhNTf₂). For example, the palladium-catalyzed reaction of vinyl triflates with acrolein, which generally cannot be used in the Heck reaction because the acrolein polymerizes, produces a β-unsaturated aldehydes.



Under the usual reaction conditions, coupling of (E) or (Z) -1-halo-1-alkenes with alkenes leads to mixtures of stereoisomeric dienes. However, stereoselective coupling reactions have been achieved by using Pd(OAc)₂, in the presence of TBAC and K₂CO₃.

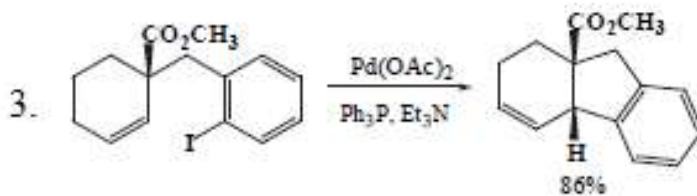
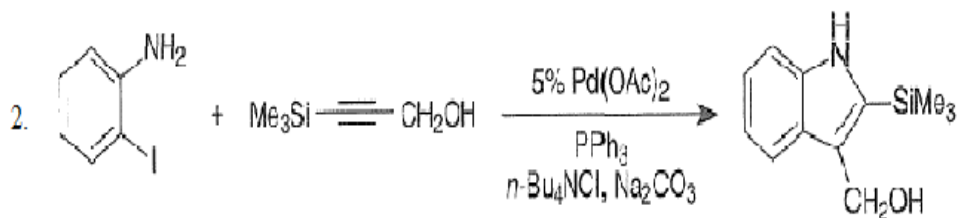
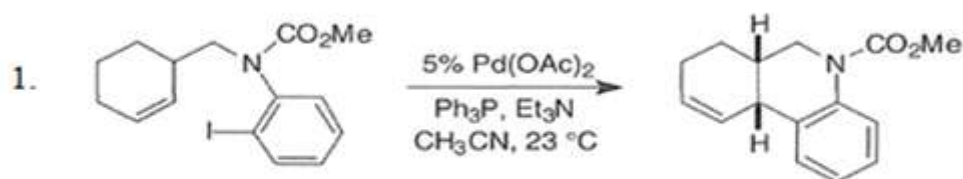


(TBAC: Tetrabutylammoniumchloride)

Heck is stereoselective for E olefin formation.

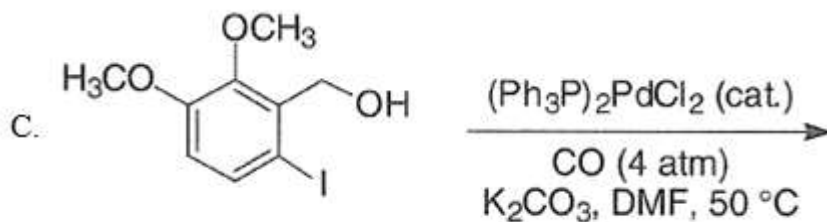
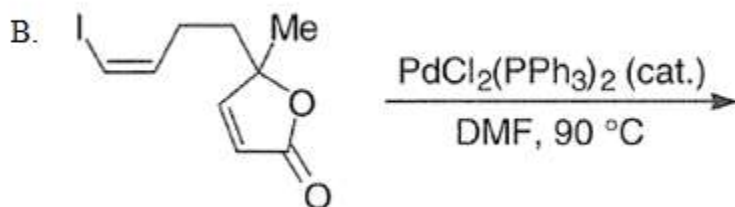
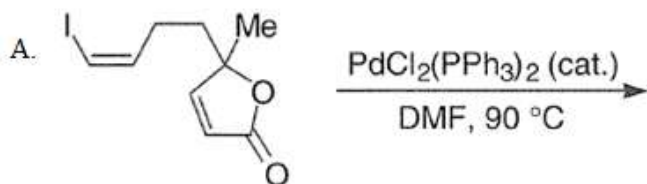
Intramolecular Heck Reaction:

For intermolecular Heck reactions with neutral Pd complexes and unactivated or electron-poor alkenes, the regioselectivity for R' insertion is under steric control, resulting in substitution at the less sterically hindered position. In contrast, with neutral Pd complexes and electron-rich alkenes (e.g. hetero atom substituted olefins), the regioselectivity of R' insertion is under electronic control, resulting in substitution to the electron-donating group.

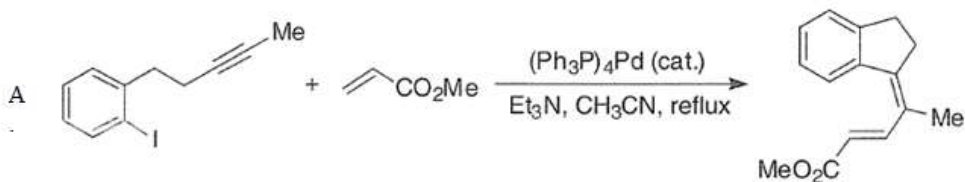


Questions:

1. Give the product of following reaction with suitable mechanism.



2. Give the suitable mechanism of following reactions

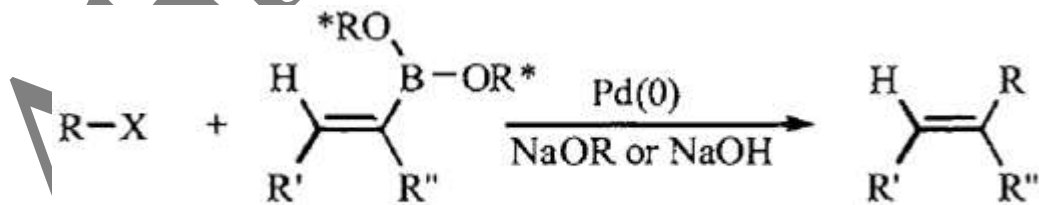


Palladium-Catalyzed Cross-coupling with organometallic reagent

Palladium-catalyzed cross-coupling reactions have common features with the Heck Coupling with Organometallic reaction but differ in that alkenyl and aryl organometallics instead of alkenes are involved in the coupling process. The role of the organometallic reagents is to transfer an alkenyl or an aryl group onto the species R-PdL, X in exchange for X (halide or triflate). Although a variety of organometallics for transmetalation have been reported, reagents containing zinc, aluminum or zirconium (Negishi reactions), boron (Suzuki reaction), and tin (Stille reaction) are the most widely used. These organometallics are more compatible with functional groups such as esters, amides, nitriles, and nitro compounds than organolithium and organomagnesium reagents. The palladium(0)-catalyzed cross-coupling of alkenyl or aryl halides and triflates with organometallics proceeds via sequential oxidative addition (to species A below), transmetalation (usually rate determining), isomerization, and reductive elimination processes. The catalysts commonly used are the Pd(0)-complexes Pd(PPh₃)₄ or Pd(dba)₃.

Suzuki Reaction (Coupling Reactions with Organoboron Compound)

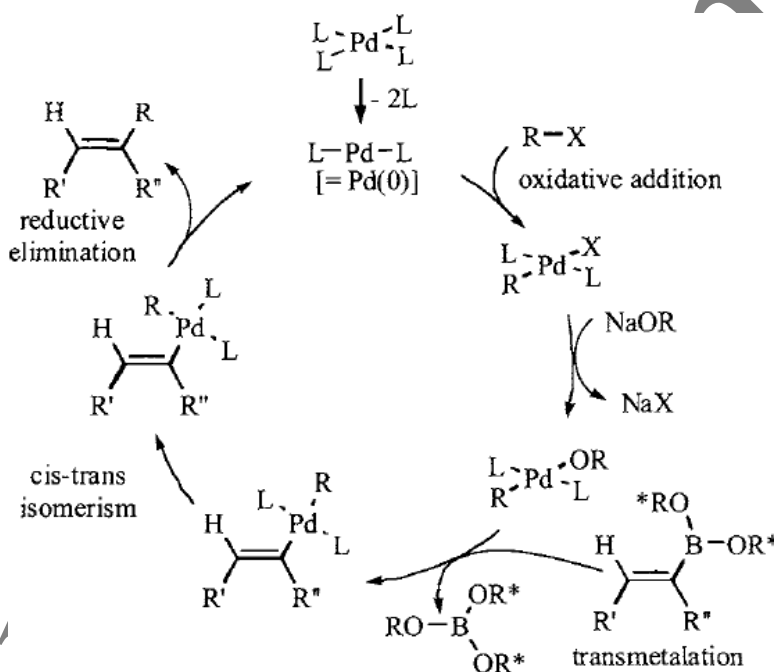
The Suzuki reaction provides a versatile, general method for the stereo- and regioselective synthesis of conjugated dienes, enynes, aryl substituted alkenes, and biaryl compounds via Pd-catalyzed cross-coupling of vinyl halides or aryl halides with vinyl-, aryl-, or alkynyl boron reagent. The wide use of this carbon-carbon bond forming reaction in organic synthesis stems from the ability to preserve the alkene geometry of both the halo alkene and alkenyl boron in the product, the tolerance of functional groups, and the ready availability of the starting materials.



Where X = I >> Br >OTf >> Cl

Mechanism:

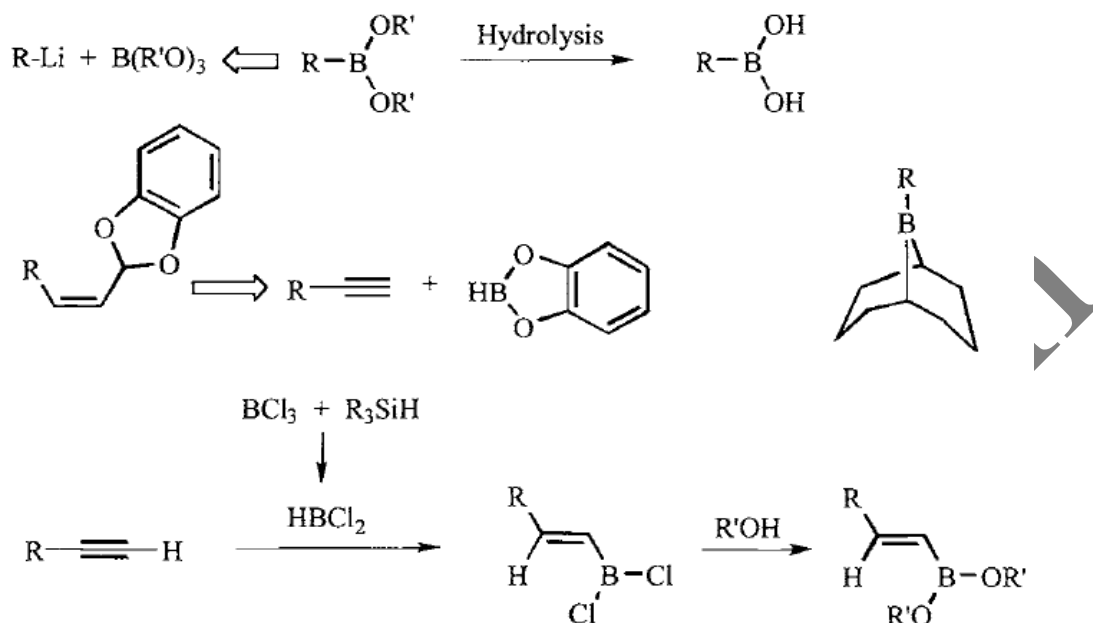
The catalytic cycle for the Suzuki cross-coupling reaction involves an oxidative addition (to form RPd(II)X) transmetalation-reductive elimination sequence. The transmetalation between the RPd(II)X intermediate and the organoboron reagent does not occur readily until a base, such as sodium or potassium carbonate, hydroxide or alkoxide, is present in the reaction mixture. The role of the base can be rationalized by its coordination with the boron to form the corresponding ate-complex, thereby enhancing the nucleophilicity of the organic group, which facilitates its transfer to palladium. Also, the base RrO^- may activate the palladium by formation of $\text{R-Pd-OR}'$ from R-Pd-X .



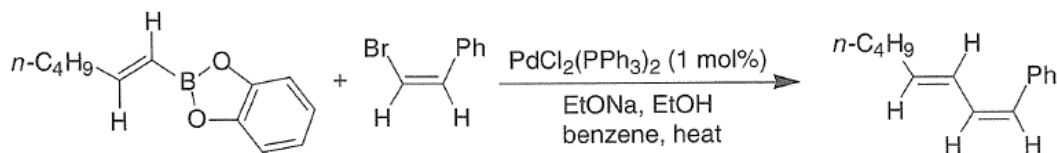
Organoboron reagents:

The organoboron reagents in Suzuki cross-coupling reactions are either organoboranes, 1-alkenyl- and arylboronic acids (RB(OH)_2), or boronate esters (RB(OR)_2). The traditional synthesis of 1-alkenyl- and aryl boronic acids and boronate esters involves treatment of Grignard or lithium reagents with trialkyl borates to produce the corresponding boronate esters. Hydrolysis of these furnishes the corresponding boronic acids. Organotrifluoroborates are crystalline solids, readily isolated and stable to air and moisture, and are excellent partners in Suzuki coupling reactions.

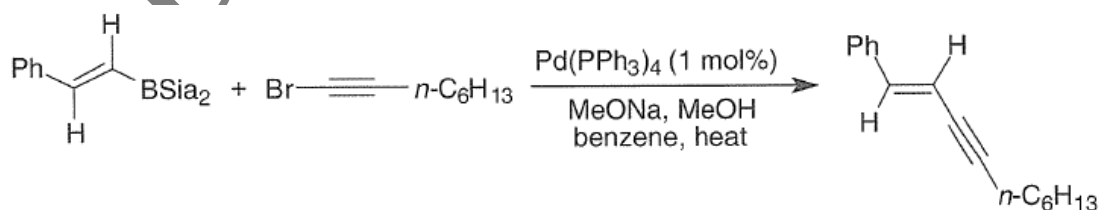
General sources of common boron reagents:



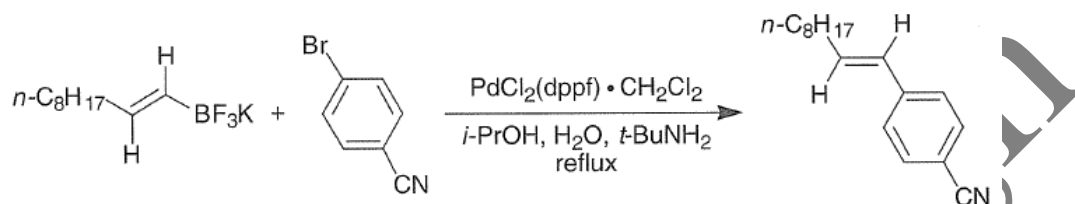
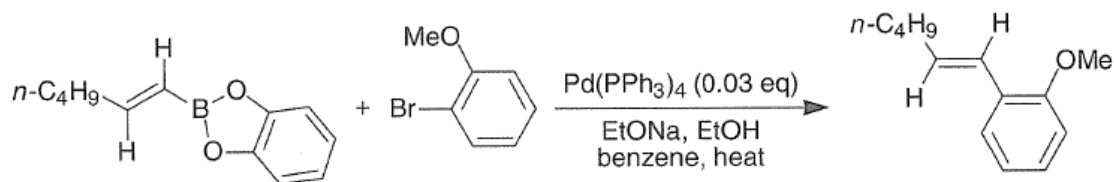
A variety of conjugated dienes, whose structural features are frequently encountered in natural products and insect pheromones, as well as dienophiles in Diels-Alder reactions, are accessible via the Suzuki reaction.



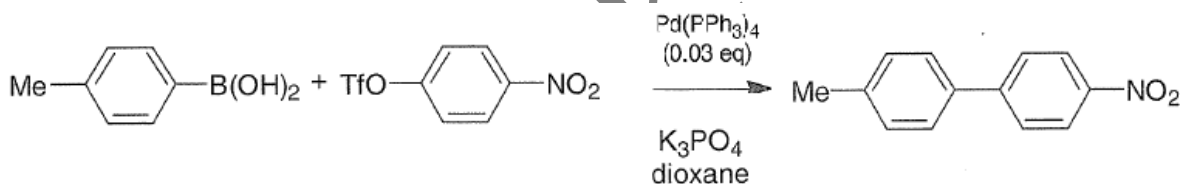
Cross-coupling of 1-alkenylboron compounds with 1-halo-1-alkynes leads to conjugated enynes, which can serve as precursors for conjugated diene.



Pd(0)-mediated arylation of 1-alkenylboronates or 1-alkenyl trifluoroboronates with haloarenes is a stereoselective method for the synthesis of aryl-substituted alkene.

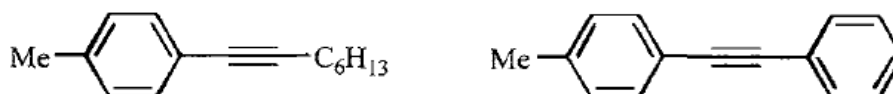
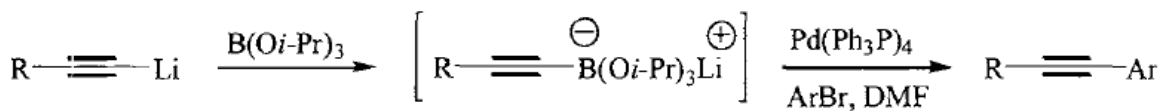


The Suzuki coupling reaction is a powerful tool for the construction of biaryl compounds and their homologues, which are key structural elements of various natural products, polymers, and compounds of medicinal interest. Aryl boronic acids and their esters are the usual substrates in reactions with aryl or heteroaromatic halides and aryl triflate.

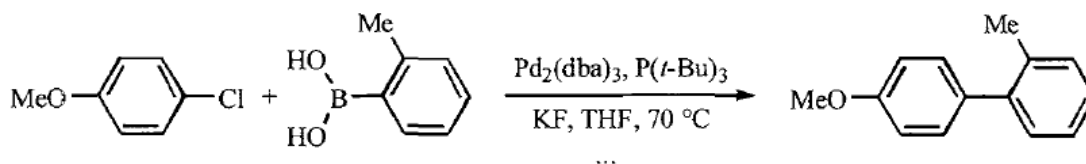


Examples:

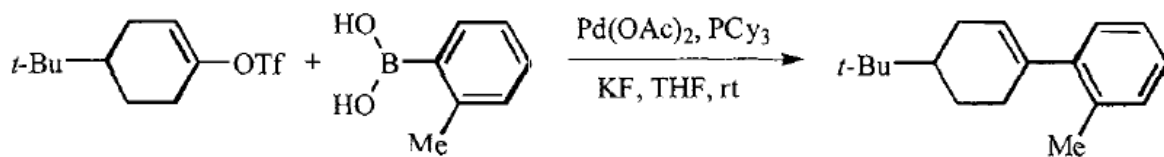
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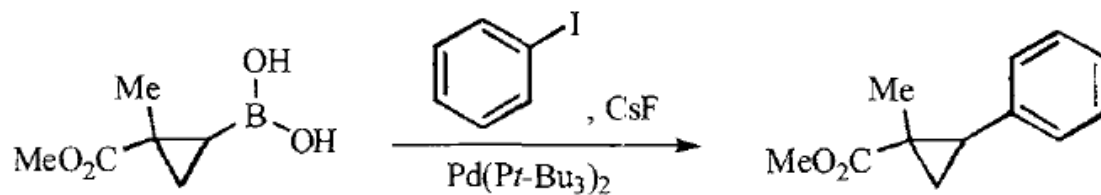
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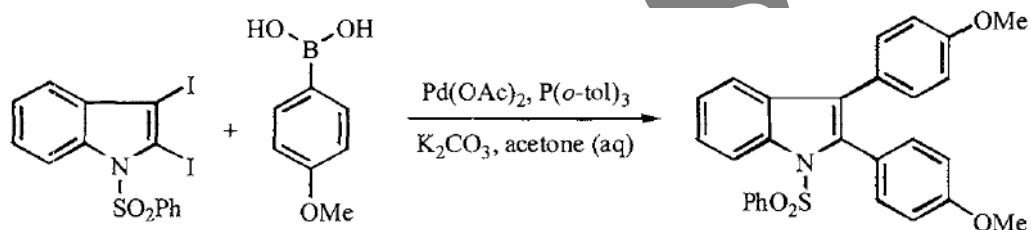
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Abhish