

III.2.12.2 Palladium-Catalyzed Cross-Coupling with Other α -Hetero-Substituted Organic Electrophiles

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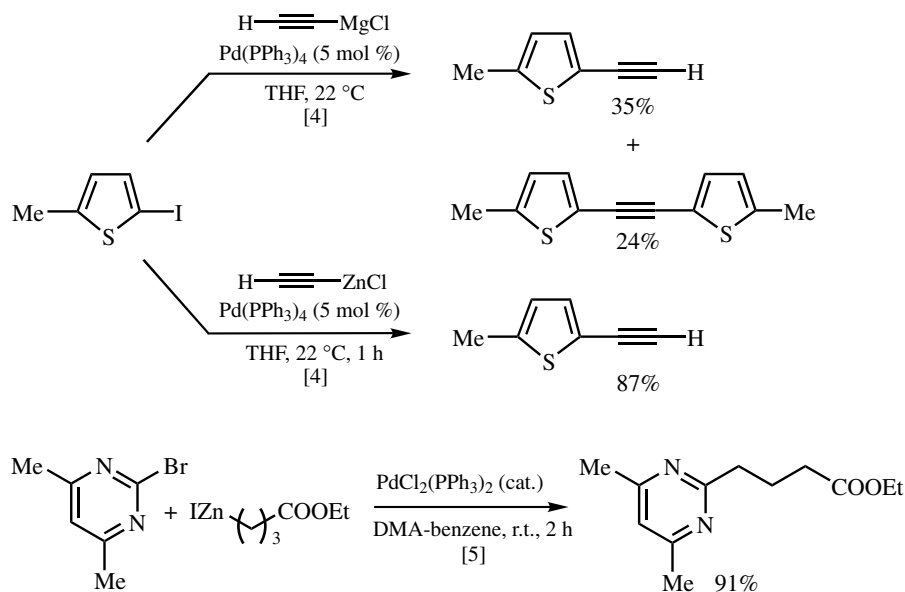
A. INTRODUCTION

α -Hetero-substituted organic electrophiles include heteroaromatics and α -hetero-substituted alkenes having some leaving group at the α -position. Since the heteroaromatics are quite stable due to aromaticity, the Pd-catalyzed coupling reaction of organometallic compounds usually proceeds without decomposition of the aromatic ring. It means that the heteroaromatics having the leaving group at the α -position just behave as aryl halides. In contrast, α -hetero-substituted alkenes having the leaving group at the α -position have three possibilities to react with organometallic compounds giving *cis*-, *trans*-, or α,α -disubstituted alkenes. In this section, the Pd-catalyzed coupling reaction with α -hetero-substituted organic electrophiles is discussed.

B. COUPLING REACTIONS WITH HETEROAROMATICS POSSESSING α -LEAVING GROUP

Since heteroaromatic compounds sometimes exhibit interesting physical properties and biological activities, construction of substituted heteroaromatics has drawn some attention. Heteroaromatics can be divided into two major categories. One is the π -electron-sufficient heteroaromatics, such as pyrrole, indole, furan, and thiophene; those easily react with electrophiles. The other is the π -electron-deficient heteroaromatics, such as pyridine, quinoline, and isoquinoline; those have the tendency to accept the nucleophilic attack on the aromatic ring. Reflecting the electronic nature of heteroaromatics, the π -electron-deficient ones are usually used as the electrophiles.^[1] The π -electron-sufficient heteroaromatics having simple structures, such as 2-iodofuran and 2-iodothiophene, have also been utilized as the electrophiles. Not only the electronic nature of the heteroaromatics but also coordination of the heteroatom to the palladium complexes influence catalytic activity. This is another reason why the coupling reaction did not proceed efficiently in some cases.

Organozinc (Negishi's protocol; see **Sect. III.2.1**),^{[2]–[5]} boron (Suzuki's protocol; see **Sect. III.2.2**),^{[6]–[8]} tin (Stille's protocol; see **Sect. III.2.3**),^{[9],[10]} copper (Sonogashira's protocol; see **Sect. III.2.8.1**),^[11] magnesium,^{[4],[12]} aluminum,^[3] silicon compounds,^[13] and siloxycyclopropanes^[14] are often used for Pd-catalyzed coupling reactions with heteroaromatics having a leaving group at the α -position (**Schemes 1** and **2**).

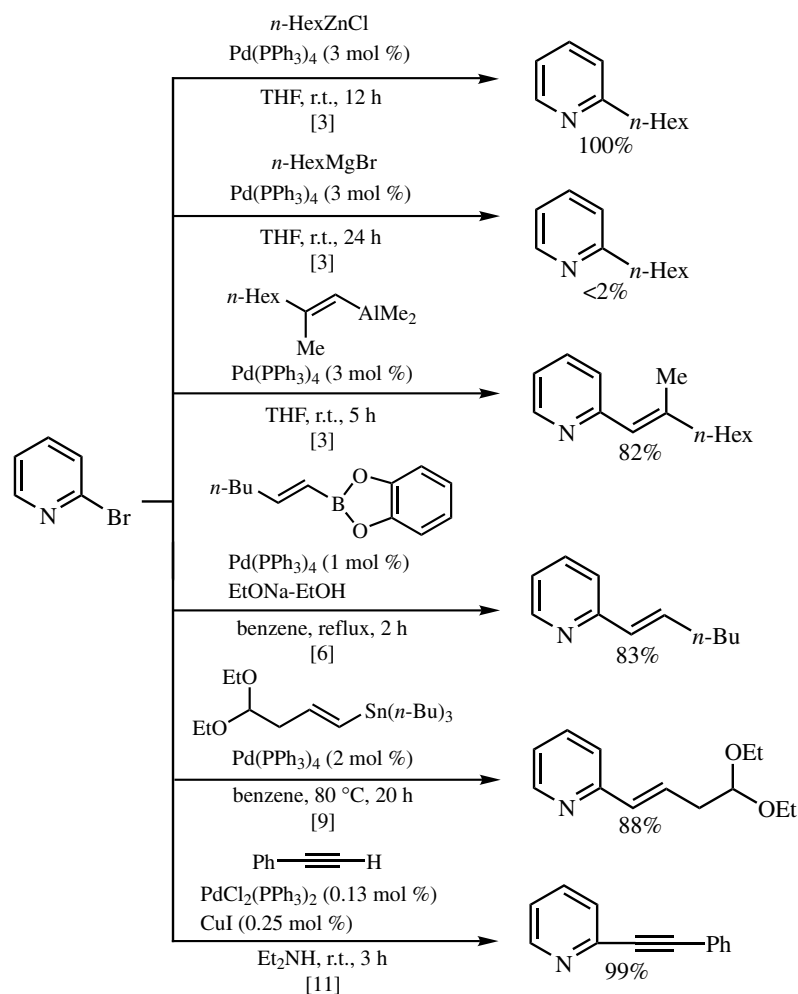


Scheme 1

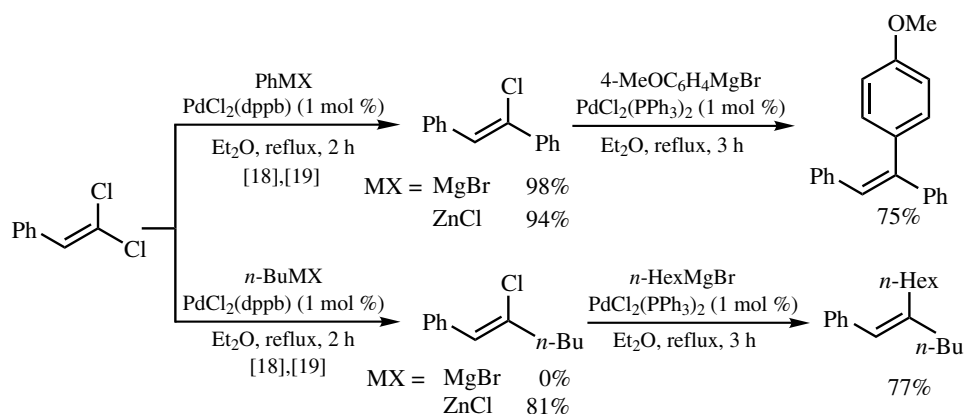
C. COUPLING WITH 1,1-DIHALOALKENES

1,1-Dihaloalkenes are easily prepared from aldehydes via the Wittig-type reaction^[15] or by carbometallation of metallated alkynes.^{[16],[17]} When the other substituent is present at the 2-position, the steric requirement around two halogens becomes different. Since the halogen *cis* to the substituent is sterically more hindered than that *trans*, the palladium complex can approach the *trans* position faster than the *cis* one. Owing to the difference of the reaction rate, the Pd-catalyzed cross-coupling reaction of organometallic compounds with 1,1-dihaloalkenes can be stopped at the *trans* monosubstituted stage. As the second halogen can be displaced by the conventional cross-coupling method, the trisubstituted alkenes can be synthesized in a stereoselective manner. The first successful report of the selective monocoupling reaction was performed by organomagnesium and zinc compounds in the presence of $\text{PdCl}_2(\text{dppb})$ catalyst (**Scheme 3**).^{[18],[19]}

For aryl metals, the *trans*-selective coupling reaction was achieved by use of either organomagnesium or zinc compounds. In the case of alkyl metals, not organomagnesium but organozinc compounds brought about fruitful results. The untouched chloride moiety at the *cis* position further coupled with organomagnesium compounds in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ to give the trisubstituted alkenes in good yields. Since organomagnesium



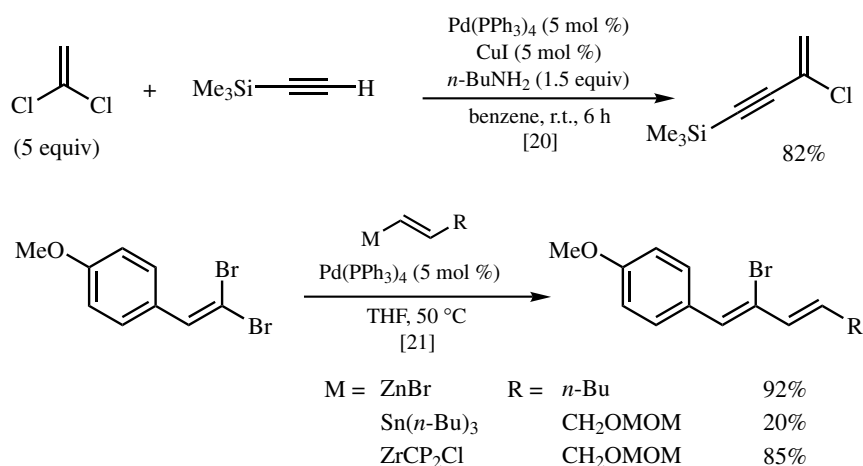
Scheme 2



Scheme 3

compounds are reactive, the catalyst plays an important role in achieving the selective monocoupling reaction.

The other organometallic compounds, such as alkynylcoppers,^[20] alkenylzincs,^[21] and alkenylzirconocenes,^[21] have also been utilized for the *trans*-selective coupling reaction of 1,1-dihaloalkenes (**Scheme 4**). The monoalkynylation of 1,1-dichloroethylene in the presence of palladium and copper catalysts is troublesome. Since dialkynylation is not easily suppressed, an excess amount of the substrate, 1,1-dichloroethylene, is required to produce the desired product.



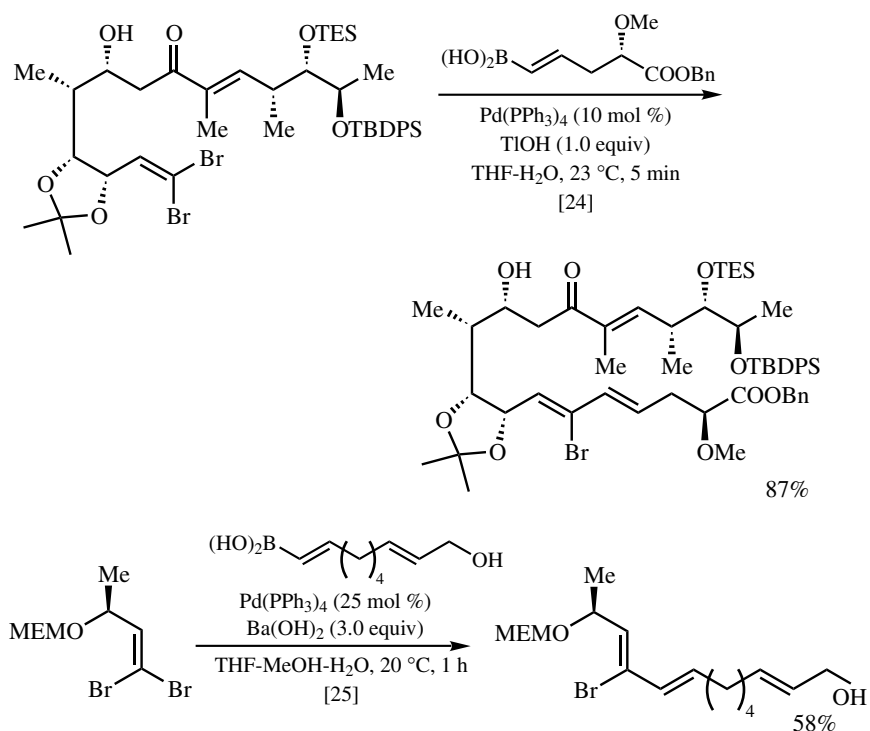
Scheme 4

Although alkenylzinc compounds having simple alkyl groups reacted with the 1,1-dibromoalkene stereoselectively, the reaction with the one having some functionality, such as the alkoxyethyl group, did not give the desired product. In contrast, use of zirconocene derivatives brings about fruitful results. Since these organometallic compounds are less reactive than organomagnesiums, the selective coupling reaction can be performed even when Pd(PPh₃)₄ is used as a catalyst.

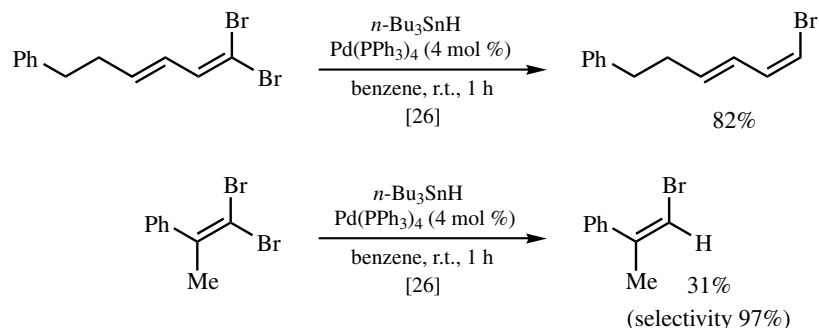
Organoborane compounds, especially boronic acid derivatives, are less reactive and have also been utilized for the *trans*-selective coupling reaction of 1,1-dibromoalkenes.^{[22]–[26]} Use of TlOH and Ba(OH)₂ as the activator of boronic acids is important to carry out the selective coupling reaction (**Scheme 5**).

Selective hydrogenolysis of one of the halogens in 1,1-dihaloalkenes is another possibility to produce disubstituted alkenes in a stereoselective manner. The reaction is achieved by using tributyltin hydride in the presence of Pd(PPh₃)₄ catalyst (**Scheme 6**).^{[26]–[28]} The catalyst also plays an important role in achieving the selective reaction. The use of electron-donating and sterically less hindered triarylphosphines, such as PPh₃ and P(*p*-MeC₆H₄)₃, is important to carry out the reaction stereoselectively.

The coupling reaction of 1,1-dihaloalkenes at the *trans* position is much faster than that at the *cis* position because of steric reasons, and therefore, the *cis* trisubstituted alkenes can be obtained in good yields. In contrast, when a good leaving group is placed at the *cis* position, the corresponding trisubstituted alkenes having *trans* stereochemistry can be produced. One typical example is use of (*Z*)-1-chloro-1-iodoalkenes, which are synthesized by treatment of (*E*)-1-chloroalkenes with butyllithium at –100 °C followed



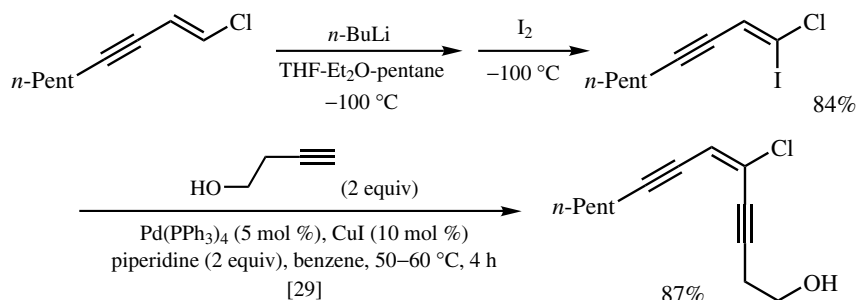
Scheme 5



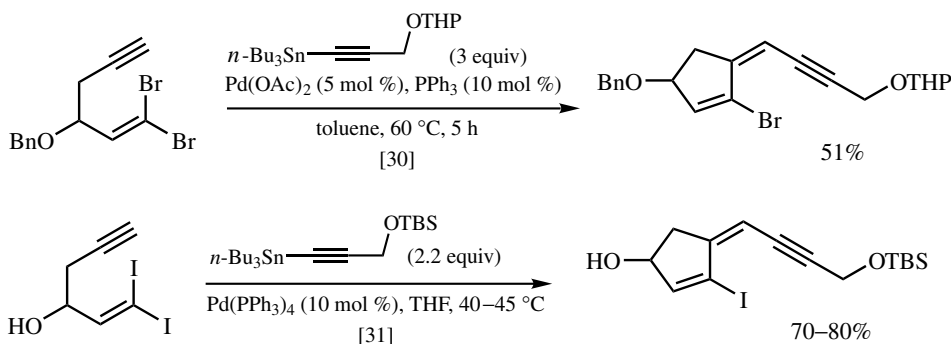
Scheme 6

by quenching with iodine.^[29] Since the iodide reacts much faster than the chloride, the Pd-catalyzed coupling reaction proceeds at the *cis* position stereoselectively (**Scheme 7**).

The other example for the *cis*-selective coupling reaction is shown in **Scheme 8**.^{[30],[31]} When alkyne is in the side chain, the palladium complex may interact with the alkyne, and thus the oxidative addition of the complex to the carbon–halogen bond at the *cis* position becomes faster than that at the *trans* position. The cross-coupling reaction of organotin compounds with alkenyl halides is slow, but the intramolecular carbopalladation proceeds smoothly followed by the coupling reaction to give the cyclized product.



Scheme 7



Scheme 8

D. SUMMARY

1. A variety of organometallic compounds can be used for the coupling reaction with heteroaromatics possessing α -leaving groups.

2. The monocoupling reaction of 1,1-dihaloalkenes can be carried out selectively by using organomagnesiums, organozincs, organozirconiums, organoborons, and organotins. With reactive organometallic compounds, such as organomagnesiums and organozincs, the use of a Pd catalyst is important to carry out the reaction successfully. A simple modification brings about fruitful results when unreactive organometallic compounds, such as organoborons and organotins are used.

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