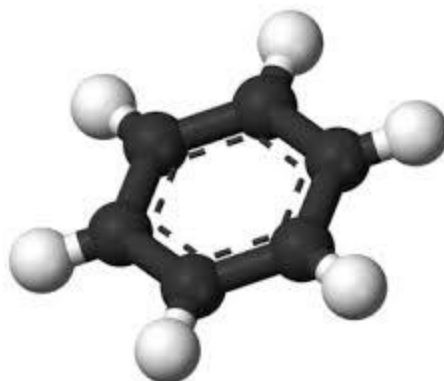


**Chem
Chula**

Aromatic – Coupling Reactions



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Recommended Textbook:

Chapter 17 in *Organic Chemistry*, 8th Edition, L. G. Wade, Jr., **2010**,
Prentice Hall (Pearson Education)

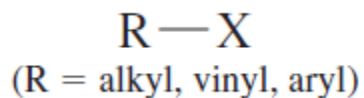
Coupling Reactions

- Organic chemists have developed new **coupling reactions** (reactions that form **C-C bonds**) using a wide variety of methods that tolerate many other functional groups.
- Some of the most successful coupling reactions use **transition metals** that change valences easily, adding and eliminating substituents as they pass from one oxidation state to another.

- **Copper** (Organocuprate Reagents)
- **Palladium**
 - Heck Reaction
 - Suzuki Reaction

Couplings Using Organocuprate Reagents

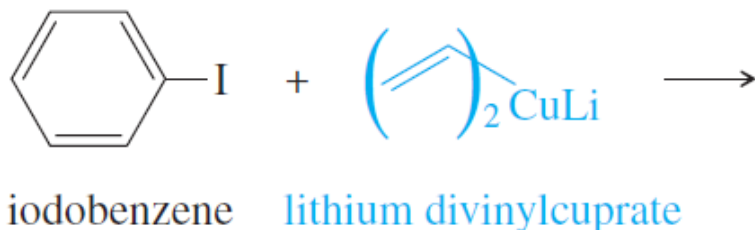
- Lithium dialkylcuprate reagents (**Gilman reagents**) are formed by the reaction of two equivalents of an **organolithium reagent** with **cuprous iodide**.



- The organocuprate can be **coupled** with an alkyl, vinyl, or aryl halide



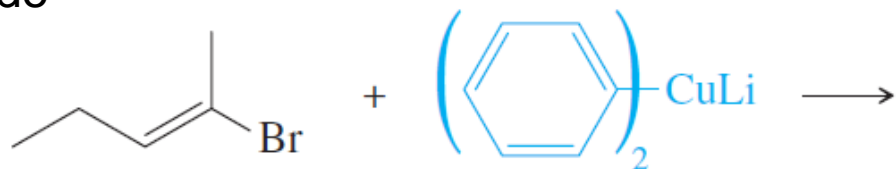
Example



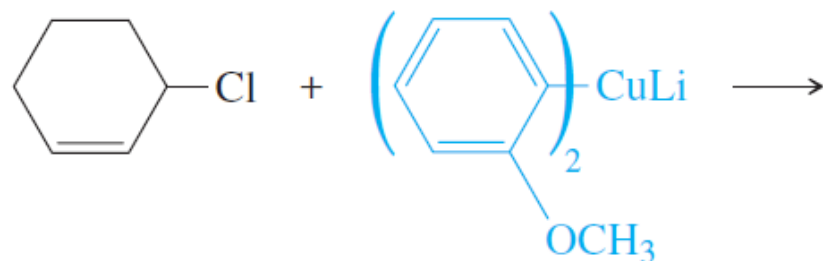
Couplings Using Organocuprate Reagents

More Examples

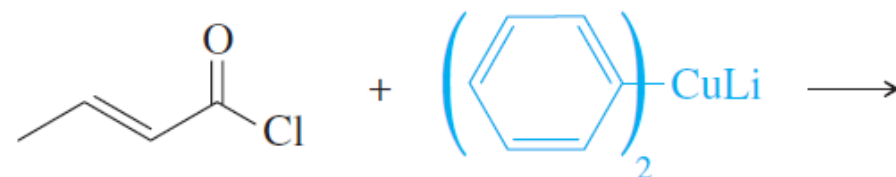
- A vinyl halide with an aryl cuprate, preserving the stereochemistry of the vinyl halide



- An alkyl halide with an aryl cuprate.



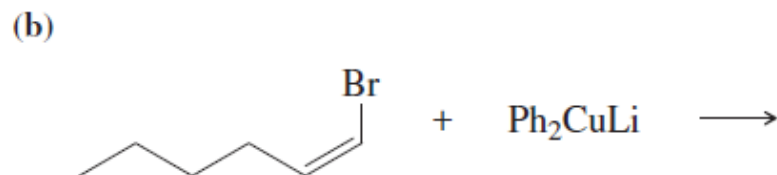
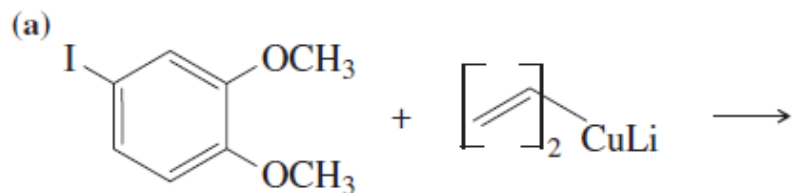
- An acyl halide with an organocuprate, giving a ketone



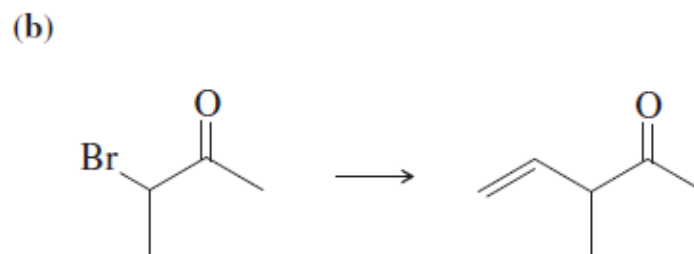
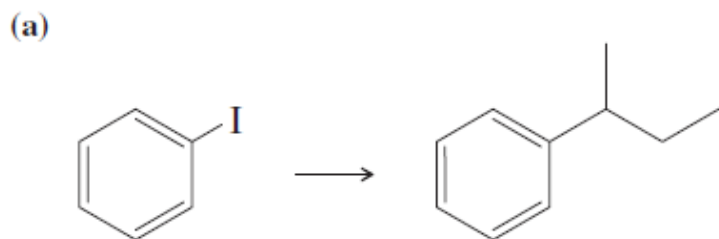
Couplings Using Organocuprate Reagents

Problems

What products would you expect from the following reactions?



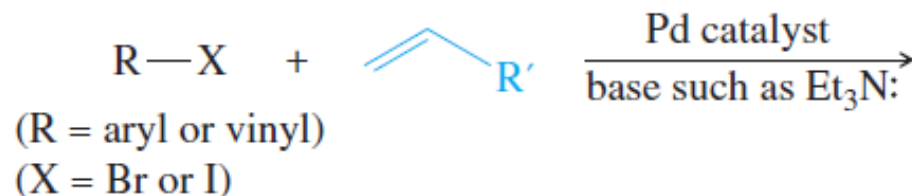
What organocuprate reagent would you use for the following substitutions?



The Heck Reaction

- The Heck reaction is the **palladium-catalyzed** coupling of an **aryl or vinyl halide** with an **alkene** to give a new C—C bond at the **less substituted** end of the alkene, usually with **trans** stereochemistry

The Heck Reaction

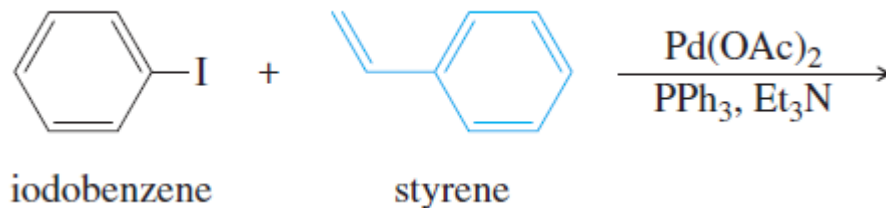


- In most cases, the **halide** is a bromide or an iodide
- the **alkene** is typically monosubstituted.
- The **palladium** catalyst might be Pd(OAc)₂ or PdCl₂ or a variety of other palladium compounds.
- A **base** such as triethylamine or sodium acetate is added to neutralize the HX released in the reaction
- Many reactions use **triphenylphosphine (PPh₃)** to complex with the palladium, which helps stabilize it and enhances its reactivity

The Heck Reaction

Examples

- An aryl halide with an aryl olefin.



- An aryl halide with a conjugated acid or ester.



- A vinyl halide with a conjugated nitrile.



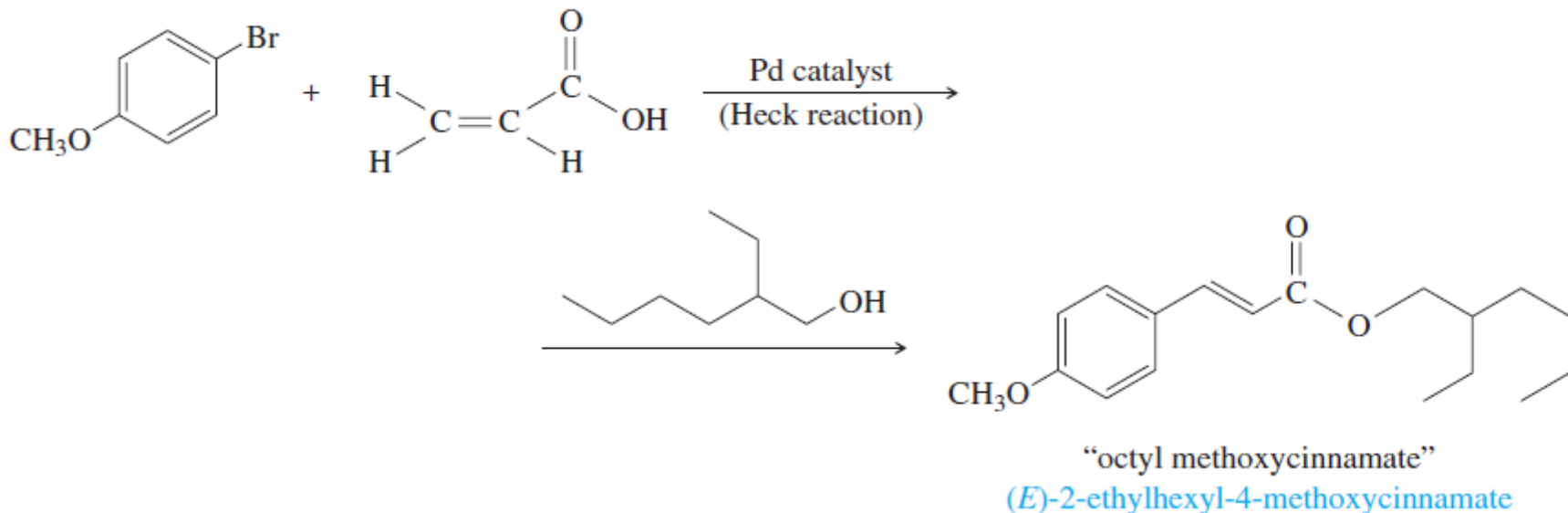
The Heck Reaction

More examples

- The industrial synthesis of naproxen, an over-the-counter analgesic and anti-inflammatory drug.



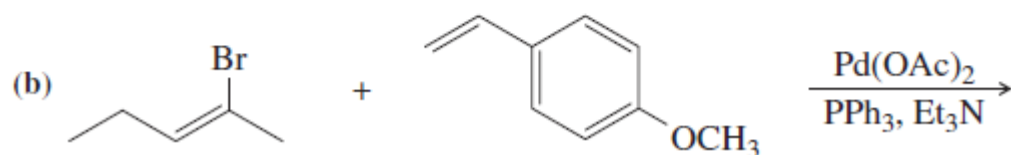
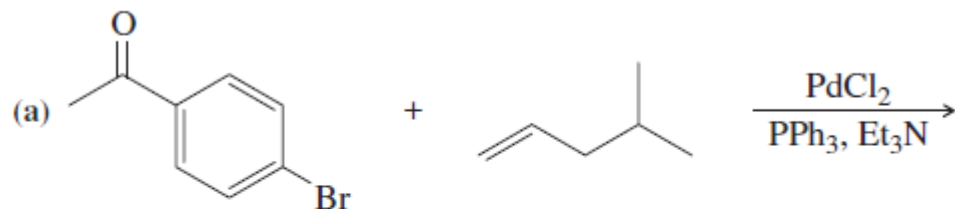
- The industrial synthesis of octyl methoxycinnamate, a common ingredient in sunscreens.



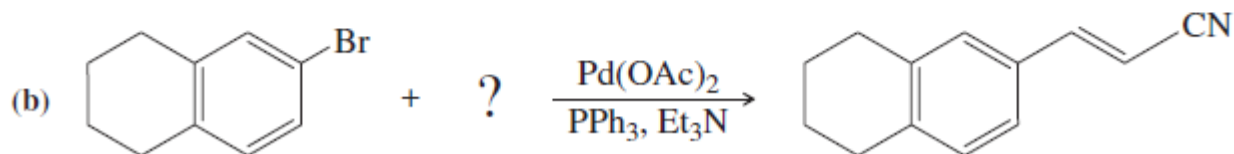
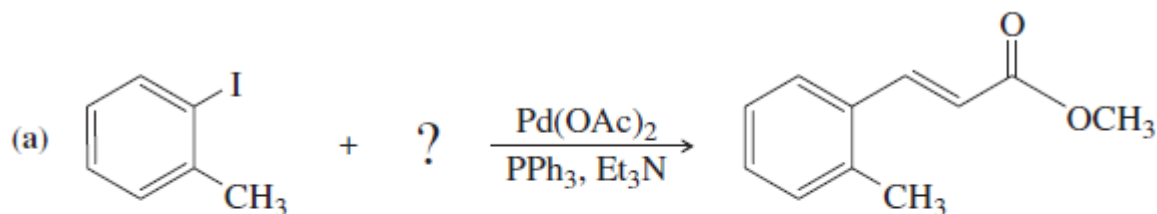
The Heck Reaction

Problems

What products would you expect from the following reactions?



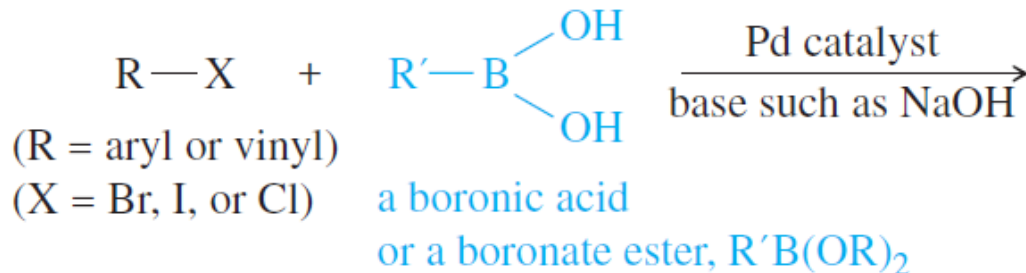
What substituted alkene would you use in the Heck reaction to make the following products?



The Suzuki Reaction

- The Suzuki reaction is a **palladium-catalyzed** substitution that couples an **aryl or vinyl halide** with an **alkyl, alkenyl, or aryl boronic acid or boronate ester**.

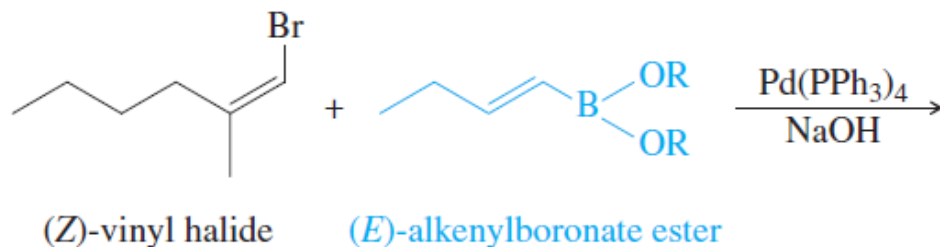
The Suzuki Reaction (Suzuki Coupling)



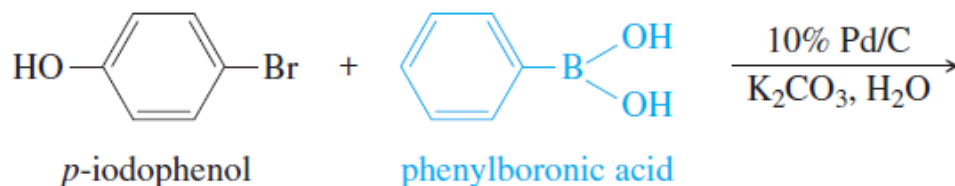
- Like the Heck reaction, the Suzuki coupling can use water as the solvent. Waterbased Suzuki reactions are attractive both for industrial processes and for labs that want to minimize the purchase and disposal of toxic solvents.

The Suzuki Reaction Examples

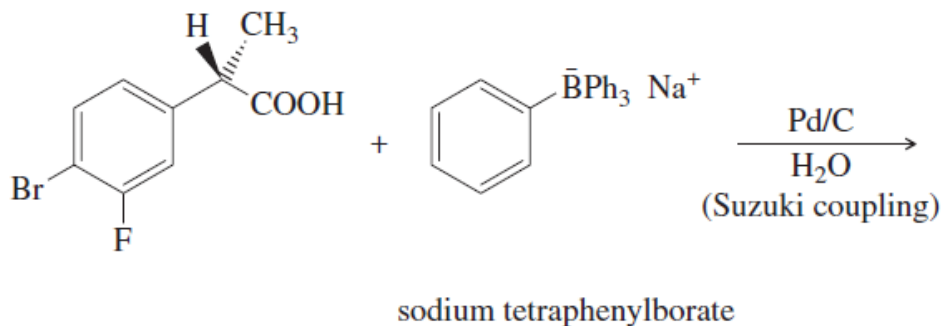
- A vinyl halide with an alkenylboronate ester, preserving the stereochemistry of the reagents.



- An aryl halide with an arylboronic acid, using palladium on carbon and water as the solvent.

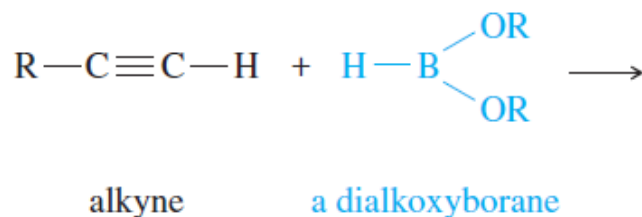
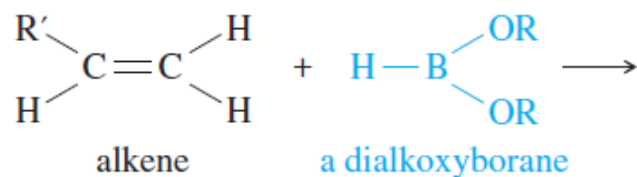


- Synthesis of the anti-inflammatory drug flurbiprofen by an environmentally efficient Suzuki coupling that uses water as the solvent and palladium on carbon as a reusable catalyst.



The Suzuki Reaction

- Alkyl and vinyl boronate esters are synthesized by the **hydroboration of double and triple bonds**, similar to the hydroboration of alkenes and alkynes

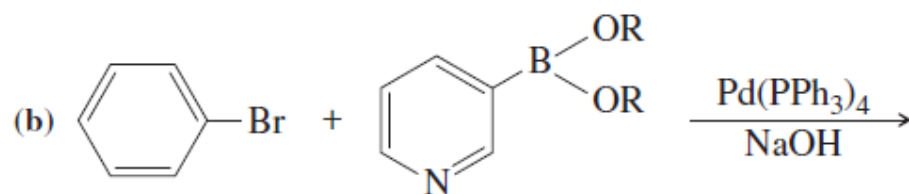
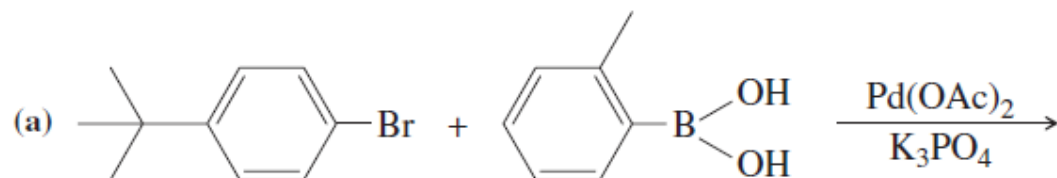


- Arylboronate esters** are made by a two-step process: First, we convert the aryl halide to the **aryllithium compound**. Addition of a **trialkyl borate** (often trimethyl borate) allows the organolithium compound to form a carbon–boron bond and expel an alkoxide group.



The Suzuki Reaction Problems

What products would you expect from the following Suzuki coupling reactions?



Show how you would use Suzuki reactions to synthesize these products from the indicated starting materials. You may use any additional reagents you need.

