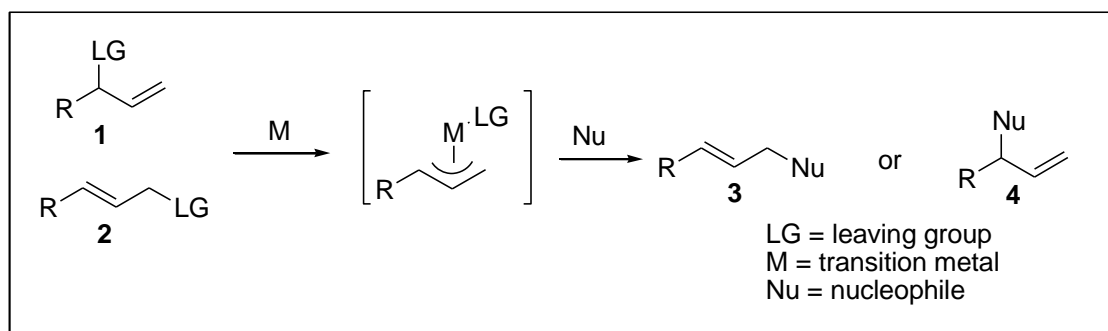


## Lecture 13

Asymmetric carbon-heteroatom bond formation is among the fundamentally important reactions. This module covers the carbon-heteroatom bond-forming reactions using transition-metal-complex as well as the chiral Lewis acid catalyzed protocols.

### 1.1 Allylic Substitution

Much effort has been devoted on controlling the regioselectivity and enantioselectivity in allylic substitution of substrates **1** or **2** (Scheme 1). The palladium-catalyzed allylic substitution is versatile, however, the (*E*)-linear product **3** is often formed. Thus, the control of regioselectivity has been recently the main focus to provide product **4**.

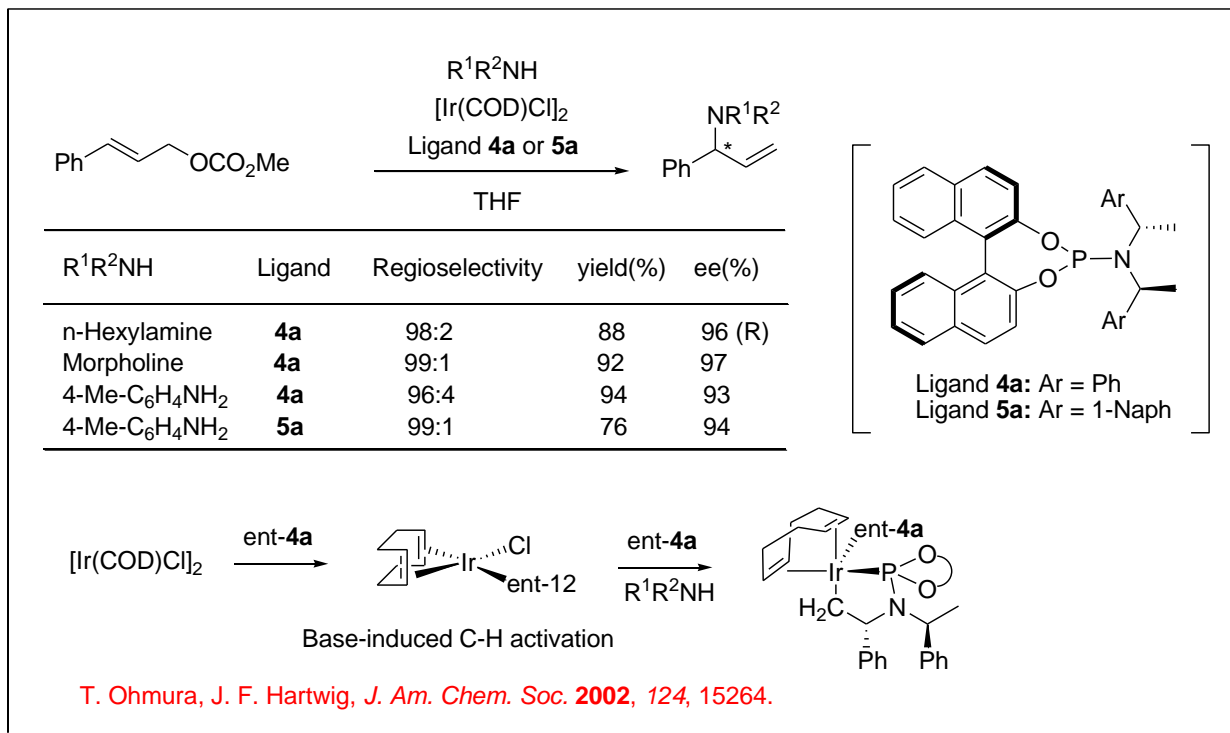


Scheme 1

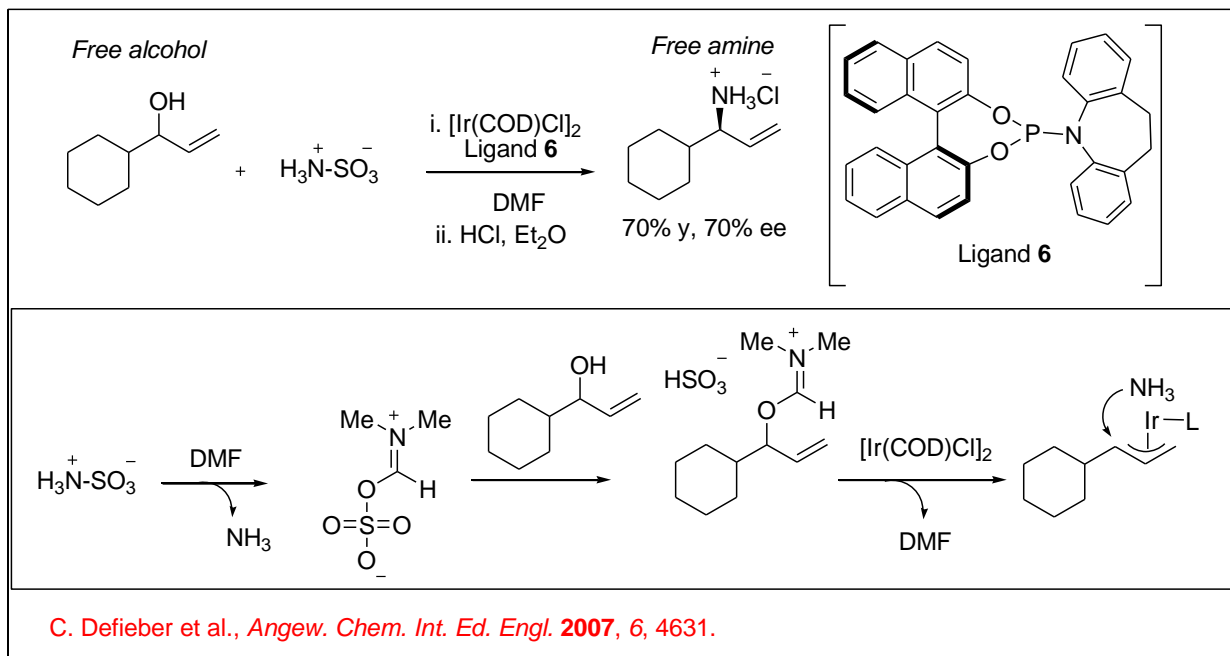
#### 1.1.1 Allylic Amination and Etherification of Allylic Alcohol Derivatives

Chiral iridium complex having phosphoramidate **4a** or **5a** has been shown to catalyze the allylic amination of carbonate to give branched product with excellent enantioselectivity (Scheme 2). An activated form of the iridium complex by *in situ* C-H activation at CH<sub>3</sub> group of a hindered ligand **4a** has been identified.

The direct reaction of allylic alcohols has been studied to give allylic amines in the presence of chiral iridium complex derived from [Ir(COD)Cl]<sub>2</sub> and ligand **6** (Scheme 3). In this reaction, sulfamic acid serves not only as a nitrogen source but also as an *in situ* activator of the hydroxyl group of the allylic alcohol

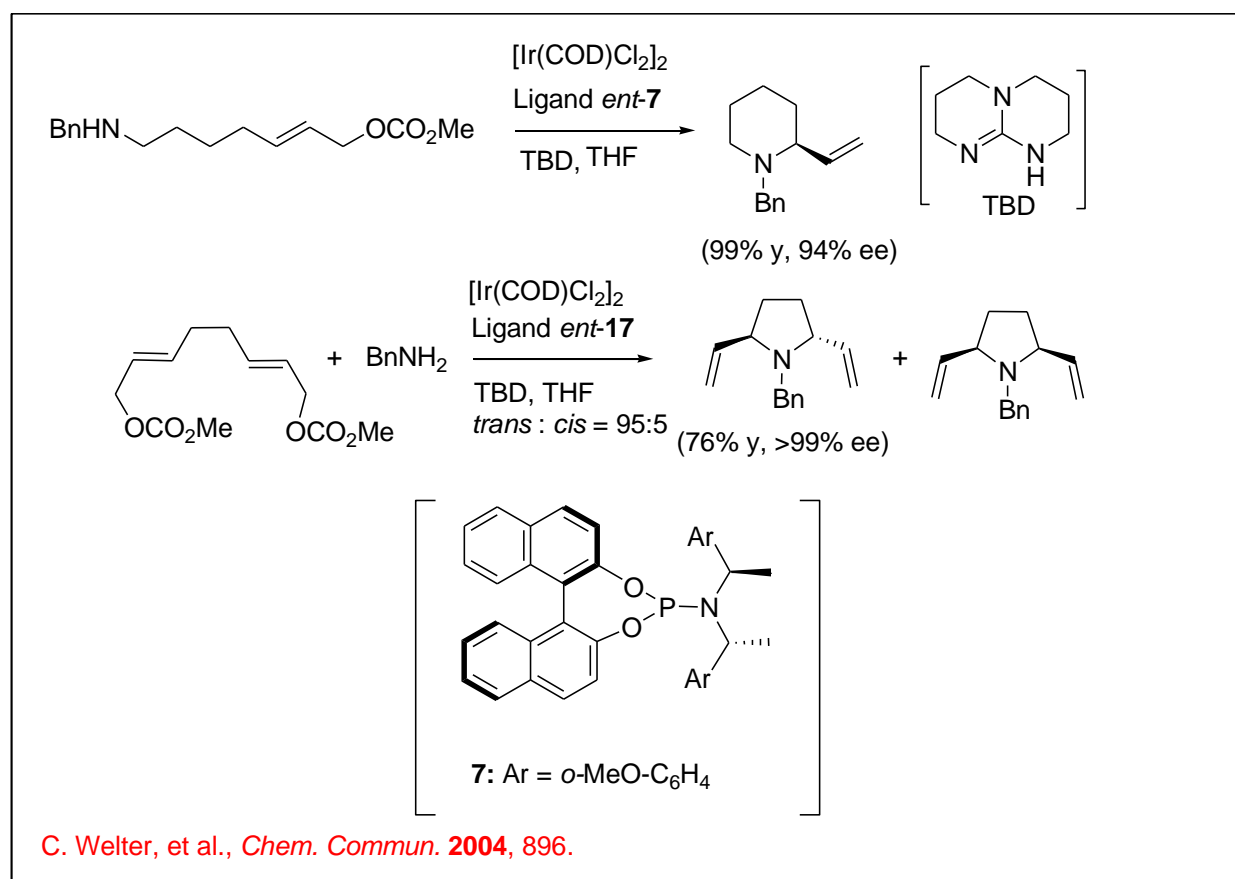


Scheme 2



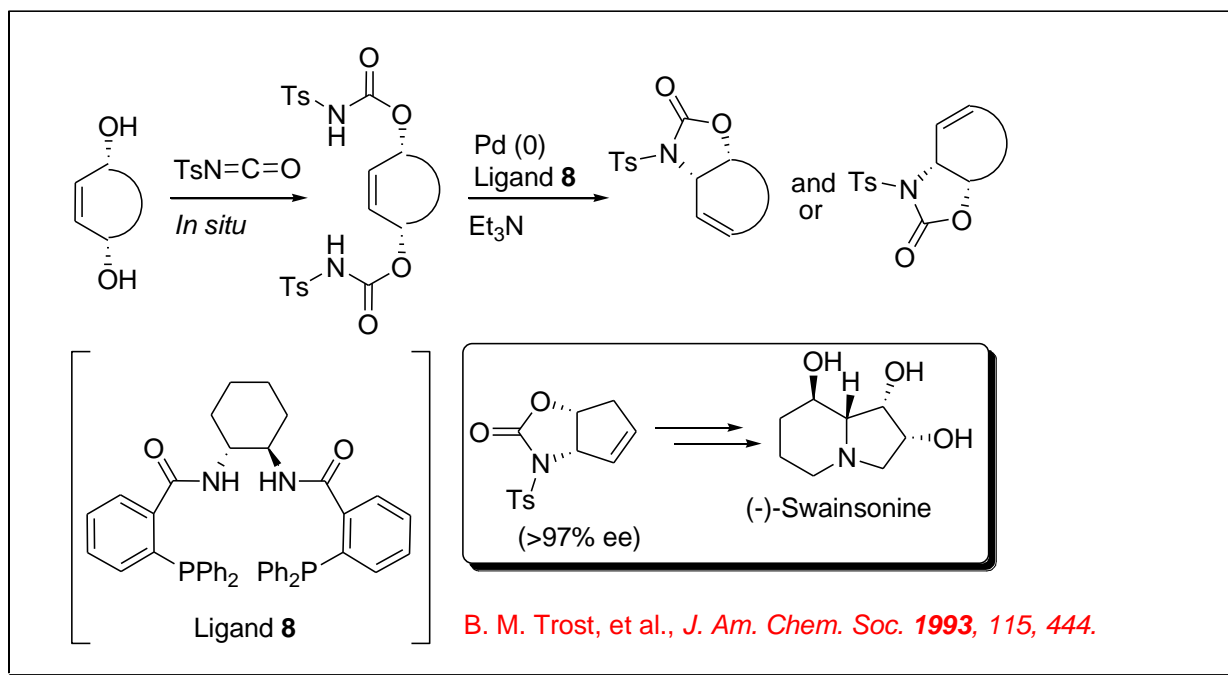
Scheme 3

Allylic amination is important for the construction of nitrogen-based heterocyclic compounds (Scheme 4). The enantioselective intramolecular allylic amination has been accomplished using chiral iridium complex derived from  $[\text{Ir}(\text{COD})\text{Cl}_2]_2$  and ligand **7**. Good enantioselectivity has been obtained upon activation using 1,5,7-triazabicyclo[4.4.0]undec-5-ene (TBD) as base. The catalytic system has also been used for the sequential aminations of *bis*-allylic carbonate *via* an inter- followed by an intramolecular reactions.



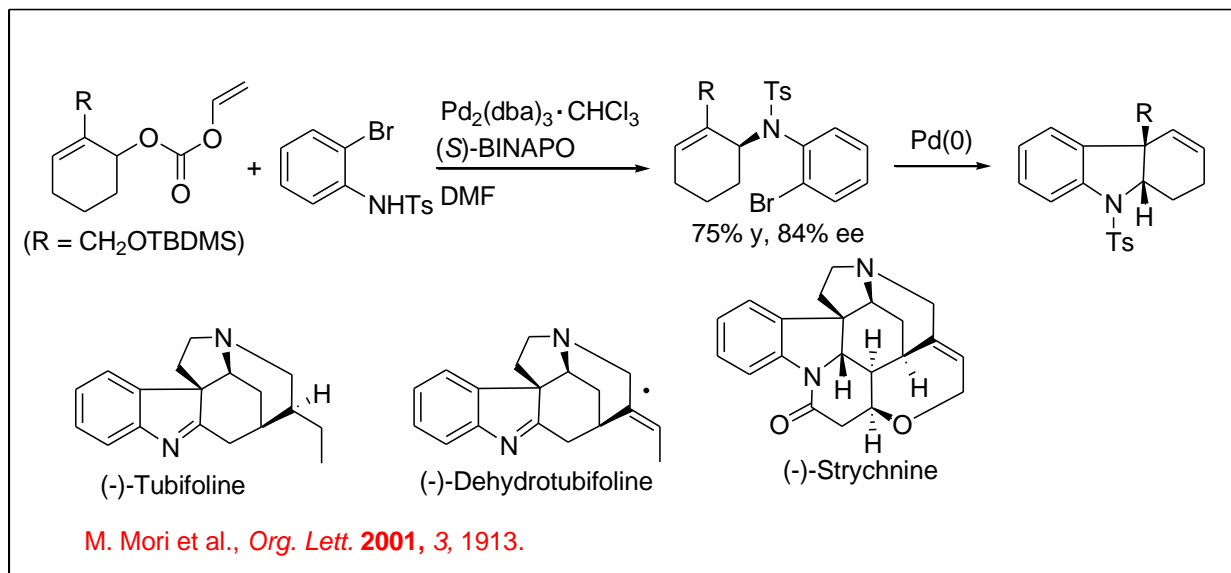
Scheme 4

Enantioselective allylic amination is also a powerful tool for the construction of natural products. For example, asymmetric desymmetrization of *meso*-diol with *p*-tosyl isocyanate using chiral palladium complex gives easy access to chiral nitrogen-substituted heterocycles which are precursor for the synthesis of (-)-swainsonine (Scheme 5).



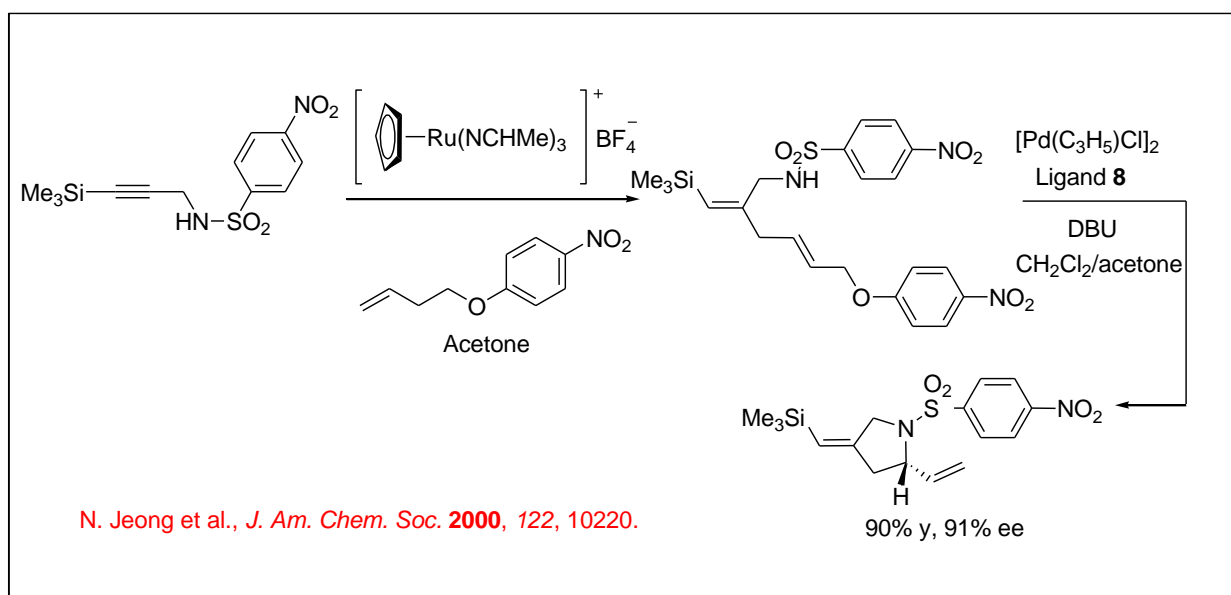
Scheme 5

The chiral palladium catalyzed enantioselective allylic amination has also been utilized for the total synthesis of (-)-tubifoline, (-)-dehydrotubifoline and (-)-strychnine (Scheme 6).



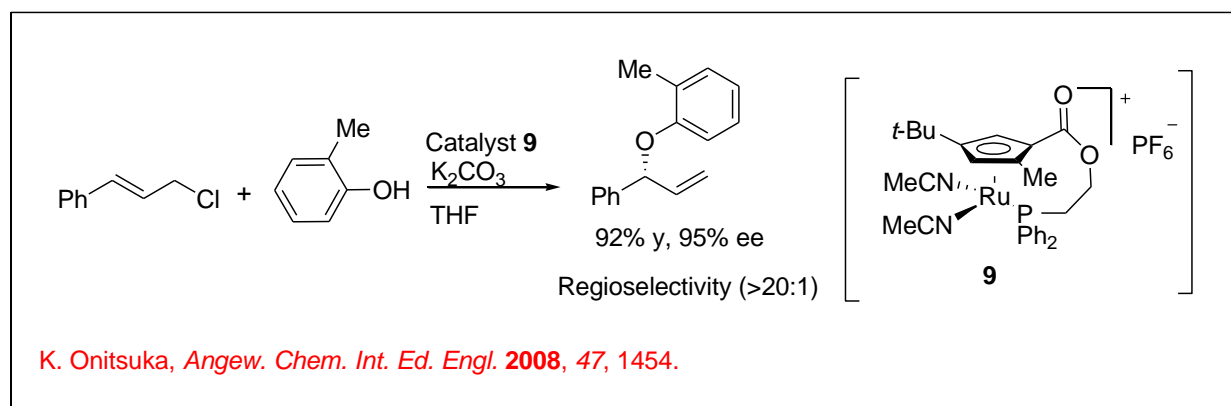
Scheme 6

The one-pot enantioselective synthesis of azacycle has been shown using a ruthenium-catalyzed ene-yne addition followed by a palladium-catalyzed asymmetric allylic amination (Scheme 7).



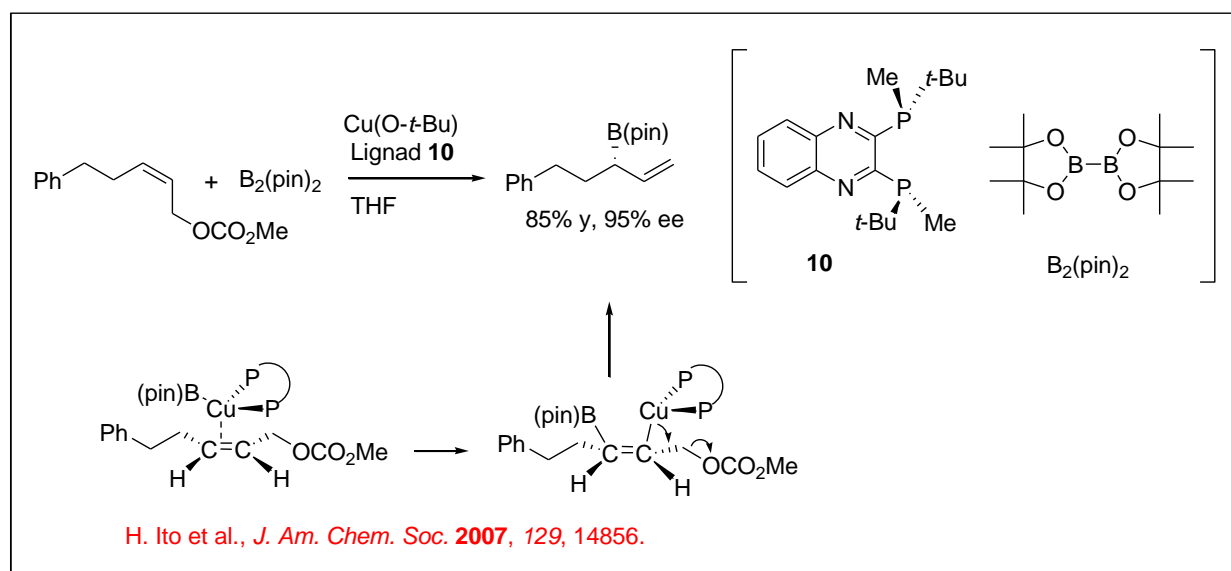
Scheme 7

The regio- and enantioselective allylic etherification has been studied using chiral ruthenium complex. For example, planar-chiral cyclopentadienyl ruthenium complex **9** catalyzes efficiently the reaction of cinnamoyl chloride with 3-methylphenol with high enantioselectivity and yield (Scheme 8).



Scheme 8

Enantioselective allylic substitution of carbonates with a diboron using copper(I)-based catalysts has been demonstrated. For example, Cu(I)-phosphine complex generated *in situ* from  $\text{Cu}(\text{O}-t\text{-Bu})$  with ligand **10** has been shown to catalyze the reaction of allylboronate with carbonate in excellent regioselectivity and enantioselectivity (Scheme 9). Addition-elimination mechanism having the generation of Cu-alkene  $\pi$ -complex and borylalkylcopper intermediate has been suggested.



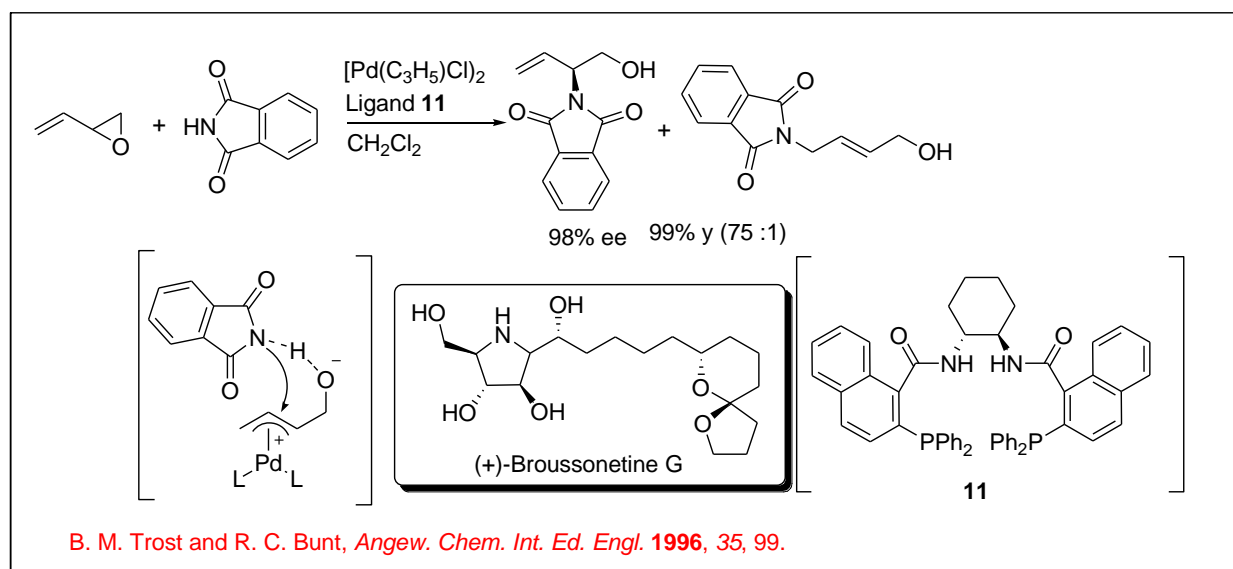
Scheme 9

### 1.1.2 Reaction of $\pi$ -Allyl Intermediates

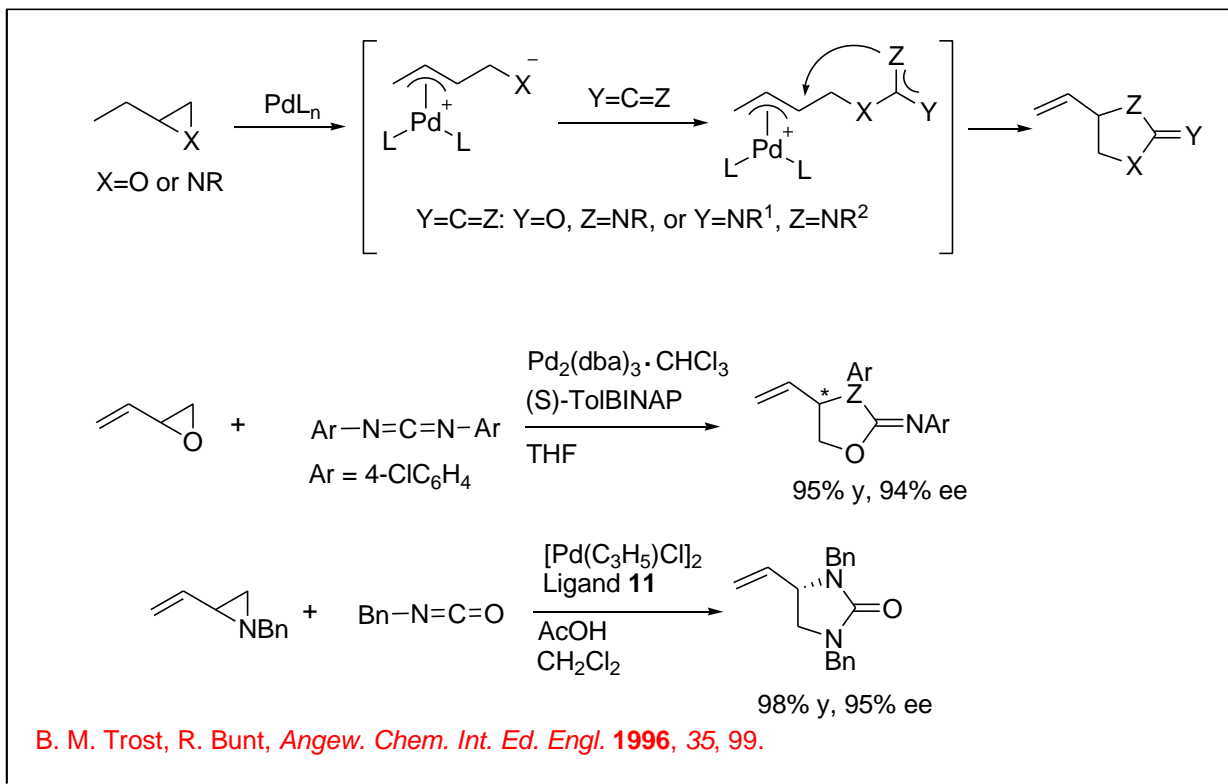
Nucleophilic attack of an amine to a  $\pi$ -allyl intermediate can afford an allylic amine derivative. For example, palladium complex derived from  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$  and ligand **11** catalyzes the reaction of racemic vinyloxirane with phthalimide in nearly quantitative yield (Scheme 10). Involvement of the hydrogen bond of the nucleophile to the oxygen leaving group is proposed to deliver the nucleophile to the adjacent carbon to provide the target molecule. The process has been utilized for the synthesis of (+)-broussonetine G.

Palladium based systems has also been utilized for the cycloaddition reaction of epoxides and aziridines with heterocumulenes (Scheme 11).

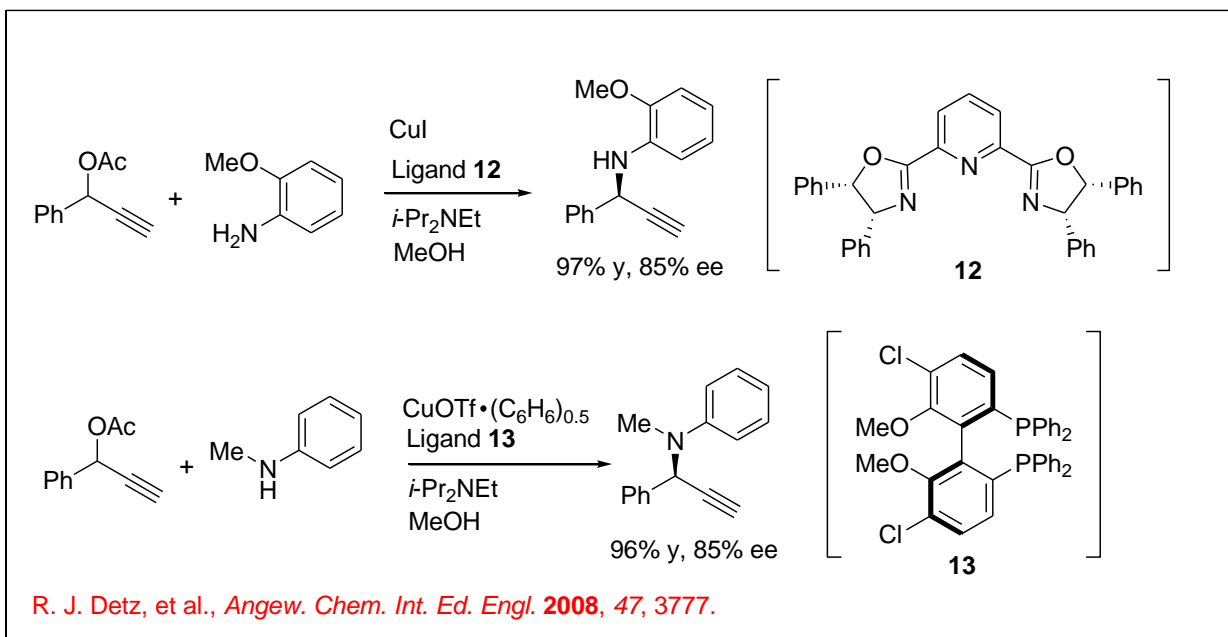
Enantioselective copper(I)-catalyzed substitution reactions of propargylic acetates with amines has been explored. For examples, copper complexes derived from copper(I) salts and ligands **12** and **13** catalyze the reaction of propargylic amination with 85% ee (Scheme 12).



Scheme 10



Scheme 11

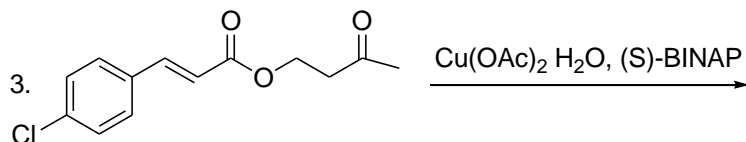
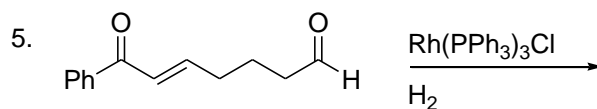
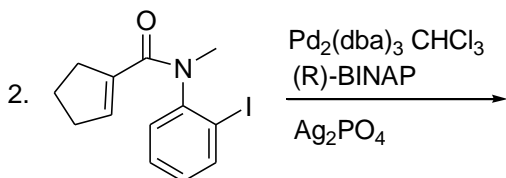
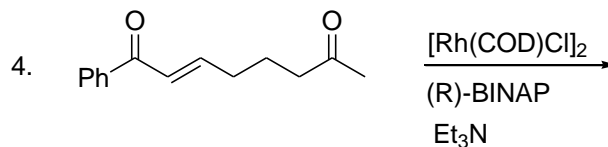
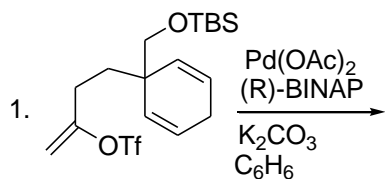


Scheme 12



**Problems**

- A. Give some examples for chiral Rh-catalyzed allylic substitution.
- B. Complete the following reactions.



**Reference**

- I. Ojima, *Catalytic Asymmetric Synthesis*, 3<sup>rd</sup> ed., Wiley, New Jersey, 2010.

