5.6: Coupling Reactions in Organic Synthesis

Oxidative addition and reductive elimination are key steps in industrial catalysis. For example, both steps are featured in palladium-catalyzed cross-coupling reactions, the subject of the 2010 Nobel Prize in Chemistry. The prize was awarded to Richard Heck of the University of Delaware, Ei-Ichi Negishi of Purdue University and Akira Suzuki of Hokkaido University. With these reactions, workers in a variety of fields can make molecules that otherwise would be quite difficult to make. These molecules in turn may be important pharmaceuticals or useful compounds for electronic displays in computers and other devices, to name just a couple.

The Negishi reaction involves catalytic addition of alkylzinc nucleophiles to vinyl halides.

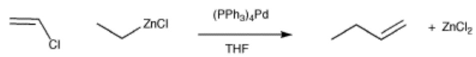


Figure 5.6.1: The Negishi cross-coupling reaction.

The catalytic cycle believed to operate for this reaction involves the crucial oxidative addition of the vinyl halide to the metal. The alkylzinc probably delivers the alkyl nucleophile to the metal via more conventional nucleophilic substitution. Once both pieces are both on the metal, they can reductively eliminate together.

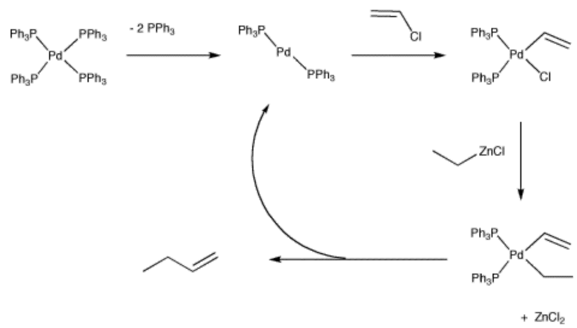


Figure 5.6.2: Catalytic cycle for the Negishi cross-coupling reaction.

Exercise 5.6.1

Explain why the vinyl halide pictured in the example above would not react directly with the alkylzinc reagent.

Exercise 5.6.2

Label each step of the catalytic cycle for the Negishi reaction with the appropriate term (oxidative addition, etc).

Exercise 5.6.3

Draw the mechanism for the Negishi reaction using curved arrow notation.

There are many other examples of coupling reactions in organic synthesis. The Suzuki reaction is somewhat similar to the Negishi reactions.

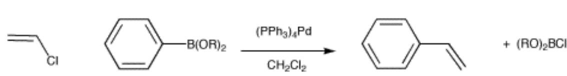


Figure 5.6.4: The Suzuki reaction.

The Heck reaction involves activation of a vinylic or aryl C-H bond.

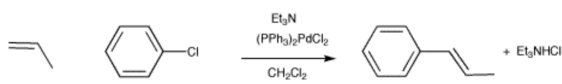


Figure 5.6.5: The Heck reaction.

Exercise 5.6.4

By analogy with the Negishi reaction, propose a catalytic cycle for the Suzuki reaction.

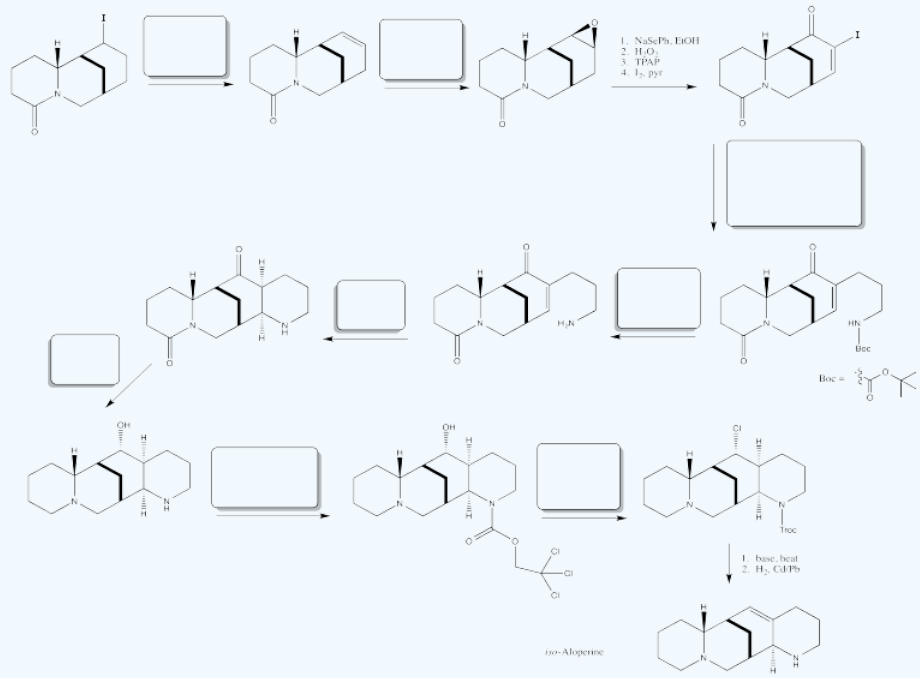
Exercise 5.6.5

Propose a catalytic cycle for the Heck reaction.

Exercise 5.6.6

iso-Aloperine

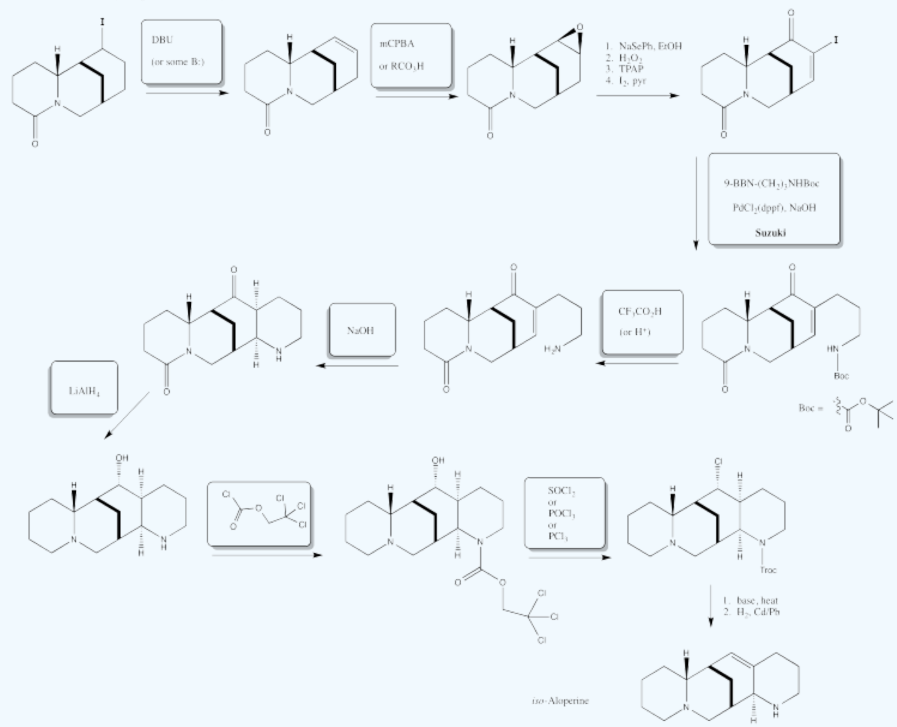
Brosius, Overman, *J. Org. Chem.* **1997**, *62*, 440.



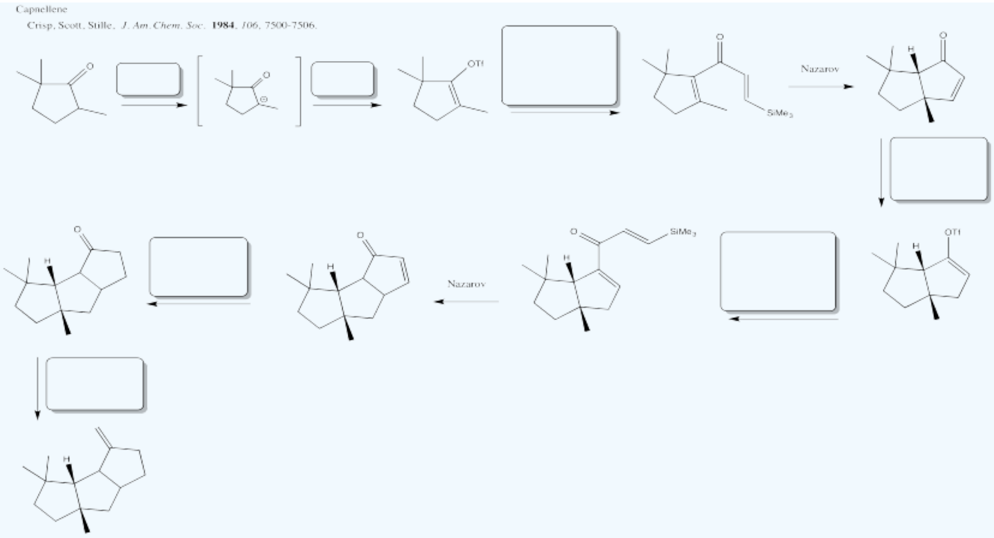
Answer

iso-Aloperine

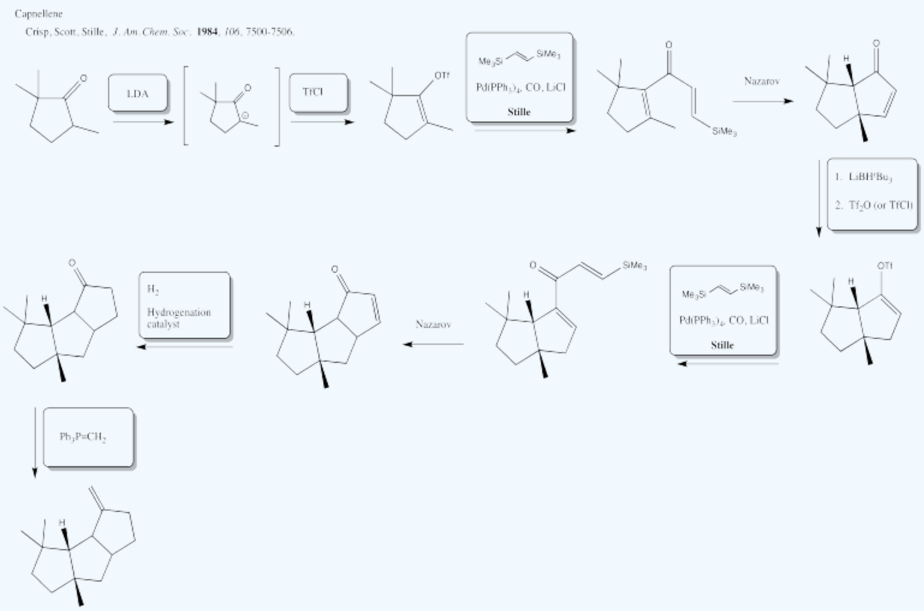
Brosius, Overman, *J. Org. Chem.* **1997**, *62*, 440.



? Exercise 5.6.7



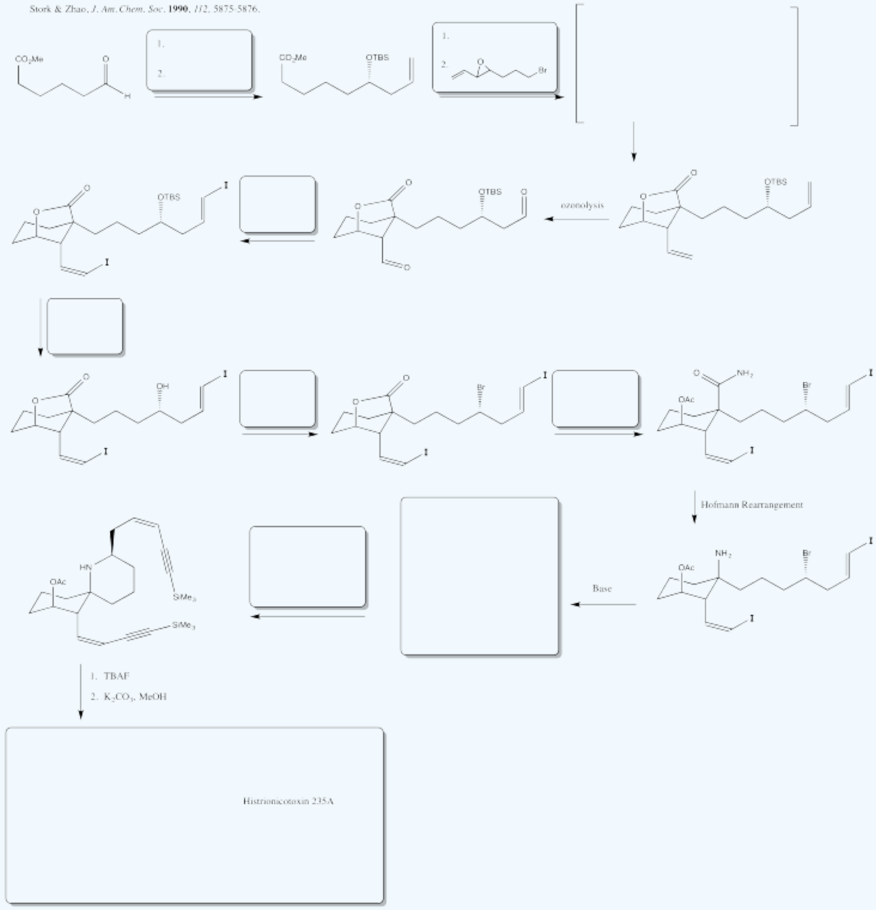
Answer



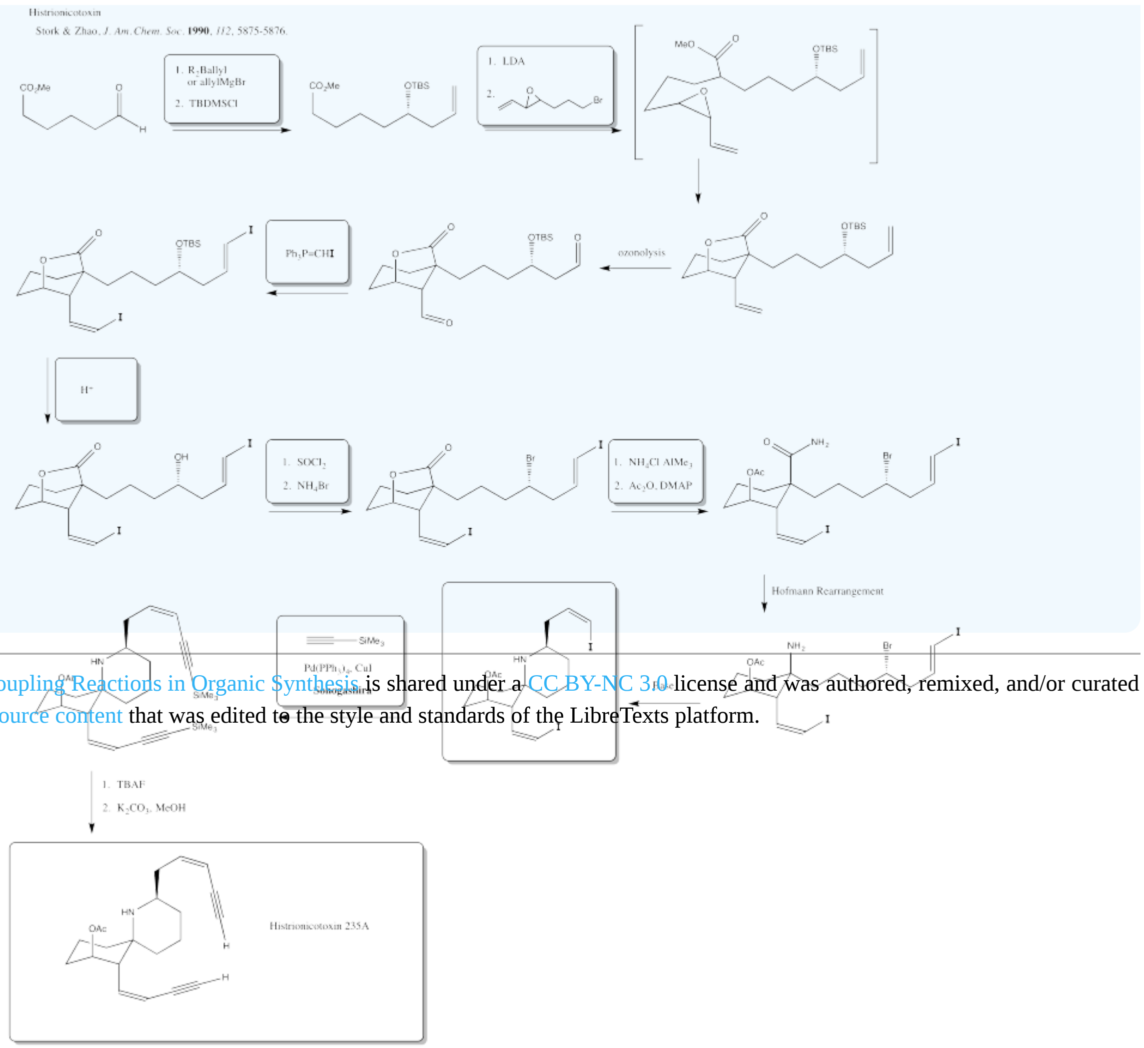
? Exercise 5.6.8

Histrionicotoxin

Stork & Zhao, *J. Am. Chem. Soc.* **1990**, *112*, 5875-5876.



Answer


Histrionicotoxin
Stork & Zhao, J. Am. Chem. Soc. 1990, 112, 5875-5876.
CO2Me
1. R2Ballyl or allylMgBr
2. TBDMSCl
OTBS
1. LDA
MeO
Br
ozonolysis
Ph3P=CHI
H+
OH
1. SOCl2
2. NH4Br
1. NH4Cl AlMe3
2. Ac2O, DMAP
OAc
NH2
Hofmann Rearrangement
HN
SiMe3
Pd(PPh3)4, CuI
Sonogashira
1. TBAF
2. K2CO3, MeOH
Histrionicotoxin 235A