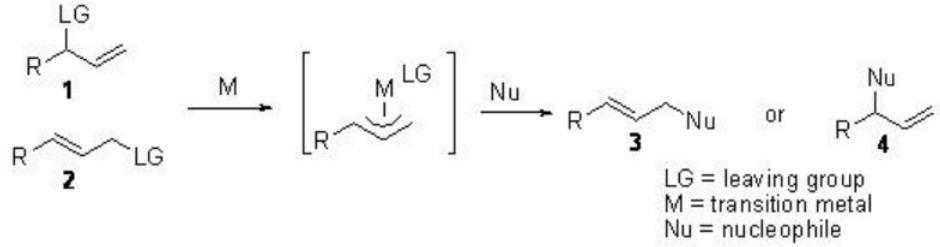
4.1: Allylic Substitution Reactions

Much effort has been devoted on controlling the regioselectivity and enantioselectivity in allylic substitution of substrates **1** or **2** (Scheme 4.1.1). 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**.

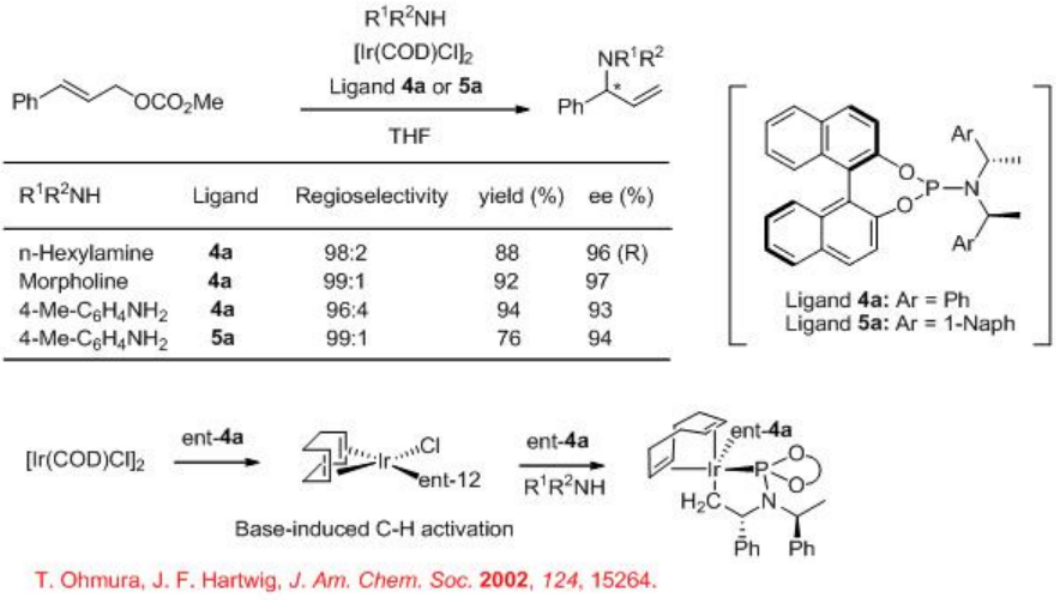


Scheme 4.1.1

4.1.1 Allylic Amination and Etherification of Allylic Alcohol Derivatives

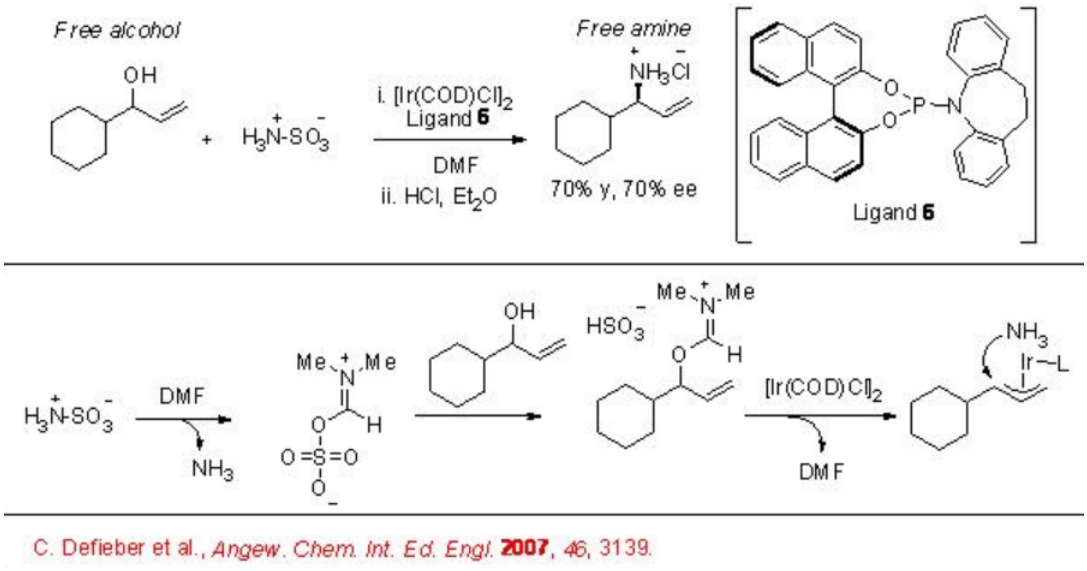
Chiral iridium complex having phosphoramidate **4a** or **5a** has been shown to catalyze the allylic amination of carbonate to give branched product with excellent enantioselectivity (Scheme 4.1.2). An activated form of the iridium complex by *in situ* C-H activation at CH_3 group of a hindered ligand **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 $[Ir(COD)Cl]_2$ and ligand **6** (Scheme 4.1.3). 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.



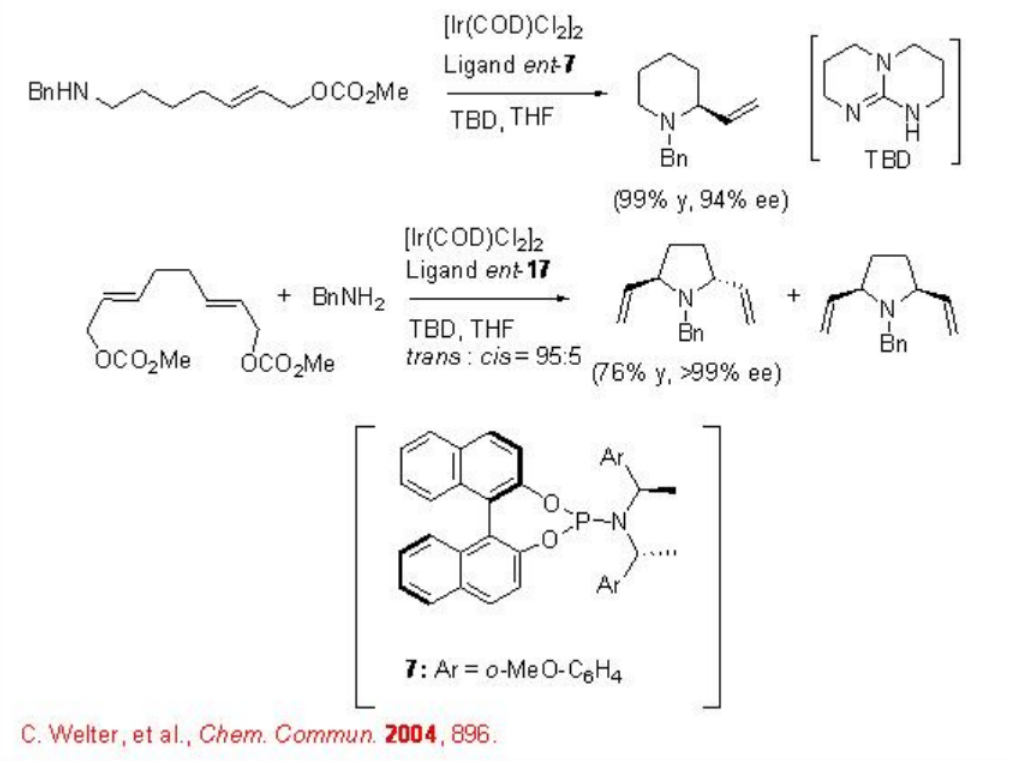
T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15264.

Scheme 4.1.2



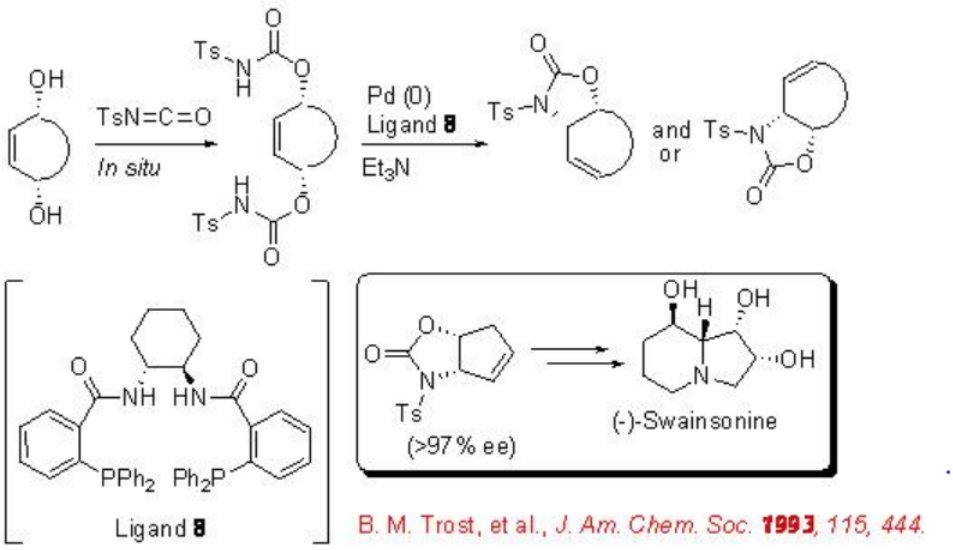
Scheme 4.1.3

Allylic amination is important for the construction of nitrogen-based heterocyclic compounds (Scheme 4.1.4). The enantioselective intramolecular allylic amination has been accomplished using chiral iridium complex derived from $[Ir(CDD)Cl_2]_2$ and ligand **7**. Good enantioselectivity has been obtained upon activation using 1,5,7-triazabicylo[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.



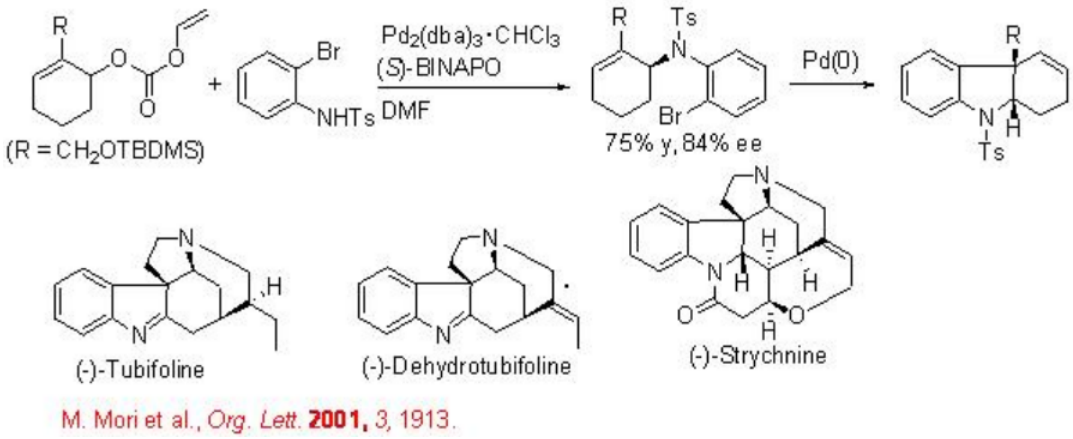
Scheme 4.1.4

Enantioselective allylic amination is also a powerful tool for the construction of natural products. For example, asymmetric desymmetrization of *meso* -diol with *p* -tosylisocyanate using chiral palladium complex gives easy access to chiral nitrogen-substituted heterocycles which are precursor for the synthesis of (-)-swainsonine (Scheme 4.1.5).



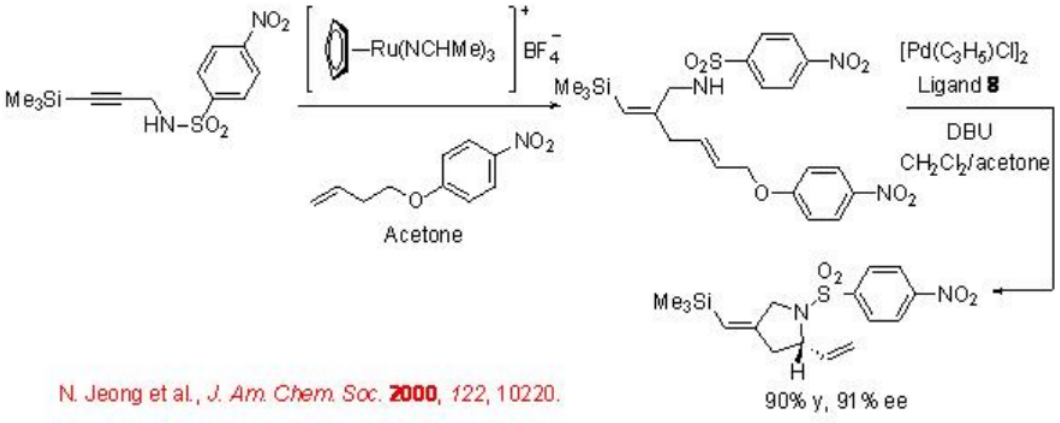
Scheme 4.1.5

The chiral palladium catalyzed enantioselective allylic amination has also been utilized for the total synthesis of (-)-tubifoline, (-)-dehydrotubifoline and (-)-strychnine (Scheme 4.1.6).



Scheme 4.1.6

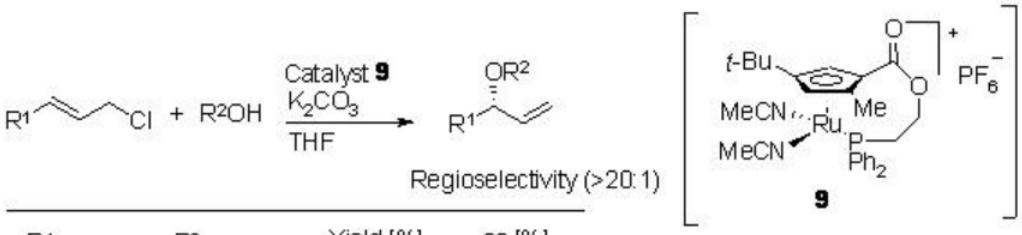
The one-pot enantioselective synthesis of azacycle has been shown using a ruthenium-catalyzed ene-yne addition followed by a palladium-catalyzed asymmetric allylic amination (Scheme 4.1.7).



N. Jeong et al., *J. Am. Chem. Soc.* **2000**, *122*, 10220.

Scheme 4.1.7

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 4.1.8).

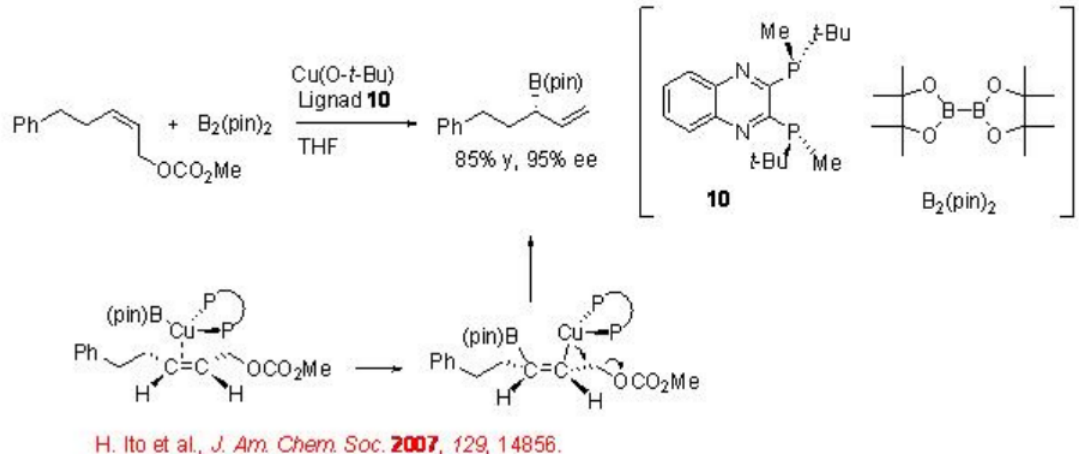


R1	R2	Yield [%]	ee [%]
Ph	Ph	99	92
Ph	4-$CF_3C_6H_4$	99	91
Ph	4-ClC_6H_4	98	93
4-$CF_3C_6H_4$	Ph	90	94
4-ClC_6H_4	Ph	96	86
Me	Ph	36	80
1-napthyl	Ph	98	82

K. Onitsuka, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 1454.

Scheme 4.1.8

Enantioselective allylic substitutions of carbonates with a diboron using copper(I)-based catalysts has been demonstrated. For example, Cu(I)-phosphine complex generated *in situ* from Cu(O-t-Bu) with ligand **10** has been shown to catalyze the reaction of allylboronate with carbonate in excellent regioselectivity and enantioselectivity (Scheme 4.1.9). Addition-elimination mechanism having the generation of Cu-alkene π -complex and borylalkylcopper intermediate has been suggested.



H. Ito et al., *J. Am. Chem. Soc.* **2007**, *129*, 14856.

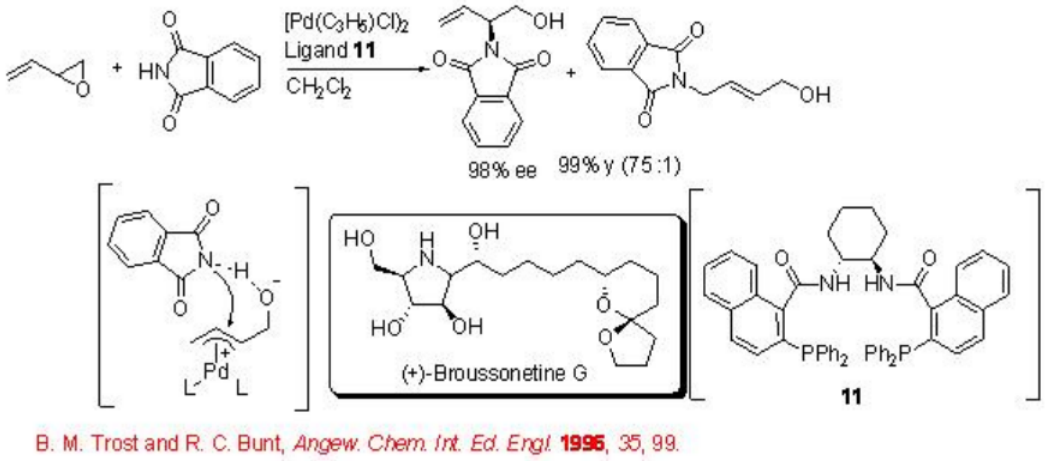
Scheme 4.1.9

4.1.2 Reaction of π -Allyl Intermediates

Nucleophilic attack of an amine to a π -allyl intermediate can afford an allylic amine derivative. For example, palladium complex derived from $[Pd(C_3H_5)Cl]_2$ and ligand **11** catalyzes the reaction of racemic vinyloxirane with phthalimide in nearly quantitative yield (Scheme 4.1.10). 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.

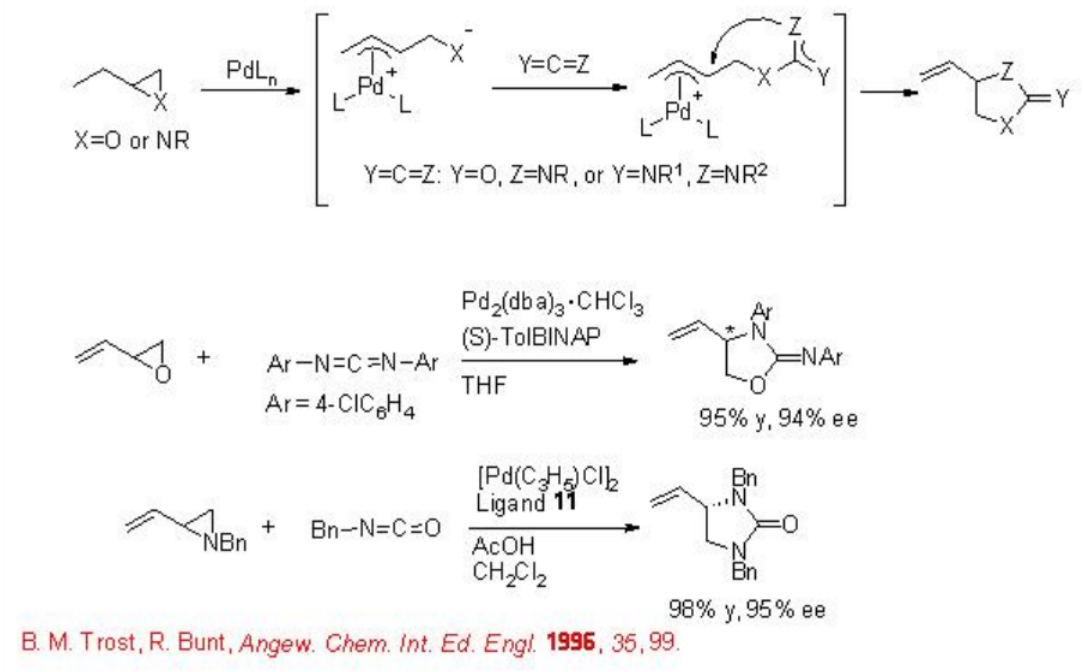
Palladium based systems has also been utilized for the cycloaddition reaction of epoxides and aziridines with heterocumulenes (Scheme 4.1.11).

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 4.1.12).

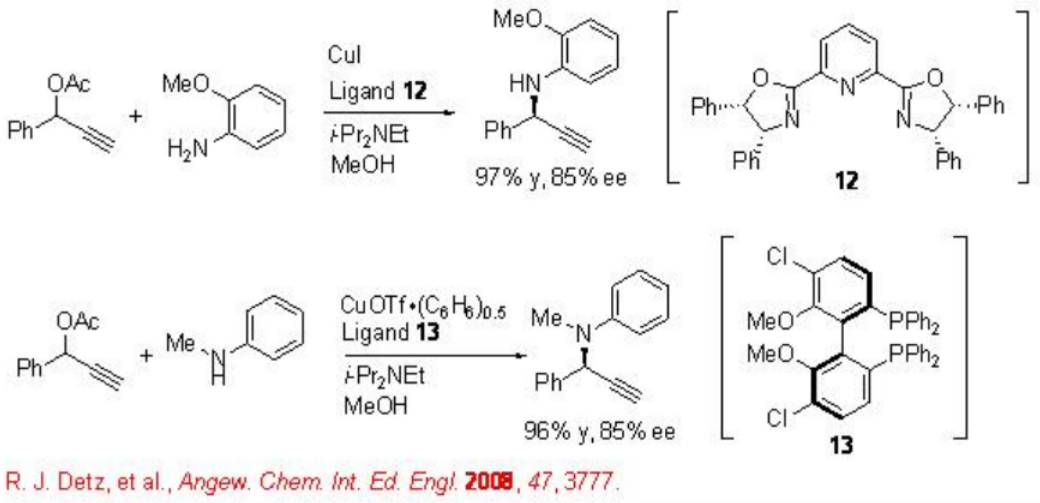


B. M. Trost and R. C. Bunt, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99.

Scheme 4.1.10



Scheme 4.1.11



Scheme 4.1.12