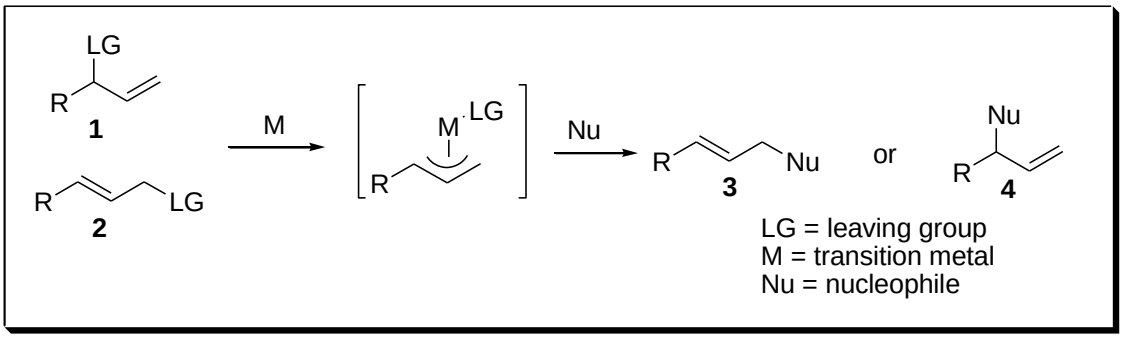
Lecture 13

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**.

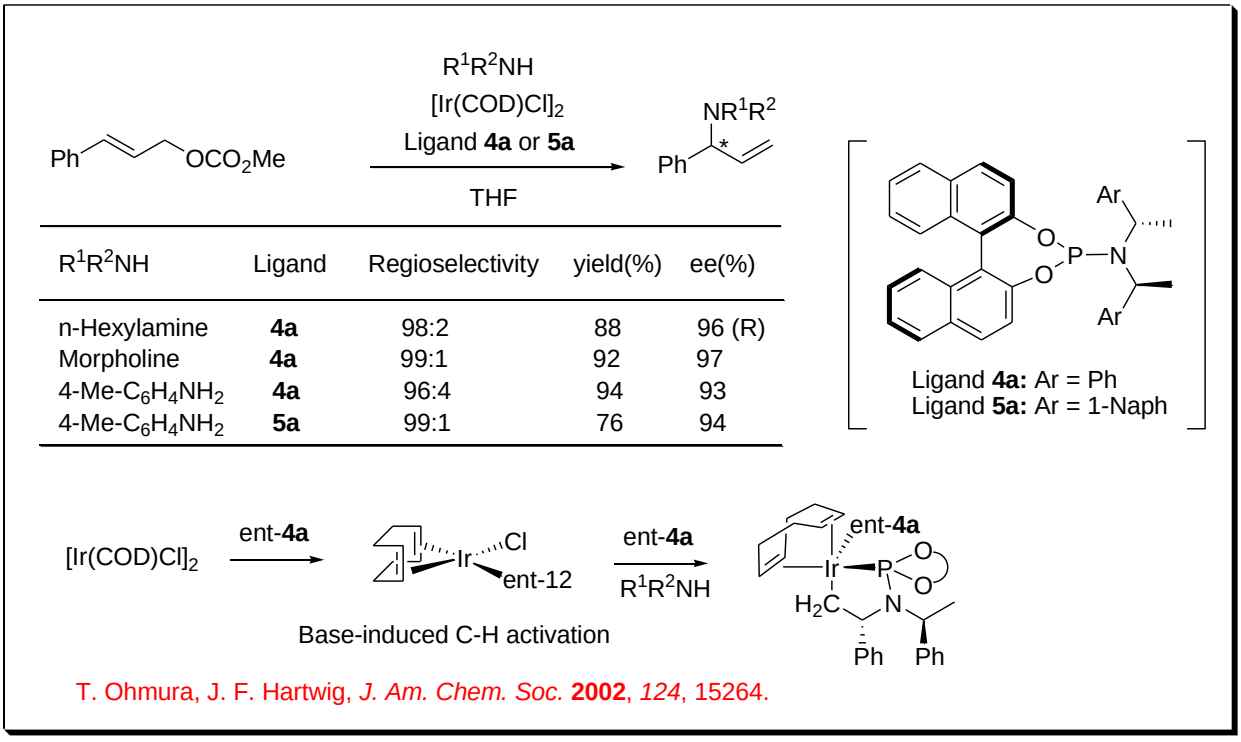


Scheme 1

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_3 group of a hindered ligand **4a** has been identified.

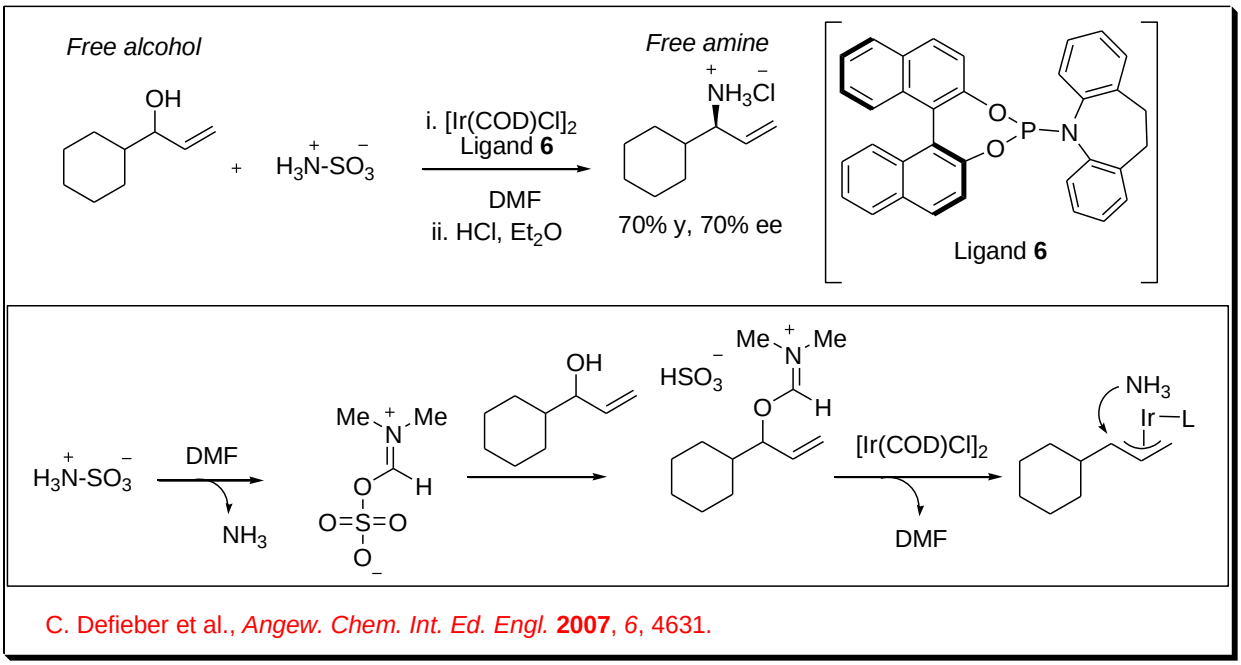
The direct reaction of allylic alcohols has been studied to give allylic amines in the presence of chiral iridium complex derived from $[Ir(COD)Cl]_2$ and ligand **6** (Scheme 3). In this reaction, sulfamic acid serves not only as a nitrogen source but also as an *in situ* activator of the hydroxyl group of the allylic alcohol



R^1R^2NH	Ligand	Regioselectivity	yield(%)	ee(%)
n-Hexylamine	**4a**	98:2	88	96 (R)
Morpholine	**4a**	99:1	92	97
4-Me-$C_6H_4NH_2$	**4a**	96:4	94	93
4-Me-$C_6H_4NH_2$	**5a**	99:1	76	94

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

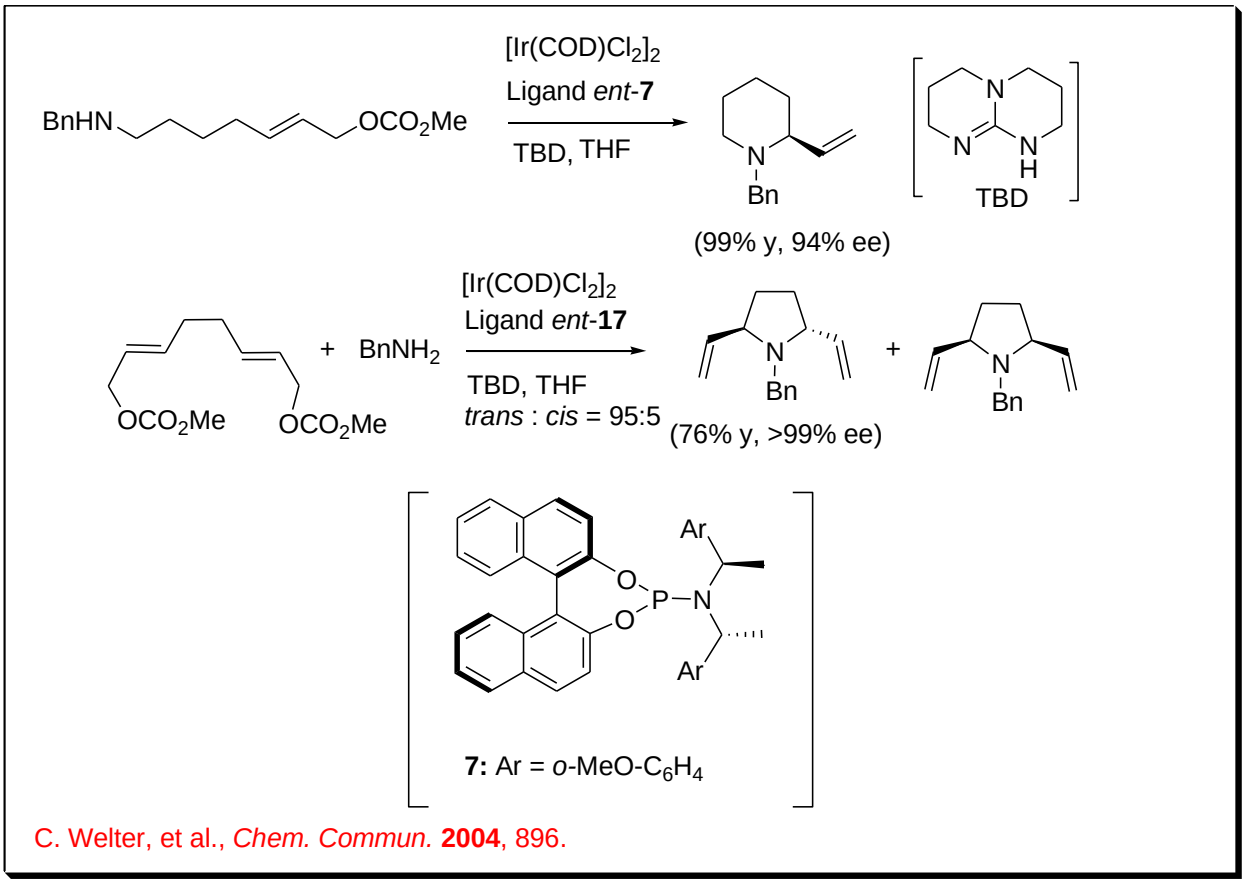
Scheme 2



C. Defieber et al., *Angew. Chem. Int. Ed. Engl.* **2007**, *6*, 4631.

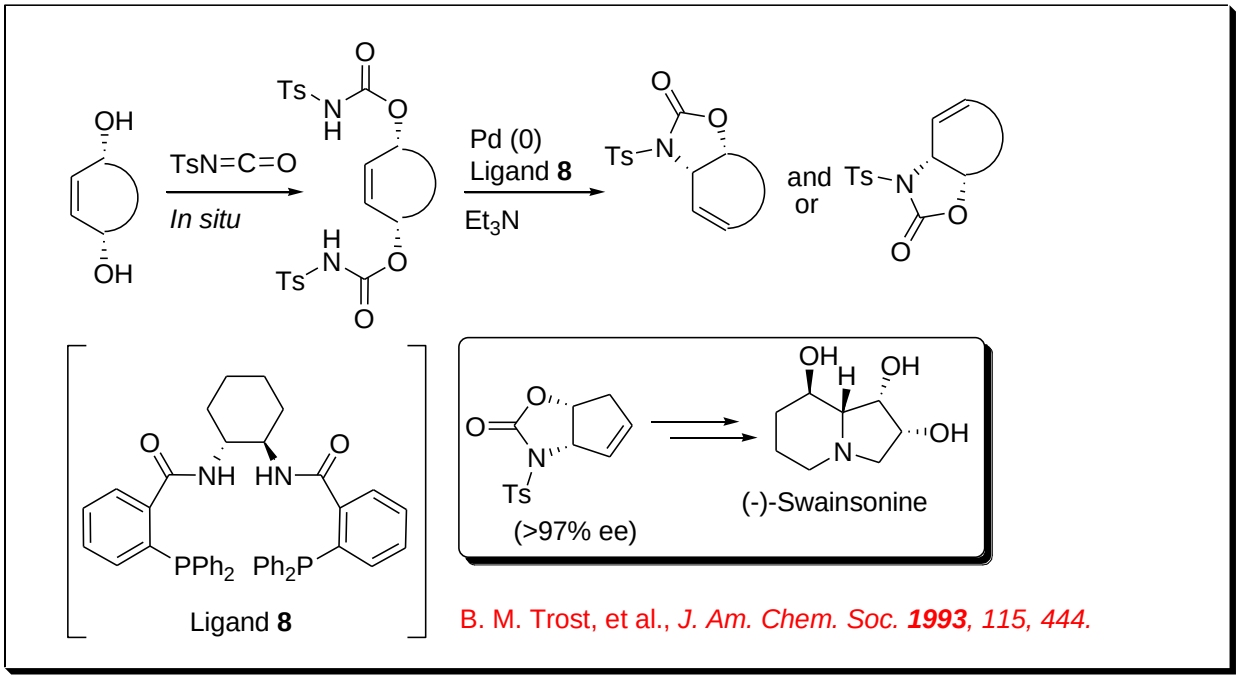
Scheme 3

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 $[Ir(CDD)Cl_2]_2$ 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.



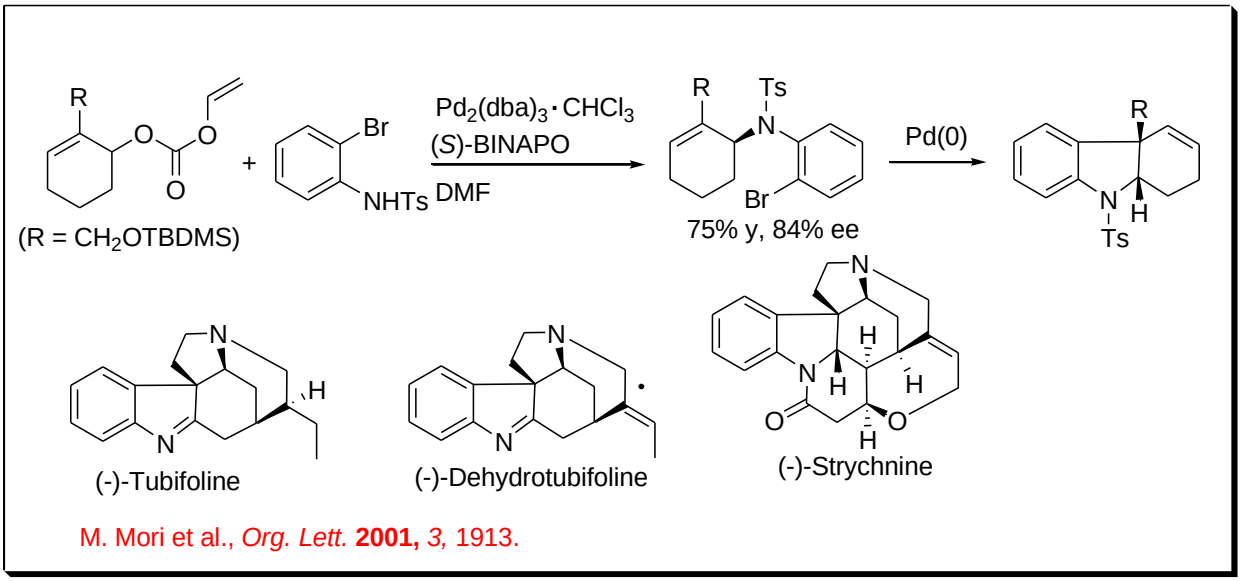
Scheme 4

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).



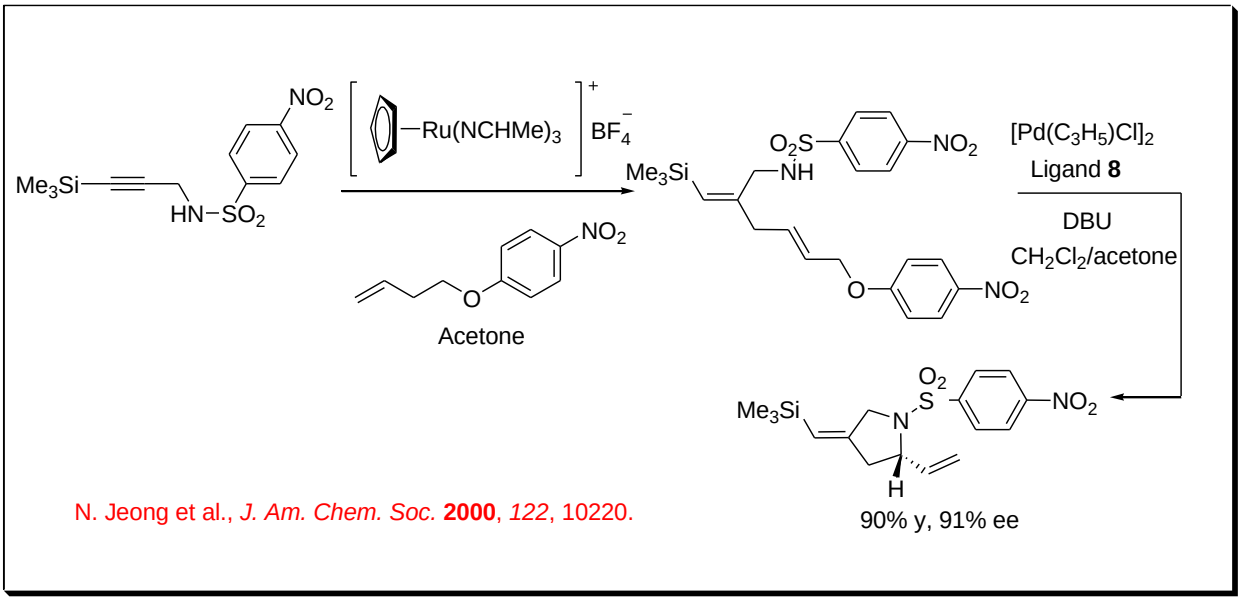
Scheme 5

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



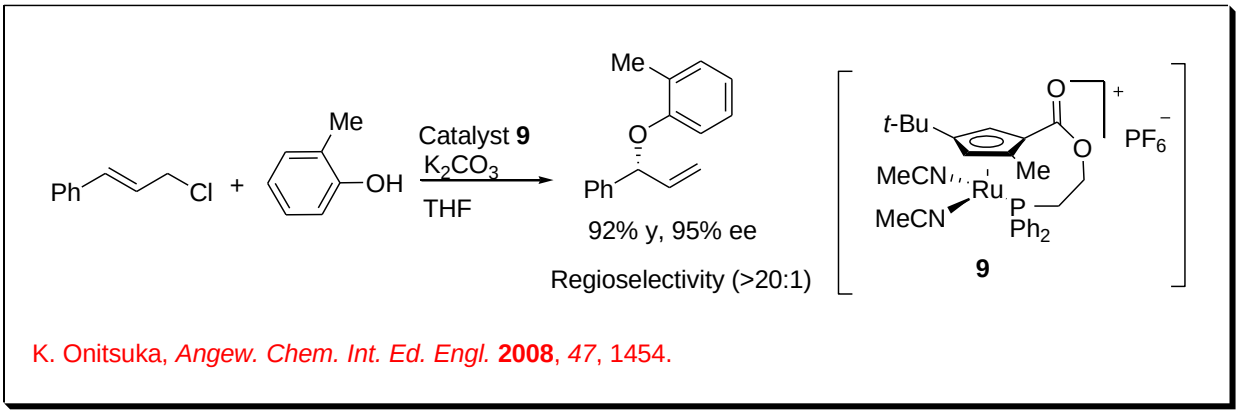
Scheme 6

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).



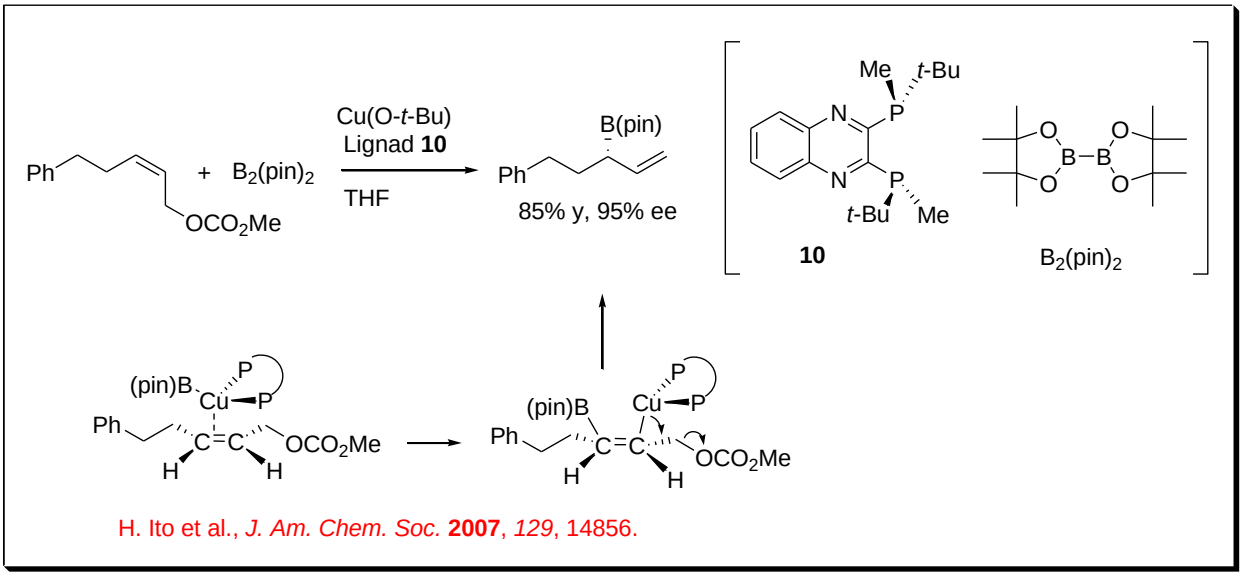
Scheme 7

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 Cu(O-t-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 π-complex and borylalkylcopper intermediate has been suggested.



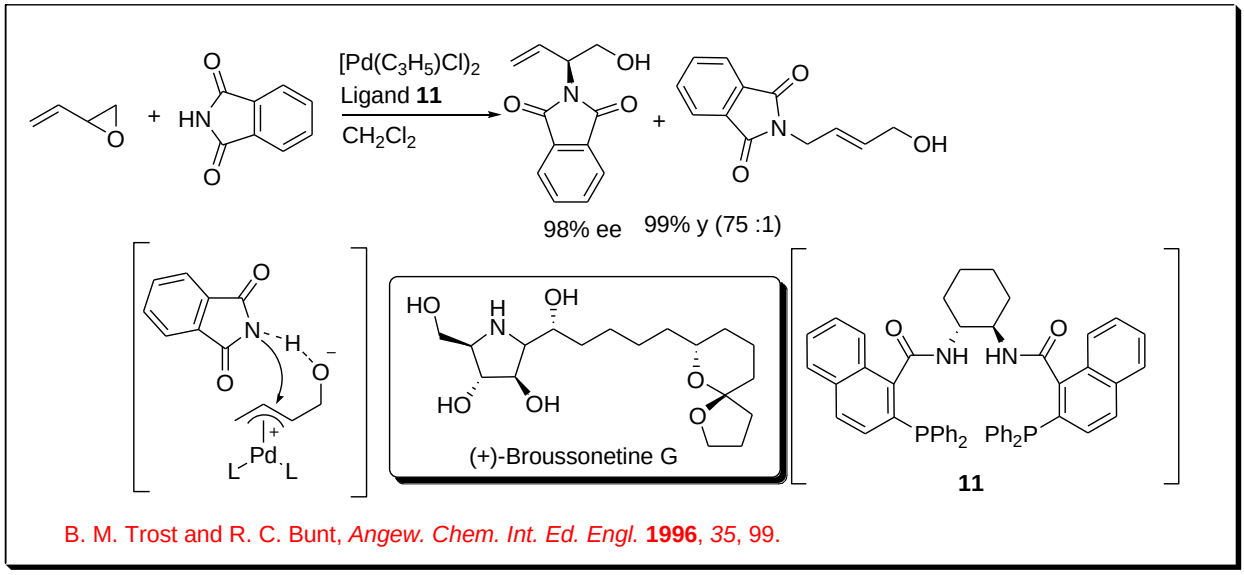
Scheme 9

1.1.2 Reaction of π-Allyl Intermediates

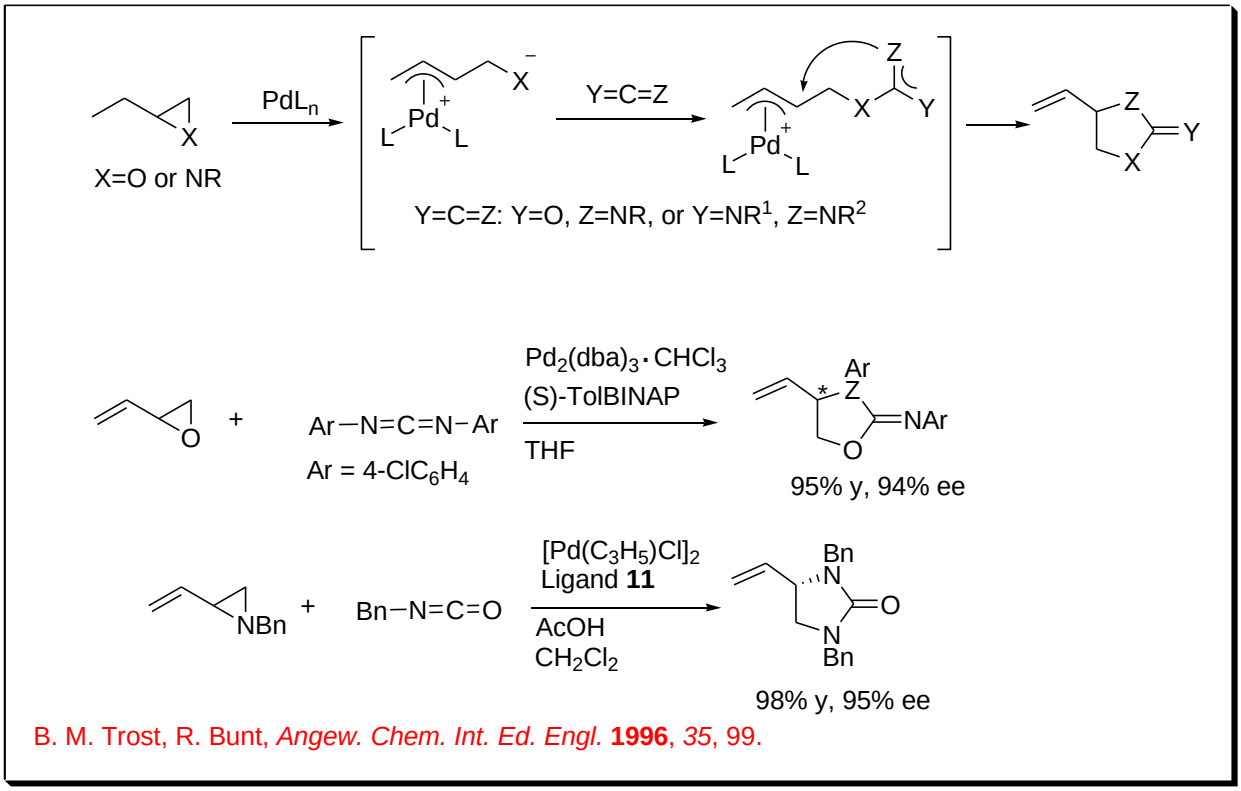
Nucleophilic attack of an amine to a π-allyl intermediate can afford an allylic amine derivative. For example, palladium complex derived from $[Pd(C_3H_5)Cl]_2$ and ligand **11** catalyzes the reaction of racemic vinyloxirane with phthalimide in nearly quantitative yield (Scheme 10). Involvement of the 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).

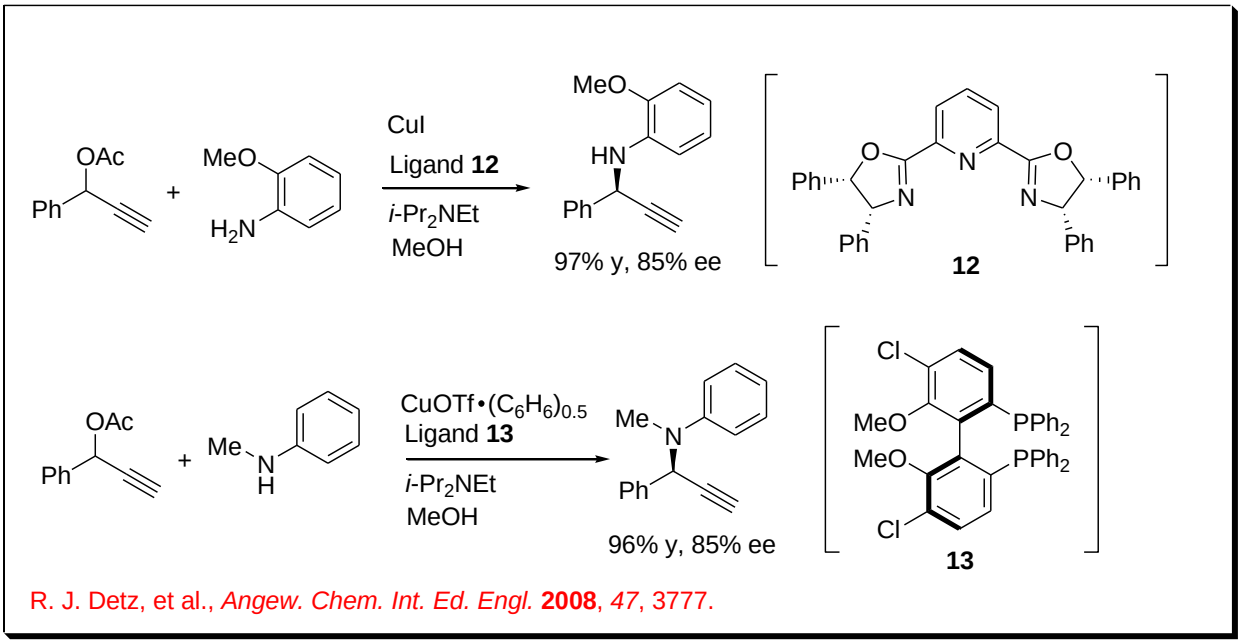
Enantioselective copper(I)-catalyzed substitution reactions of propargylic acetates with amines has been explored. For examples, copper complexes derivеded from copper(I) salts and ligands **12** and **13** catalyze the reaction of propargylic amination with 85% ee (Scheme 12).



Scheme 10



Scheme 11

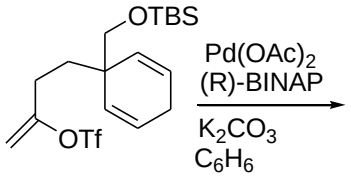


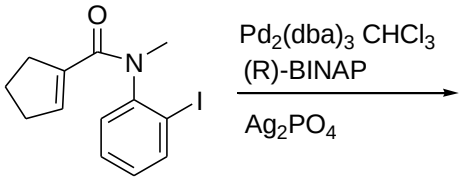
Scheme 12

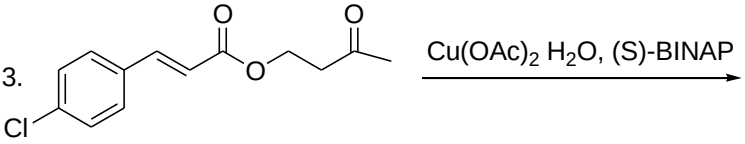
Problems

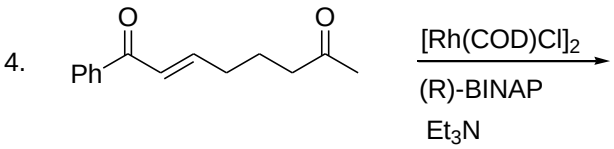
A. Give some examples for chiral Rh-catalyzed allylic substitution.

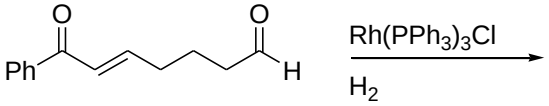
B. Complete the following reactions.

1. 

2. 

3. 

4. 

5. 

Reference

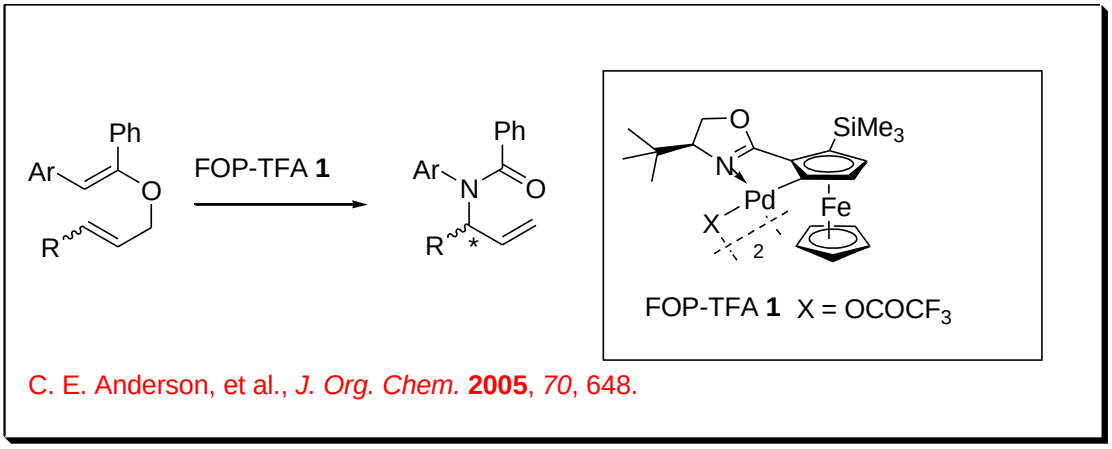
I. Ojima, Catalytic Asymmetric Synthesis, 3rd ed., Wiley, New Jersey, 2010.

Lecture 14

Carbon-Heteroatom Bond-Forming Reactions II

4.2 Aza-Claisen Rearrangement and Related Reactions

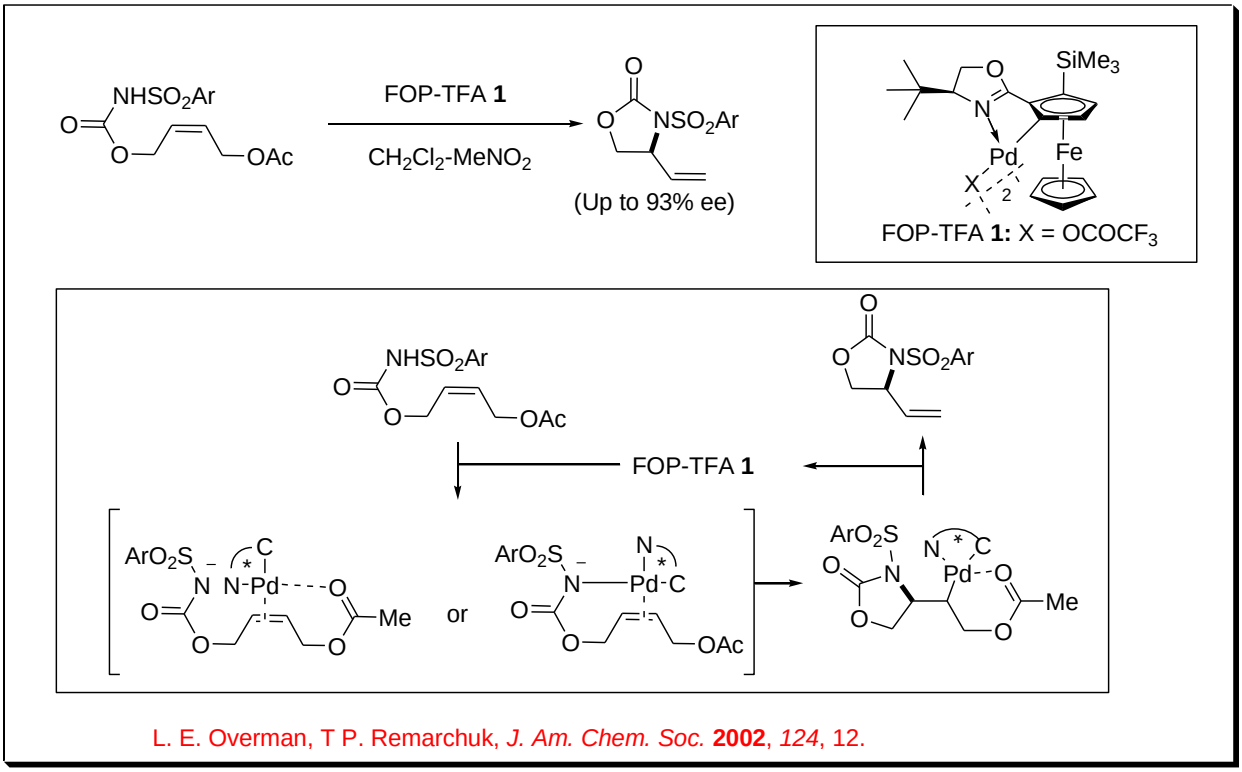
Aza-Claisen rearrangement, known as the Overman rearrangement, has been extensively studied that allows us to synthesize chiral allylic amines from achiral allylic imidates with excellent enantioselectivity. For example, prochiral *N*-arylbenzimidates can be converted into chiral *N*-arylbenzamides in the presence of ferrocenyloxazoline palladacycle, FOP-TFA, (Scheme 1).



Scheme 1

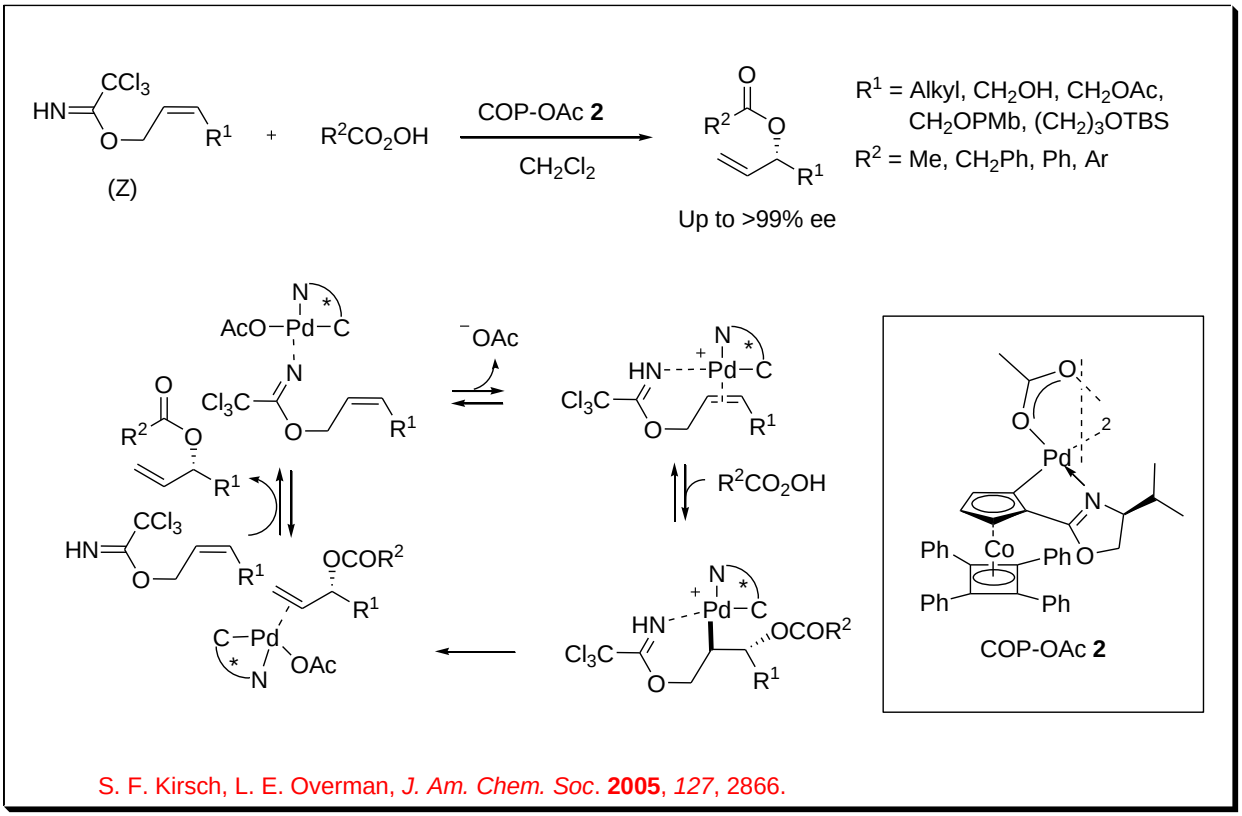
This catalytic system has also been shown to promote the cyclization of allylic N-arylsulfonylcarbamates to give five-membered nitrogen containing heterocycles (Scheme 2). An involvement of aminopalladation of the alkene followed by insertion of the alkene into the Pd-N has been proposed.

This procedure has also been extended for the allylic etherification reaction. For example, the reaction of (*Z*)-allylic trichloroacetimidates with carboxylic acids in the presence of COP-OAc gives chiral allylic esters in high enantiopurity (Scheme 3). Under these reaction conditions, *E*-stereoisomer show inferior results. In these reactions, the COP-OAc activates the carbon-carbon double bond for attack by external oxygen nucleophile and the trichloroacetimidate group serves as a leaving group along with templating the catalyst to the double bond.



L. E. Overman, T P. Remarchuk, *J. Am. Chem. Soc.* **2002**, *124*, 12.

Scheme 2

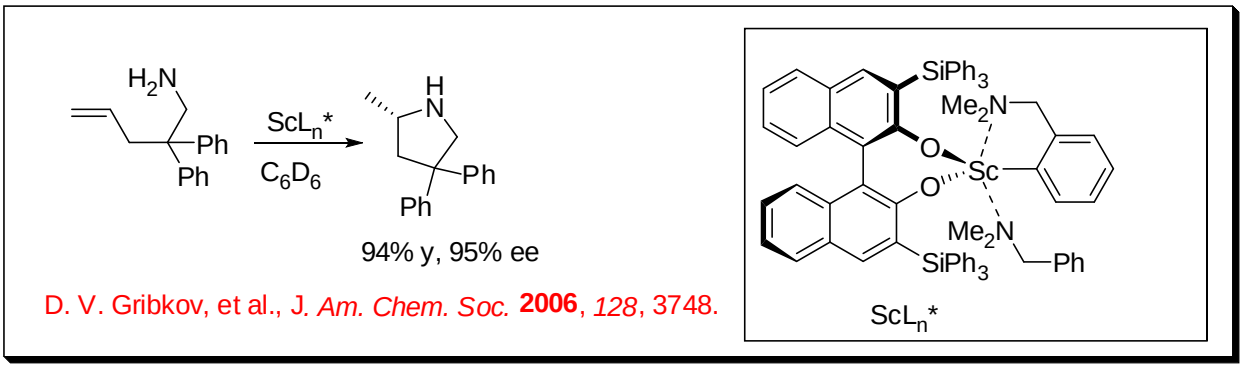


S. F. Kirsch, L. E. Overman, *J. Am. Chem. Soc*. **2005**, *127*, 2866.

Scheme 3

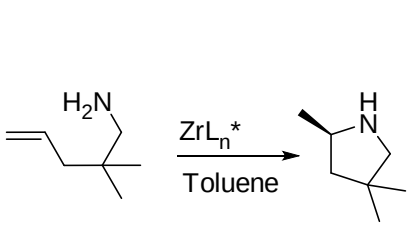
4.3 Hydroamination of Alkenes

Scandium 3,3'-tris(phenylsilyl)binaphtholatecan be used as a highly active catalyst for the synthesis of pyrrolidine *via* intramolecular hydroamination (Scheme 4).

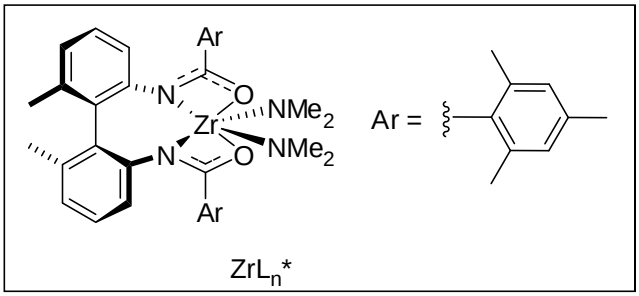


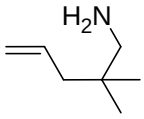
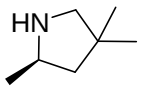
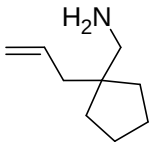
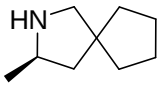
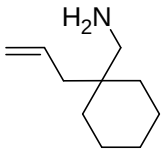
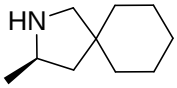
Scheme 4

Chiral neutral zirconium amidate has been used for hydroamination of primary aminoalkenes with 93% ee (Scheme 5).



80% y, 93% ee



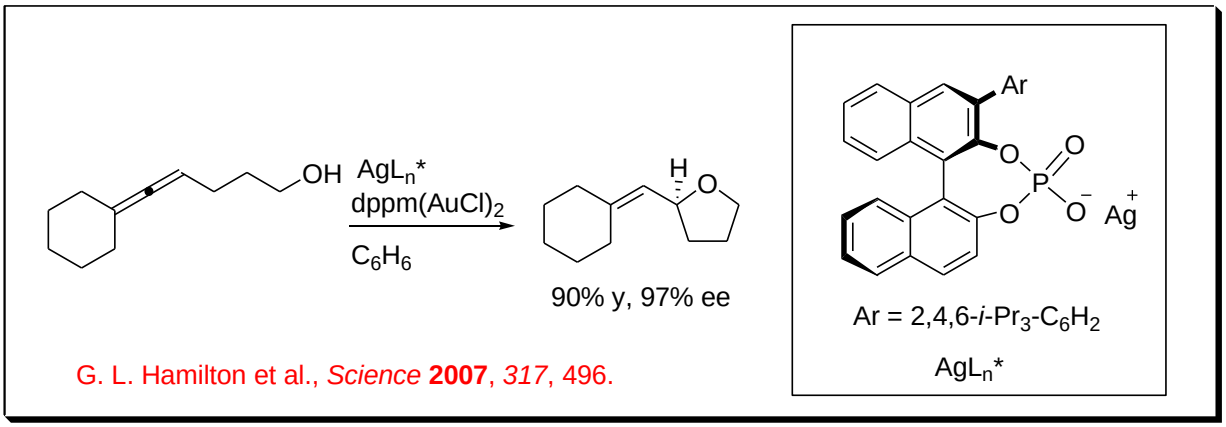
Aminoalkene	Product	Yield [%]	ee [%]
		80	93
		91	88
		96	82

M. C. Wood, et al., *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 354.

Scheme 5

4.4 Hydroalkoxylation of Allenes

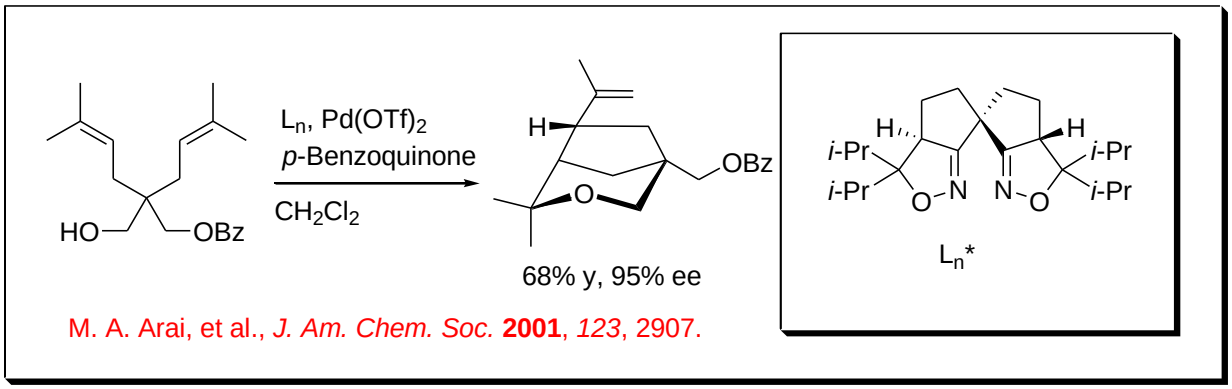
Hydroalkoxylation of allenes has been accomplished using a catalytic 1:2 mixture of the dppm$(AuCl)_2$ and chiral silver phosphonate to give furan with 97% ee (Scheme 6).



Scheme 6

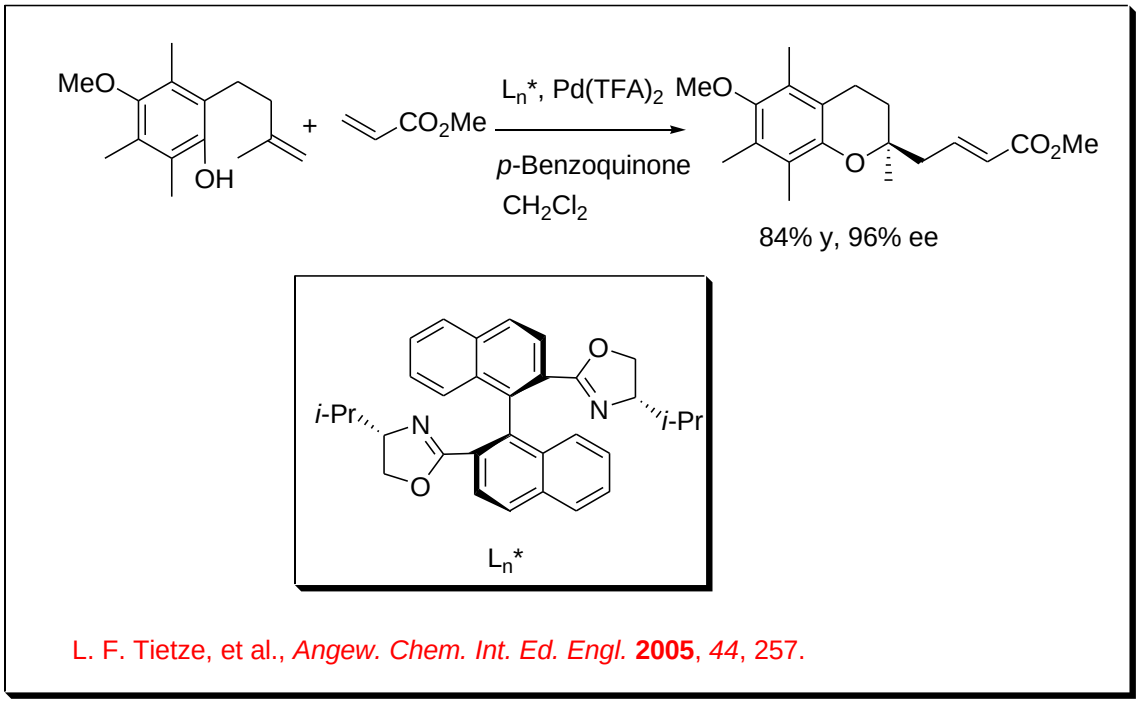
4.5 Oxidation Reactions

Wacker-type tandem cyclization reaction of alkenyl alcohol is reported using chiral palladium(II)-spirobis(isoxazoline) with excellent enantioselectivity (Scheme 7). In this reaction, benzoquinone reoxidizes the reduced palladium(0) to palladium(II) species.



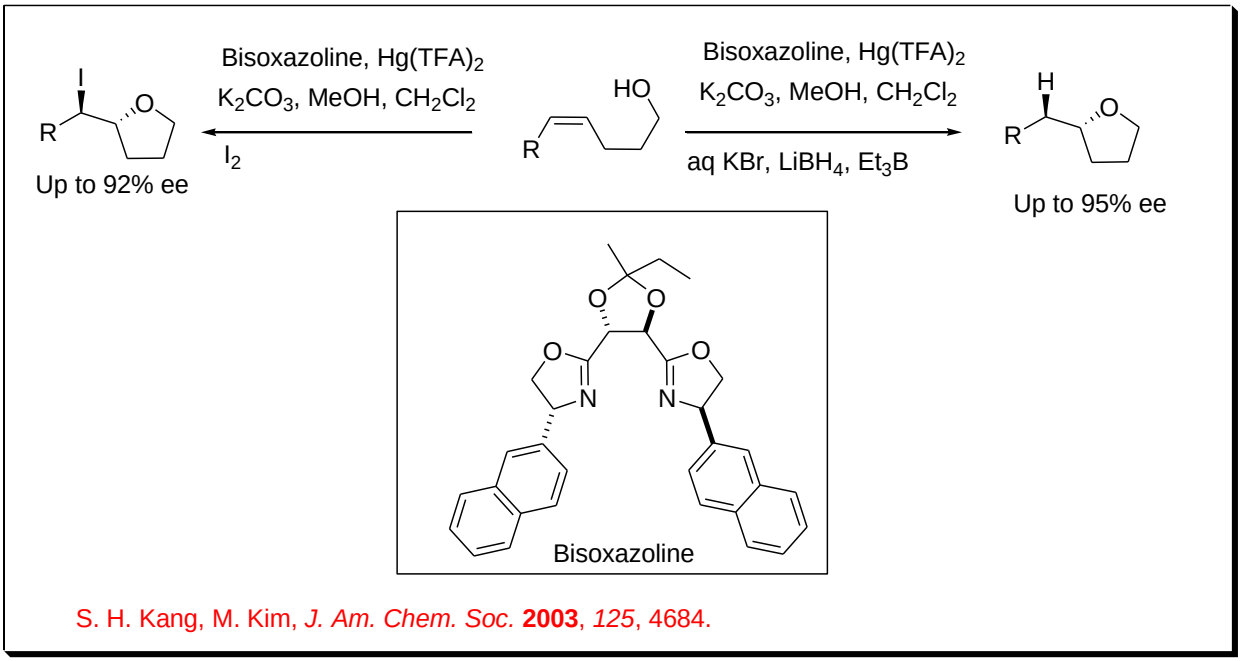
Scheme 7

Palladium complex derived from $Pd(TFA)_2$ and (*S,S*)-BOXAX has been found to be effective for the synthesis of chiral chroman framework in the presence of benzoquinone (Scheme 8).



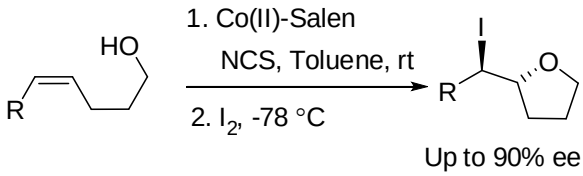
Scheme 8

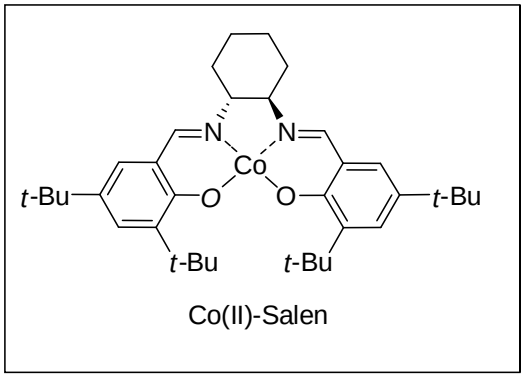
The mercury(II) complex derived from $Hg(TFA)_2$ and bisoxazoline has been used for the mercuriocyclizationwith high enantioselectivity (Scheme 9).



Scheme 9

Chiral cobalt(II)-salen has been used for the enantioselective intramolecular iodoetherification to procure 2-substituted tetrahydrofurans with up to 90% ee (Scheme 10).





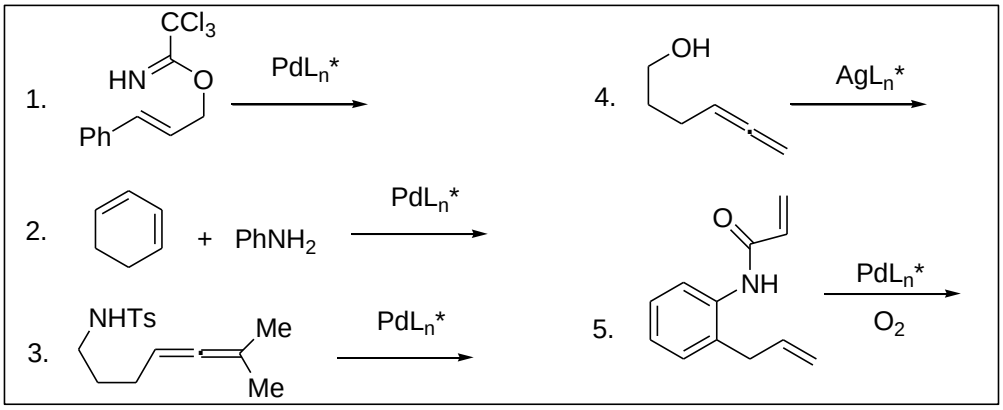
R	Yield [%]	ee [%]
$(CH_2)_3Ph$	94	84
Me	96	67
Et	89	82
n-Pr	85	85
i-Pr	83	73
$(CH_2)_3OTr$	89	90

S. H. Kang, et al., *J. Am. Chem. Soc.* **2003**, *125*, 15748.

Scheme 10

Problems

C. Complete the following reactions.



D. Provide some examples for the chiral Y and Au-catalyzed hydroamination reactions.

Reference/Text Book

1. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

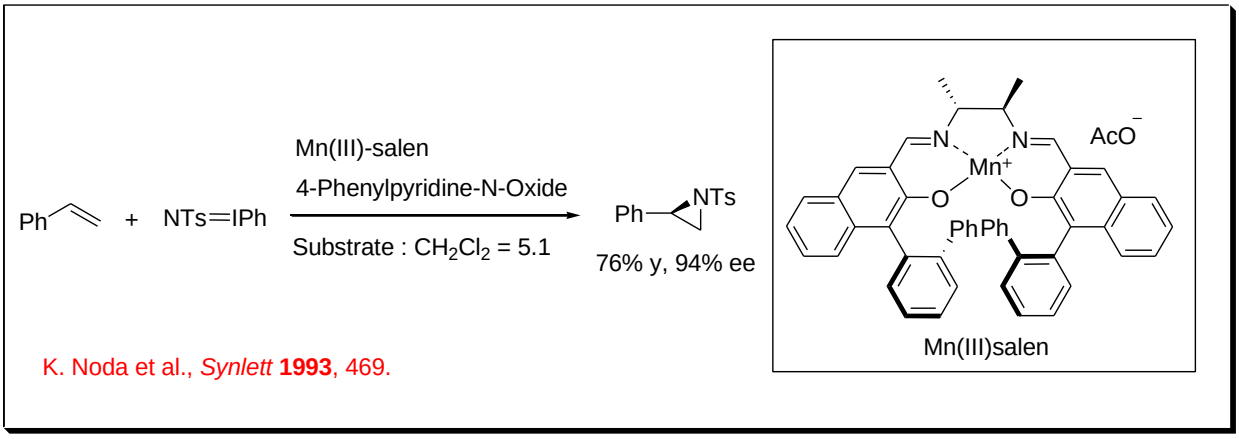
2. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

Lecture 15

Carbon-Heteroatom Bond-Forming Reactions III

4.6Aziridination of Alkenes

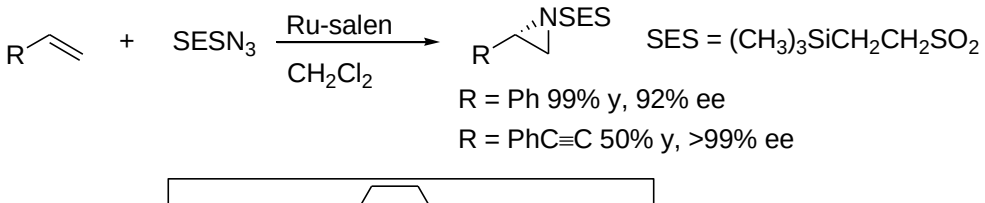
The aziridination of alkenes has been successfully accomplished using chiral Mn-salen with 94% ee. The presence of catalytic amount of 4-phenylpyridine-*N*-oxide leads to enhancement in the enantioselectivity (Scheme 1).



Scheme 1

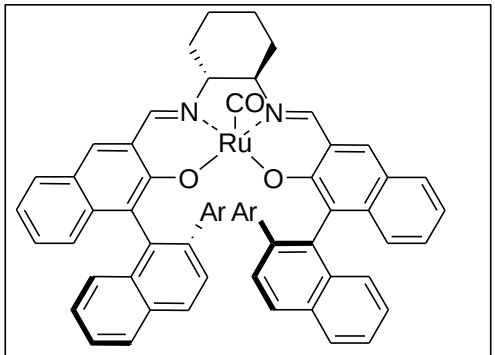
Chiral Ru(salen)(CO) can be utilized for the aziridination using 2-(trimethylsilyl)ethanesulfonyl (SES) group as a nitrene precursor, because the SES group is an easily removable *N*-protecting group under milder conditions (Scheme 2). These reaction conditions are compatible for the reactions of conjugated alkenes with high enantioselectivity.

Although the aziridination of alkenes has been explored well, the reaction of enols remains elusive. The aziridination of enols generally lead to □-amino ketones via the ring opening process of the aziridine intermediates. The chiral dirhodium complex, Rh_2(*S*-TFPTTL)$_4$, catalyses efficiently the amination of enol ethers employing NsN=IPh as nitrogen source (Scheme 3). The use of the *N*-2-nitrophenylsulfonyl (Ns) group is synthetically valuable, because the alkylation and deprotection of *N*-monosubstituted Ns-amide takes under milder conditions. The application of this protocol has been shown in the formal synthesis of (-)-metazocine.



R = Ph 99% y, 92% ee

R = PhC≡C 50% y, >99% ee

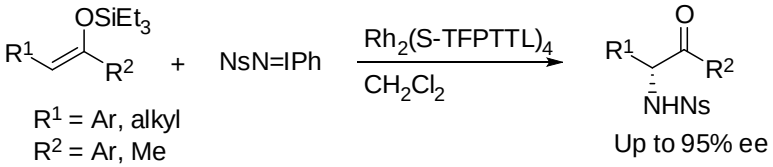


Ru-salen

Ar = 3,5-Cl_2-4-$(CH_3)_3SiC_6H_2$

H. Kawabata et al., *Tetrahedron Lett.* **2006**, *47*, 1571.

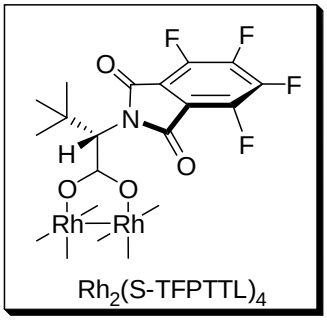
Scheme 2



R^1 = Ar, alkyl

R^2 = Ar, Me

Up to 95% ee



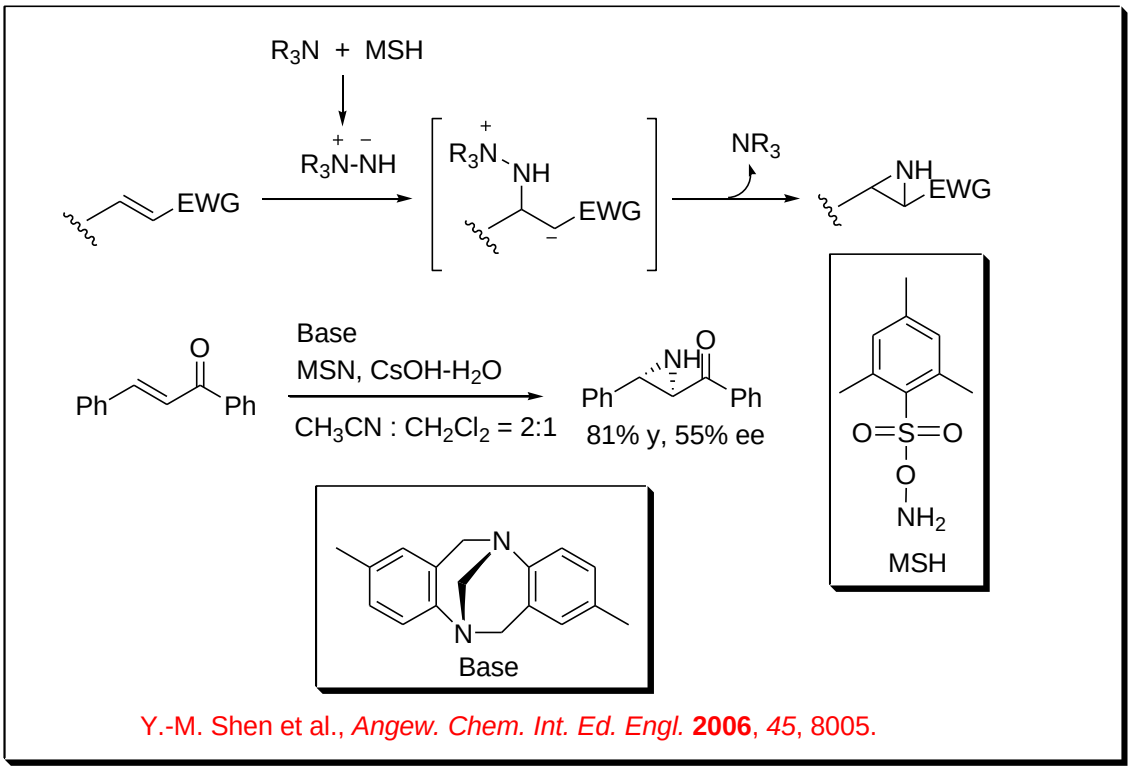
Rh_2(S-TFPTTL)$_4$

R^1	R^2	Yield [%]	ee [%]
Ph	Me	94	95
4-ClC_6H_4	Me	95	84
4-$MeOC_6H_4$	Me	91	78
$CH_3(CH_2)_3$	Me	81	47
Me	Ph	97	93
Me	4-ClC_6H_4	94	90
Me	4-$MeOC_6H_4$	98	95

M. Anada et al., *Org. Lett.* **2007**, *9*, 4559.

Scheme 3

The use of chiral amine has been demonstrated for the reaction of electron deficient alkenes. For example, the use of aminimide as an effective NH-transfer reagent for the aziridination of electron deficient alkenes is reported (Scheme 4). In this reaction, in situ generation of a hydrazinium salt from tertiary amine and O-mesitylenesulfonylhydroxylamine (MSH), deprotonation of the hydrazinium salt to form an aminimide, and subsequent aziridination is involved.



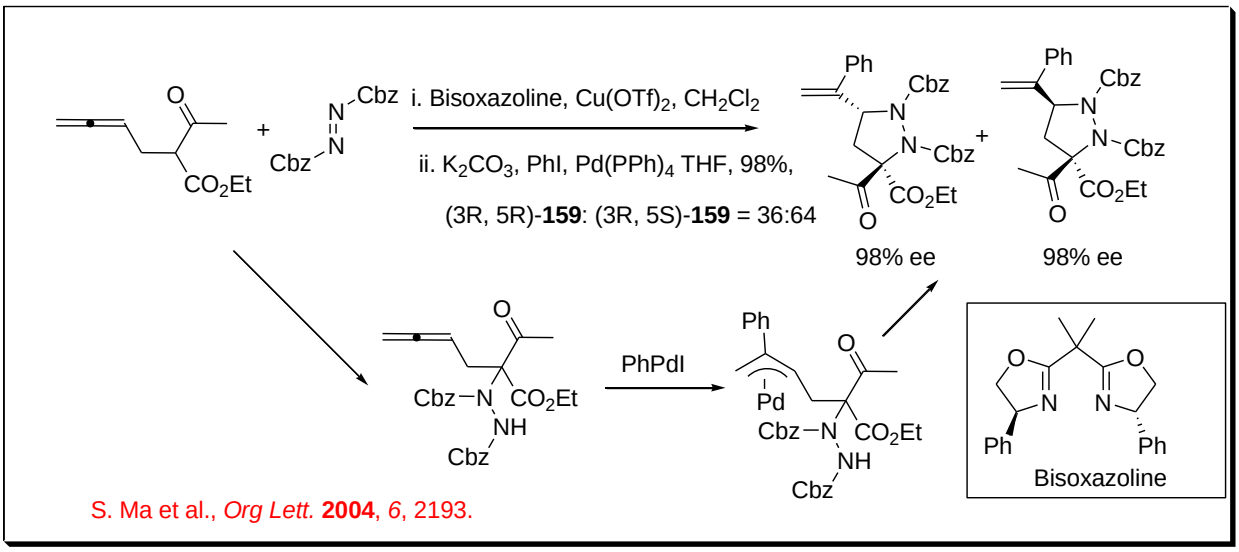
Y.-M. Shen et al., *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 8005.

Scheme 4

4.7Amination of Carbonyl Compounds

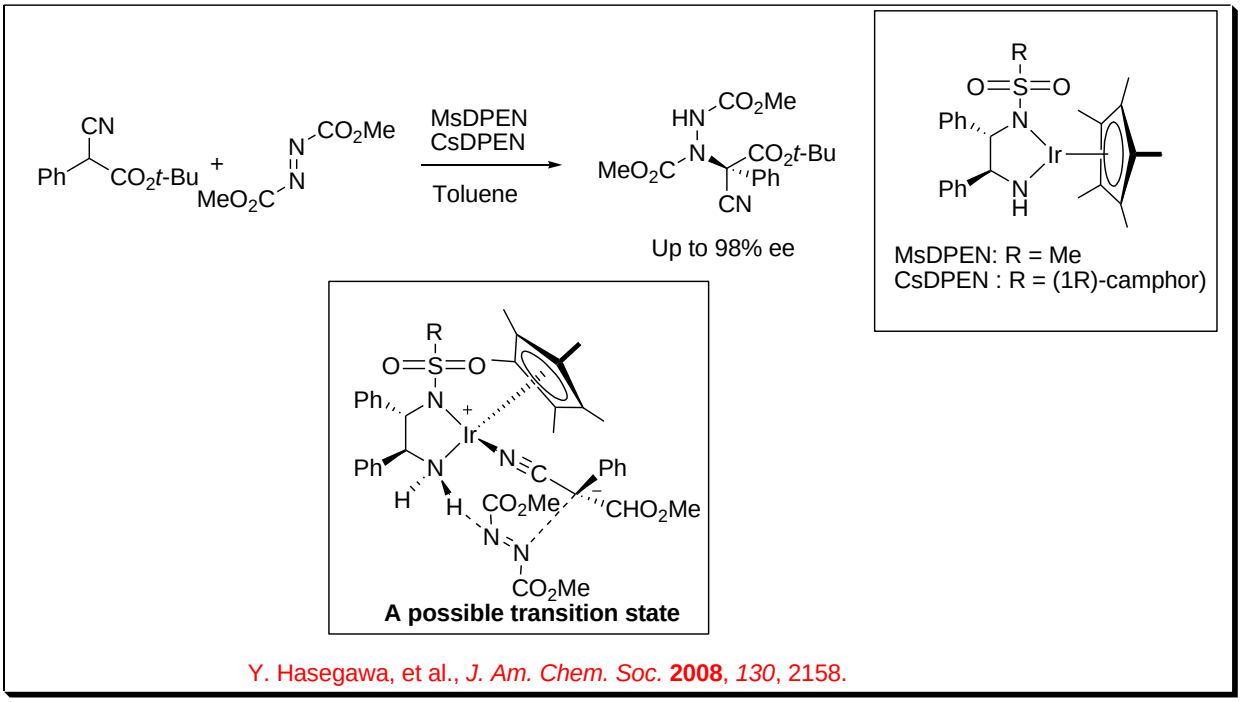
The electrophilic Amination reaction is useful technology for the introduction of an amine functionality next to carbonyl carbon. Asymmetric version of this process has been considerably explored. Recently, the use of the combination of copper and palladium based catalytic system has been demonstrated for the asymmetric one-pot tandem addition-cyclization reaction of 2-(2',3'-dienyl)-β-keto esters, aryl halides, and dibenzylazodicarboxylate to afford pyrazolidine

(Scheme 5). An involvement of π-allylpalladium intermediate *via* the carbopalladation of allene has been proposed.



Scheme 5

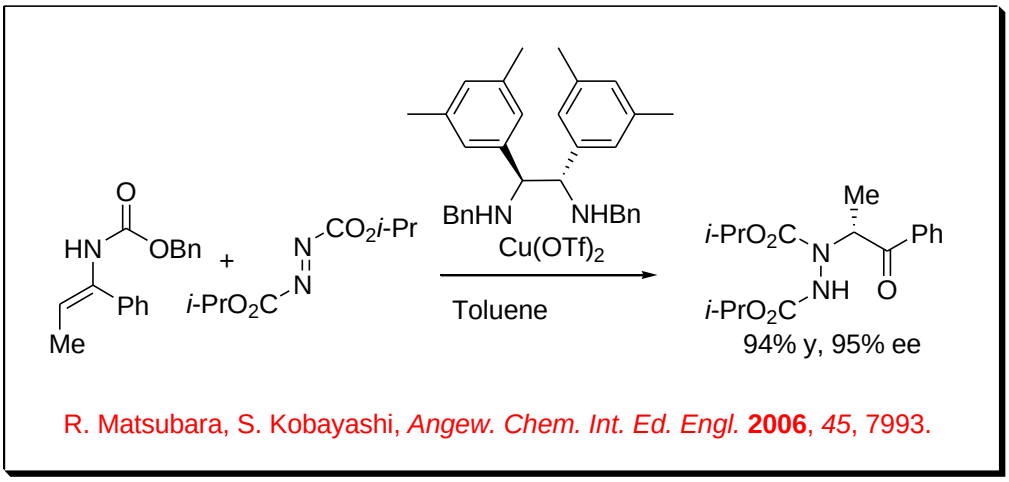
The use of bifunctional chiral amide iridium complex for the direct amination of α-substituted α-cyanoacetate with azodicarboyxlate has been demonstrated with excellent enantioselectivity (Scheme 6). In this reaction, the chiral amide complexmay be involved in the deprotonation of cyanoacetate that would lead to the formation of *N*-bound nitrile complex; thus, cyanoacetate and azodicarboxylate are activated sequentially by the bifunctional catalyst that could facilitate the transformation.



Y. Hasegawa, et al., *J. Am. Chem. Soc.* **2008**, *130*, 2158.

Scheme 6

Using chiral diamine-copper(II) the amination of anecarbamates can be accomplished with excellent enantioselectivities (Scheme 7). Under these conditions, the changing the enecarbamate geometry from *Z* to *E* resulted in a dramatic improvement of the reactivity.

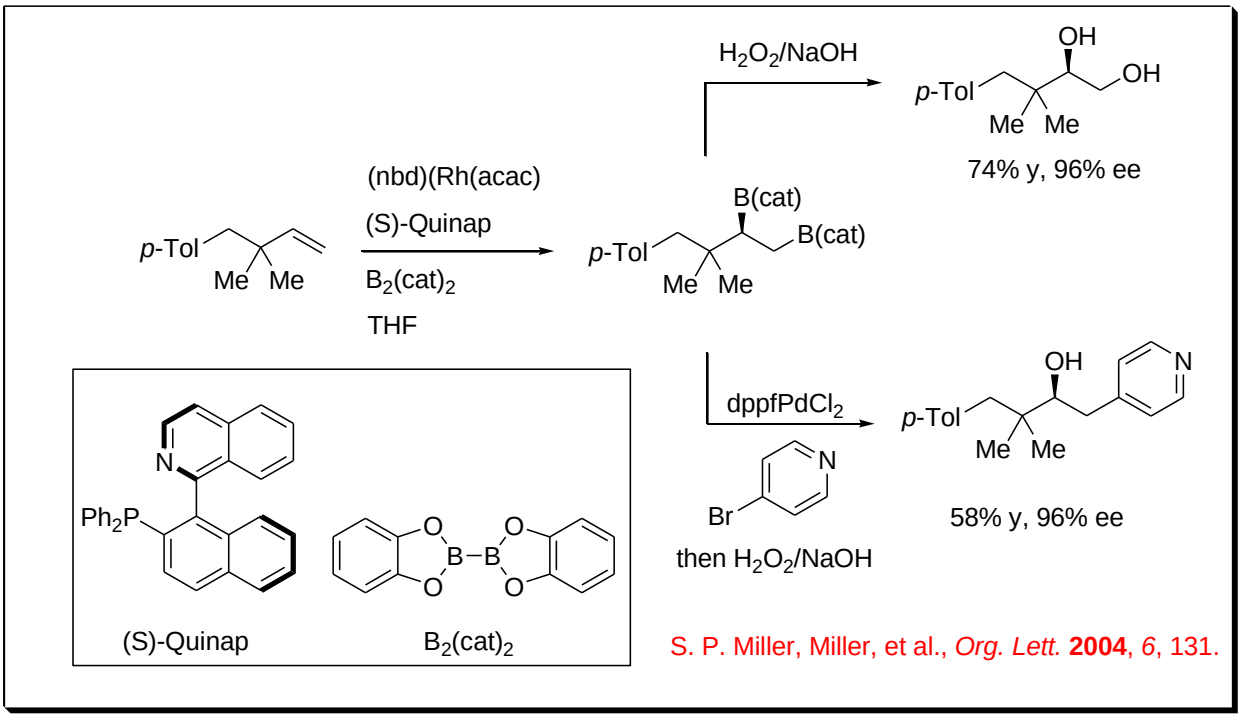


R. Matsubara, S. Kobayashi, *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 7993.

Scheme 7

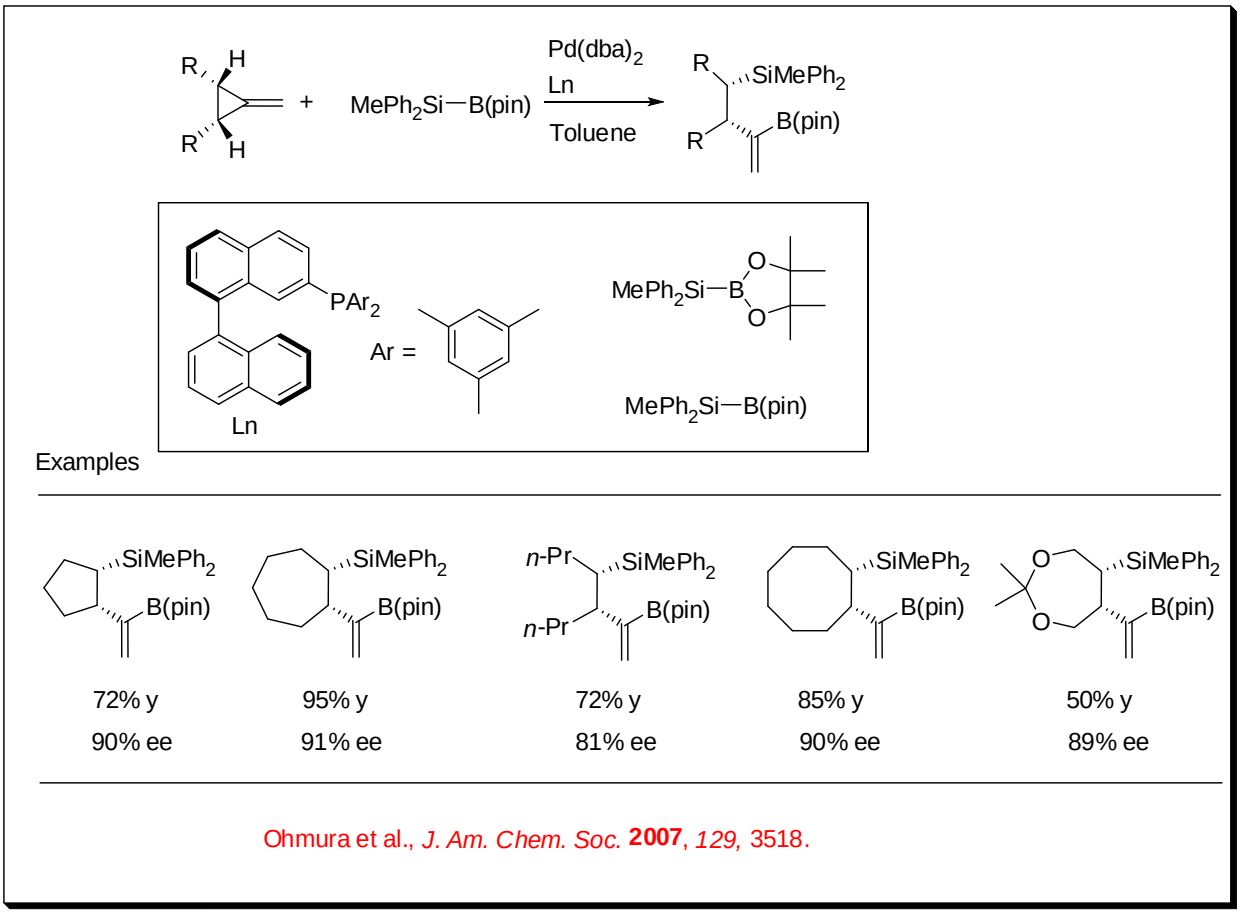
4.8 Boration of Alkenes

Organoboranes are useful reagents for organic synthesis. Recently, catalytic methods have been developed for enantioselectiveboration of unsaturated substrates. For example, the diboration of alkenes with bis(catecholato)diboron using rhodium(I) salt and (*S*)-quinap can be accomplished (Scheme 8). Oxidation of the diborane derivatives can lead to chiral 1,2-diols. Furthermore, tandem diboration, Suzuki cross-coupling and oxidation reaction of can lead to carbohydroxylation with similar enantioselectivity.

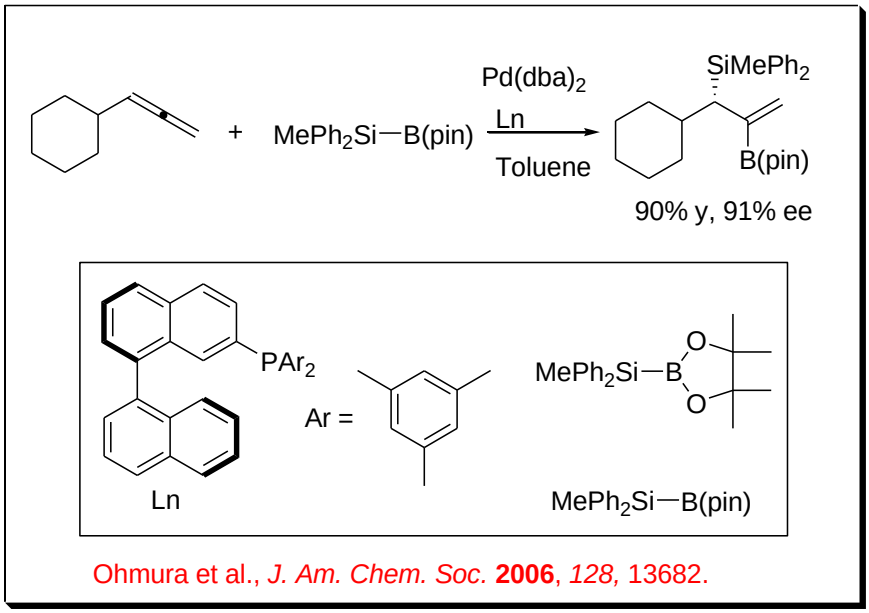


Scheme 8

The asymmetric silaboration of symmetrically substituted *meso*-methylcyclopropanes can be accomplished *via* carbon-carbon bond cleavage employing chiral palladium-catalyzedboration with $Me_2PhSiB(pin)$ as the silylboron reagent (Scheme 9). The catalytic system is also effective for the silaboration of mono-substituted allene to give allylsilane with good enantioselectivity (Scheme 10).

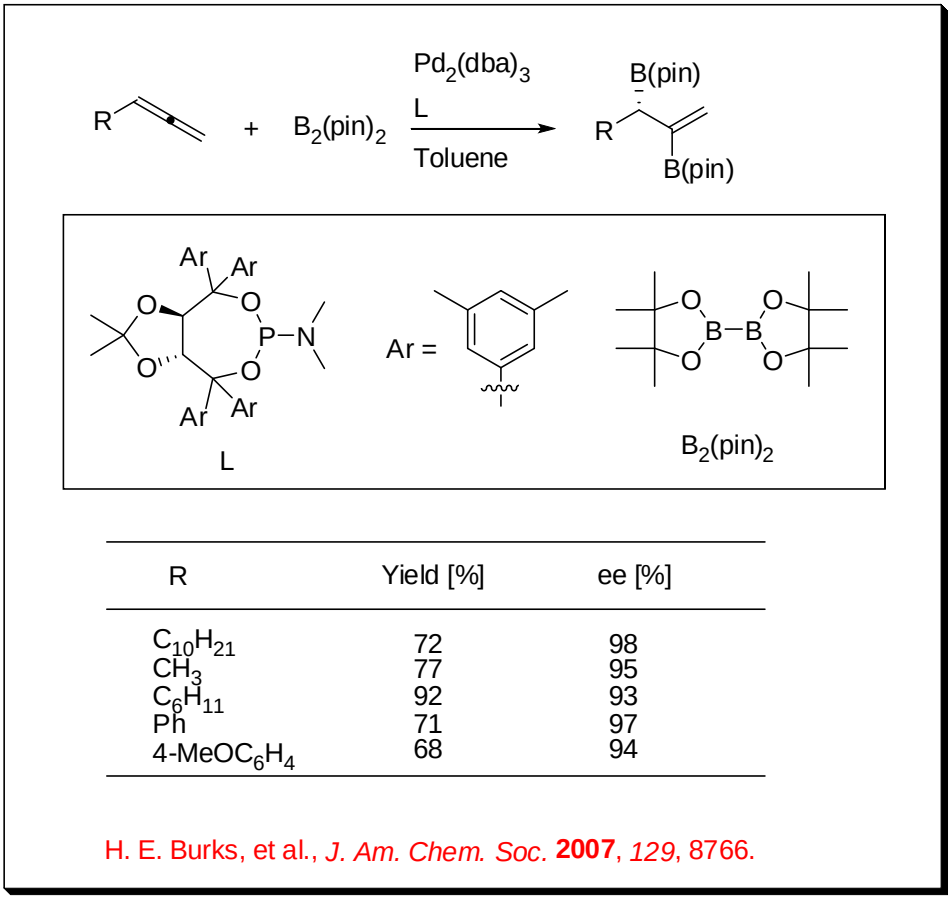


Scheme 9


Pd(dba)2
Ln
Toluene
MePh2Si—B(pin)
SiMePh2
B(pin)
90% y, 91% ee
PAr2
Ar =
Ln
MePh2Si—B
O
O
MePh2Si—B(pin)
Ohmura et al., J. Am. Chem. Soc. 2006, 128, 13682.

Scheme 10

The diboration of terminal allenes is also demonstrated using palladium complex derived from $Pd(dba)_2$ and a chiral phosphoramidite to give 1,2-bis(boronate)ester with high enantioselectivity (Scheme 11). The rate determining step involves the oxidative addition of the diboron to Pd, which is followed by the transfer of both boron groups to the unsaturated substrate *via* a π-allyl complex.



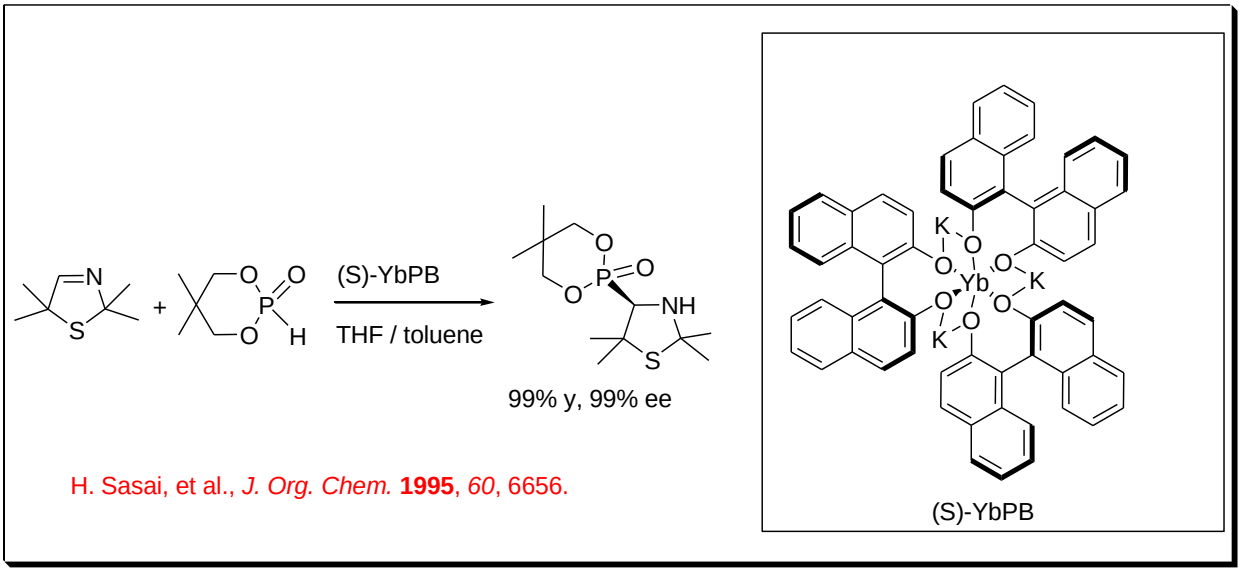
R	Yield [%]	ee [%]
$C_{10}H_{21}$	72	98
CH_3	77	95
C_6H_{11}	92	93
Ph	71	97
4-$MeOC_6H_4$	68	94

H. E. Burks, et al., *J. Am. Chem. Soc.* **2007**, *129*, 8766.

Scheme 11

4.9 Hydrophosphonylation of Imines

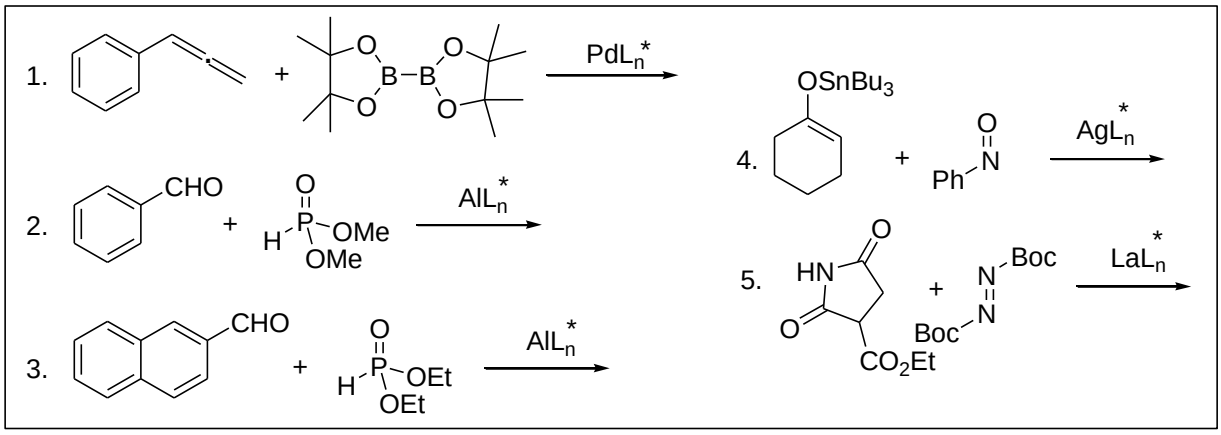
The hydrophosphonylation of aldehydes and imines affords an effective route for the formation of C-P bonds.Recently, the reaction of cyclic phosphate with cyclic imines has been shown employing bimetallic chiral (*S*)-YbPB with excellent enantioselectivity (Scheme 12).



Scheme 12

Problems

E. Predict the major product for the following reactions.



F. Describe asymmetric oxygenation of carbonyl compounds.

Reference/Text Book

3. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

4. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.