CHAPTER II

LITERLATURE REVIEW

Malaria is a disease affected to 300 million humans globally, and causes more than 1 million deaths annually. It is estimated that a third of these fatalities occur in children under 5 years old. Although this disease is found primarily in the tropics and subtropics, it has been observed far beyond these boundaries. It is transmitted by the infected female Anopheles mosquito. The specific protozoan organisms causing malaria are from the genus *Plasmodium.* Only four of approximately 100 species cause malaria in humans. The remaining species affect birds, monkeys, livestock, rodents, and reptiles. The four species that affect humans are: *P. flaciparium*, *P. viax*, *P. mararíae*, and *P. ovale*. Concurrent infections by more than one of these species are seen in endemically affected regions of the world. Such multiple infections further complicate patient management and the choice of treatment regimens.

Malaria has essentially been eradicated in most temperate-zone countries. However, more than 1000 cases of malaria were documented recently in United States' citizens returning from travel abroad. Today, malaria is found in most countries in Africa, Central and South America, and Southeast Asia. It is reported to be on the increase in Afghanistan, Bangladesh, Brazil, Burma, Cambodia, Columbia, China, Iran, India, Indonesia, Mexico, the Philippines, Thailand, and Vietman. Infection from Plasmodia can cause anemia, pulmonary edema, renal failure, jaundice, shock, cerebral malaria, and, if not treated in a timely manner, can result in death.

Types of Malaria

Malarial infections are known according to the species of the parasite involved.

Plasmodium Falciparum. *Plasmodium falciparum* infection has an incubation period (time for mosquito bite to clinical symptoms) of 1-3 weeks (average of 12 days). The

P. falciparum life cycle in man begins with the bite of an infected female mosquito. The parasites in the sporozoite stage enter the circulatory system through which they can reach the liver in about an hour. These organisms grow and multiply 30,000-40,000 folds by asexual division within liver cell in 5-7 days. Then, as merozoites they leave the liver to re-enter the blood stream and invade the erythrocytes, red blood cell (RBCs.), where they continue to grow and multiply further for 1-3 days. Specific receptors on the surface of the erythrocytes serve as binding sites for the merozoite. These infected RBCs rupture, releasing merozoites in intervals of about 48 hours. Chemicals released by the ruptured cell in turn cause activation and release of additional substances associated with the patients' symptoms. The clinical symptoms include chills, fever, sweating, headaches, fatigue, anorexiam, nausea, vomiting and diarrhea. Some of the released merozoites are sequestered in vital organs (brain and heart) where they continue to grow. Recurrence of the clinical symptoms on alternate days leads to the terminology of tertian malaria. The *P. falciparum* parasite can also cause RBCs to clump and adhere to the wall of blood vessels. Such phenomenons have been known to cause partial obstruction and sometimes restriction of the blood flow to vital organs like the brain, liver and kidneys. Reinfection of RBCs can occur, allowing further multiplication and remainifestation of the malaria symptoms. Some merozoites develop into make and female sexual forms, called gametocytes, which can then be acquired by the female mosquito after biting the infected human. Gametocytes mature in the mosquito's stomach to form zygotes. Growth of the zygotes leads to formation of oocysts (spherical structures located on the outside wall of the outside wall of the stomach). Sporozoite develop form the oocysts, are released into the body cavity of the mosquito, and migrate to the salivary gland of the insect form which they can be transmitted to another human following a mosquito bite. The life cycle of the malaria parasites is shown in the Figure 7.

Plasmodium Vivax. *Plasmodium vivax* (benign tertian) is the most prevalent form of malaria. It has an incubation period of 1-4 weeks (2 weeks average). This form of maliaria can cause spleen rupture and anemia. Relapses (renewed manifestations of erythrocytic infection) can occur. These results from the periodic release of dormant parasites (hypnozoites) form the liver cells. The erythrocytic forms are generally considered to be susceptible to treatment.

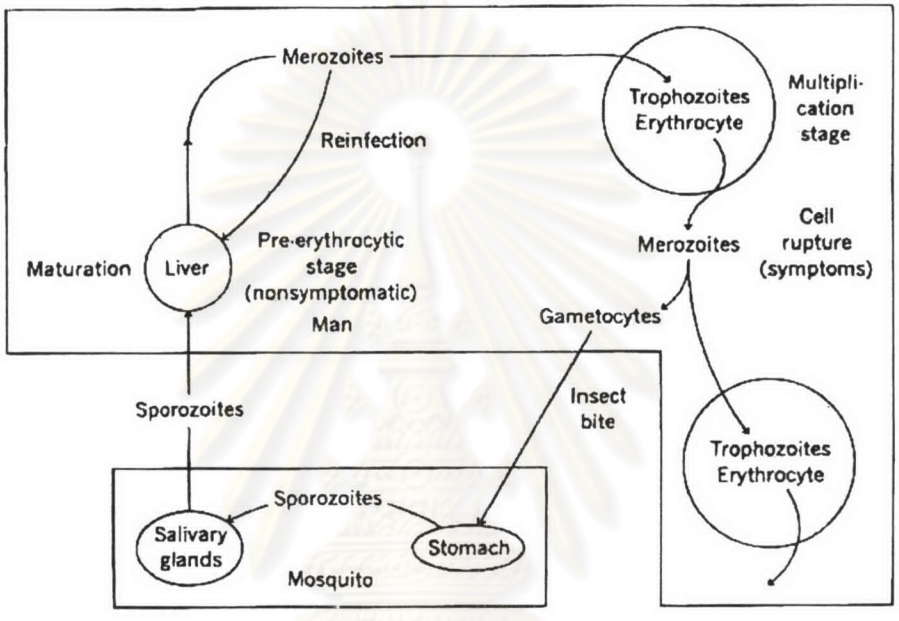


Figure 7 The life cycle of malarial protozoa.

Plasmodium Malariae. *Plasmodium malariae* is responsible for quarntan malaria. It has an incubation period of 2-4 weeks (average of 3 weeks). The asexual cycle occurs every 72 hours. In addition to the usual symptoms, this form also causes nephritis. This is the mildest form of malaria and does not relapse. The RBC infection associated with *P. malariae* can last for many years. The *P. malariae* is quite unlikely to become resistant.

Plasmodium Ovale. *Plasmodium ovale* has an incubation period of 9-18 days (14 days average). Relapses have been known to occur in individuals infected with this plasmodium. The relapse may be indicative of ovale tertian malaria and is associated

with the ability of the organism to lie dormant in hepatic tissue for extended periods of time.

Types of Chemotherapy

Tissue Schizonticides. These drugs eradicate the exoeryhrocytic liver-tissue stages of the parasite which prevents the parasite's entry into the blood. Drugs of this type are useful for prophylaxis. Some tissue schizonticides can act on the long-lived tissue form(hypnozoites of *P. vivax* and *P. ovale*), and thus can prevent relapses.

Blood Schizonticides. These drugs destroy the erythrocytic stages of parasites and can cure cases of falciparum malaria or suppress relapses. This is the easiest phase to treat because drug delivery into the blood stream can be accomplished rapidly.

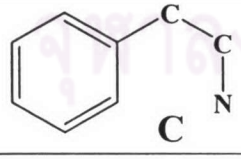
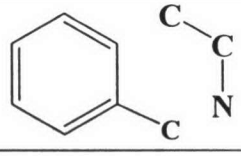
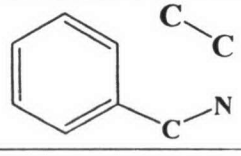
Gametocytocides. Agents of this type kill the sexual forms of the plasmodia (gametocytes), which are transmittable to the Anopheles mosquito, thereby preventing transmission of the disease.

Sporontocides (sporozooiticides). These drugs act against sporozoites and are capable of killing these organisms as soon as they enter the blood stream following a mosquito bite.

General Methods for the Preparation of Tetrahydroisoquinoline Compounds

There are number of methods for isoquinoline ring construction and the most frequently used processes are summarized in Table 2.

Table 2 General methods for isoquinoline ring construction.

Disconnection approach	Reaction	Products
	Bischler-Napieralski	3,4-dihydroisoquinolines
	Pictet-Spengler	1,2,3,4-tetrahydroisoquinolines
	Pomeranz-Fritsch	isoquinolines
	Schlittler-Muller	isoquinolines

In general, the synthetic method of isoquinoline ring system can be classified systematically in five ways (Apsimon, 1977, vol. 3) according to the mode of formation of the pyridine ring (Figure 8). The first type involves ring closure between the benzene ring and the carbon atom, which forms the C_1-position of the resulting isoquinoline ring. The second type uses bond formation between the C_1-position and nitrogen atom and the third type uses cyclization by the combination of nitrogen atom with the C_3-position. The fourth type is due to the formation of isoquinoline ring by ring closure between the C_3 and C_4 position and the fifth type necessitate ring closure between the benzene ring and C_4-position.

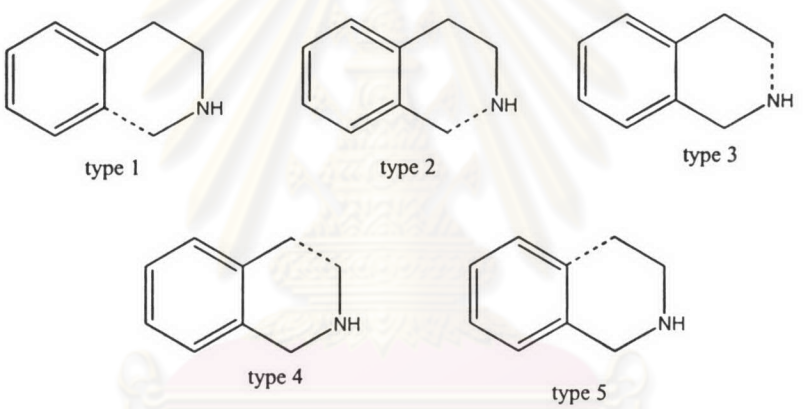
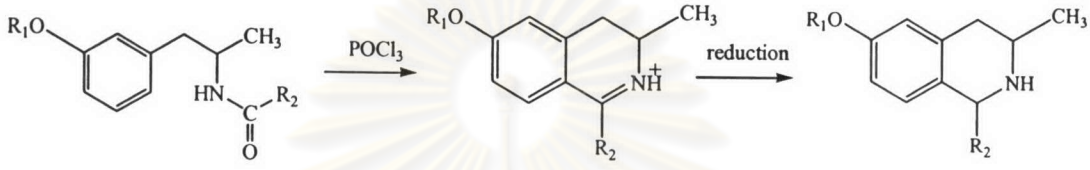


Figure 8 The general synthetic methods of 1,2,3,4-tetrahydroisoquinoline

Although all of these reaction types are known, the most popular and common reaction are the type 1 and 5. This investigation has been followed by type 1, the classical formation as the Bischer-Napieraski, the Pictet-Spengler. Moreover, the other reaction, especially cyclization through *O,N*-acetal intermediate route, which has been modified by conventional methods to give a mild and efficient reaction was described as following (Kubo *et al.*,1987).

1. The Bischler-Napieralski Reaction

The Bischler-Napieralski reaction consists of the cyclodehydration of β-phenylethylamide (amide compound) by heating at high temperatures with Lewis acid such as phosphorus pentaoxide or phophoryl chloride (phophorus oxychloride). Subsequently, a 3,4-dihydroisoquinoline which is reduced to a 1,2,3,4-tetrahydro-isoquinoline with sodium borohydride (Figure 9). However, the yield is very poor under the high temperature condition.



The use of low temperature and mild condensing agents can improve the yield of the reaction. Therefore, it has become the most frequently used method for preparing isoquinoline and tetrahydroisoquinoline derivatives.

The Bischler-Napieralski reaction involves an electrophilic attack upon an aromatic ring by a carbonium ion catalyzed by an acid-catalyzed reaction. The reactivity of the aromatic nucleus depends on electron density at the cyclized position as shown in Figure 9.

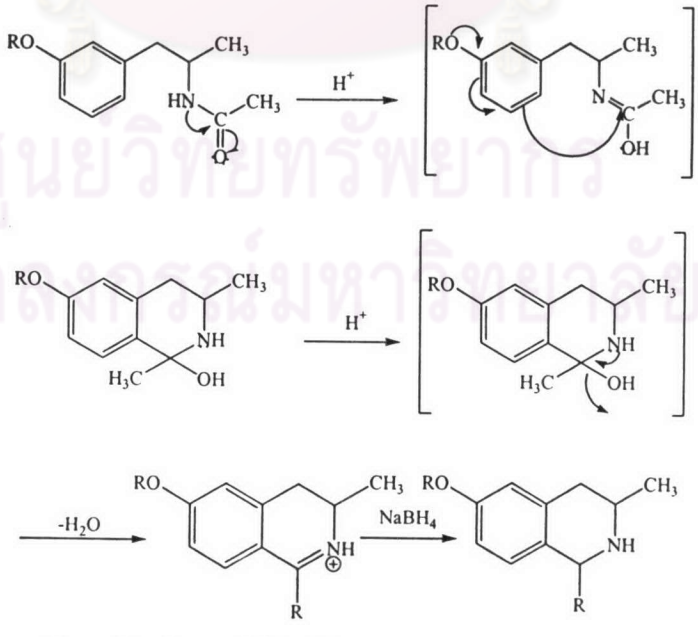


Figure 9 The proposed mechanism of Bischler-Napieralski cyclization

2. The Pictet-Spengler Reacion

The Pictet-Spengler reaction, which is one of the special cases of the Mannich reaction, consists of the condensation between a β-arylethylamine and a carbonyl compound to yield a 1,2,3,4-tetrahydroisoqiboline. Becker and Decker carried out the reaction two steps as the intermediate azomethine was often formed by Schiff base reaction before fused rind by concentrated acid.

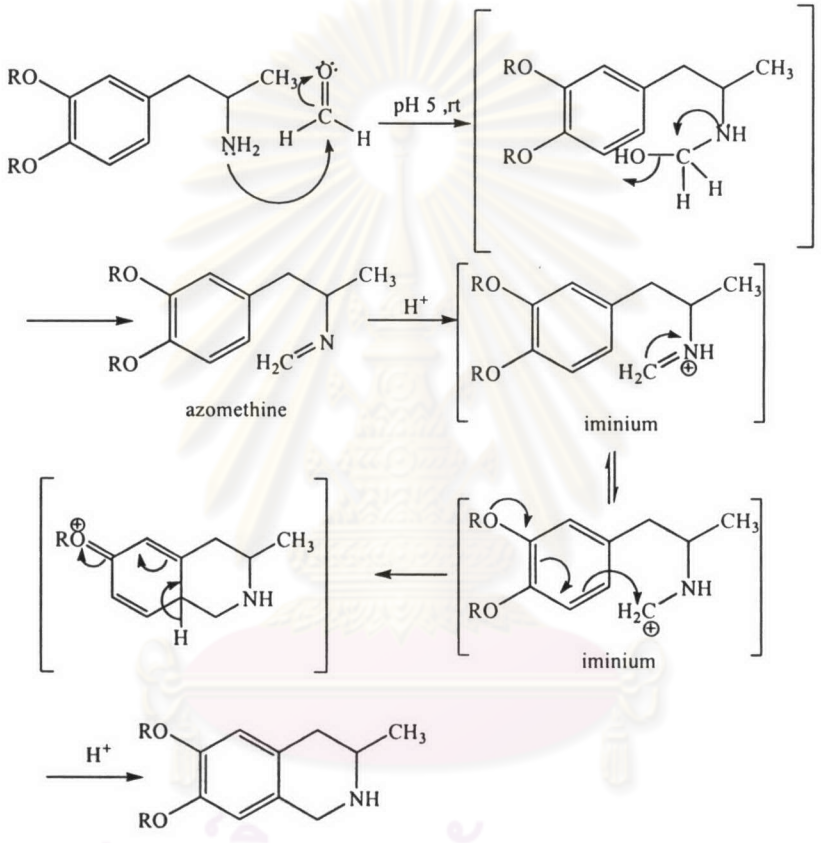


Figure 10 The proposed mechanism of Pictet-Spengler reaction

The electronic mechanism of the Pictet-Spengler reaction has not yet been investigation completely, but it is well known that Schiff base is isolated as an intermediate in some case and cyclized by acid (Figure 10). This reaction also depends upon the great electron density at the cyclized position. Thus, the *meta*-position of electron donating group on aromatic ring of phenylethylamine is responsible for the reactivity of the cyclization. Formaldehyde as carbonyl compound has been employed

most frequently in the conventional Pictet-Spengler reaction. Generally, the yield of this reaction is quite high.

3. Other synthetic reactions.

Several modifications of the synthesis have been developed with extensive applicability. Very useful in this respect, iminium ions can prepared from *N*-oxide with sulphur dioxide, acetic anhydride, or trifluoroacetic anhydride (Bather *et al.*, 1978) (Figure 11).

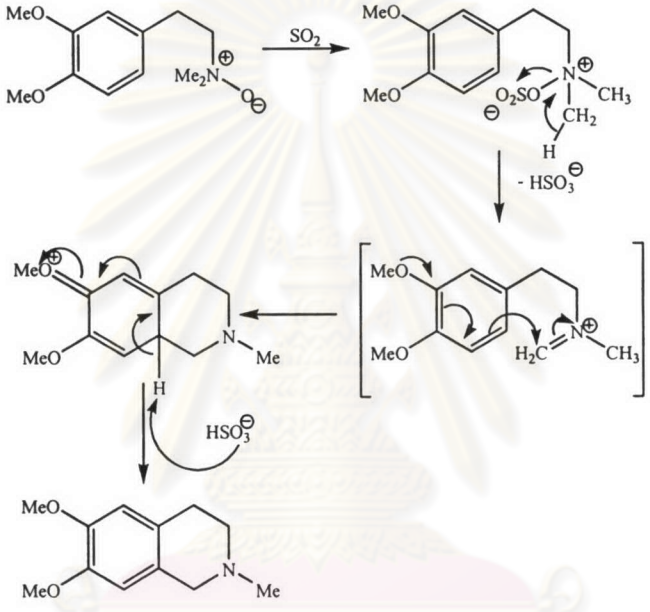


Figure 11 The synthetic mechanism of THIQ derivatives through *N*-acyliminium from *N*-Oxide

Then, one derived from a suitable constructed system should be able to undergo intermolecular electrophilic substitution to give a tetrahydroisoquinoline. Later, a various acyl chlorides such as sulfonyl chlorides (Lukanov *et al.*, 1987), acetyl chloride (Venkov *et al.*, 1989) were used to adduct with azomethines to give *N*-acyliminium before synthesized to tetrahydroisoquinoline (Figure 12). In addition, carbonyl compounds were used to prepare *N*-acyliminium (Mollov *et al.*, 1978; Lukanov *et al.*, 1987; Venkov and Lukanov, 1996). It's found that the reaction can be carried out with the same results in an acyl chloride.

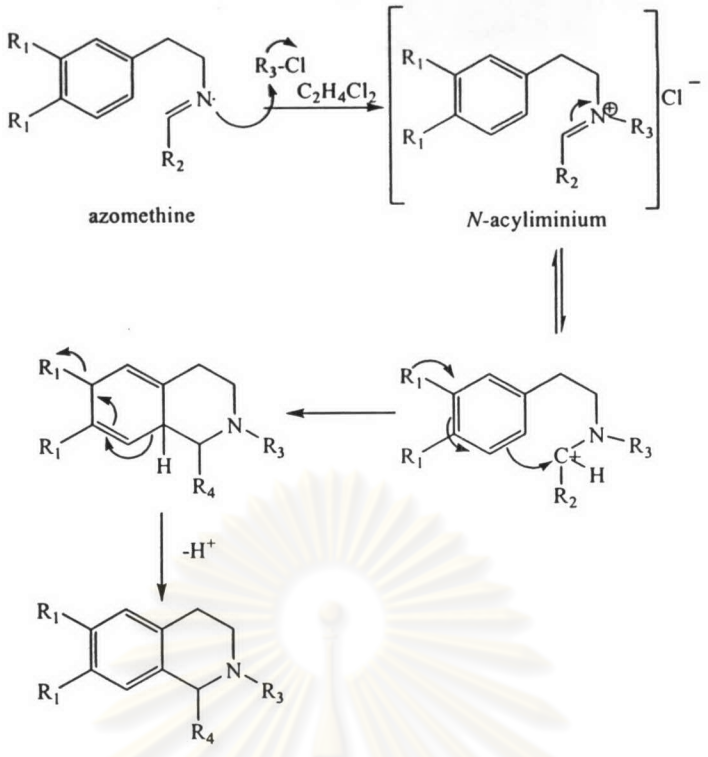


Figure 12 The synthetic mechanism of tetrahydroisoquinoline through *N*-acyliminium from azomethine

In 1987, Kubo and co-workers reported the synthesis of 1,2,3,4-tetrahydro-isoquinoline through *O,N*-acetal intermediate. This method is mild and efficient procedure with application (Figure 13) (Kubo *et al.*, 1987).

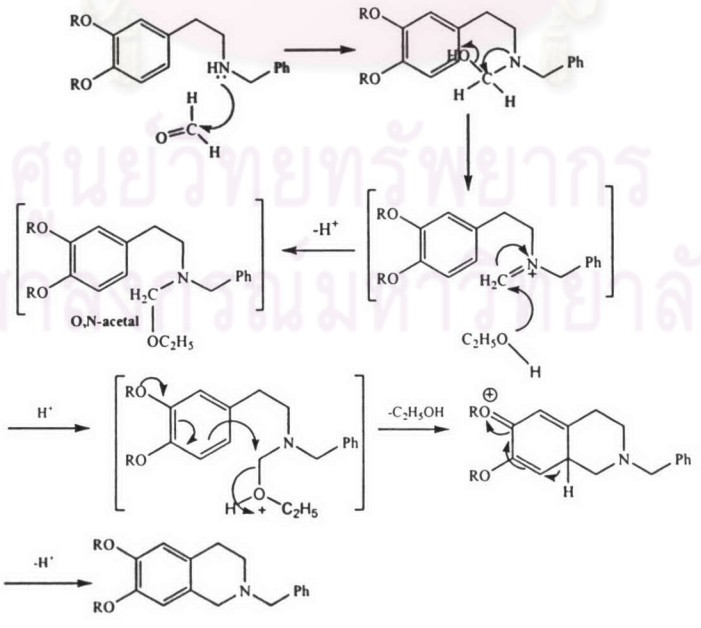
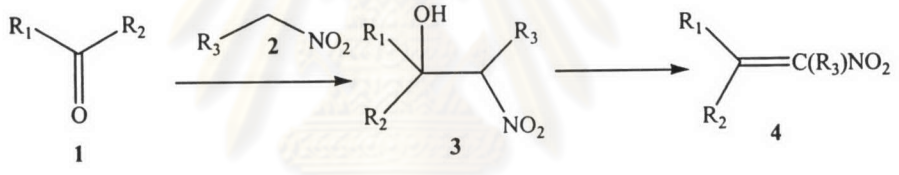


Figure 13 The proposed mechanism of *O,N*-acetal cyclization reaction

General methods concerning the preparation of 3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives

1. Preparation of Nitroalkenes from Aldehydes and Ketones

The most versatile preparation of nitroalkenes 4 involves the Henry condensation reaction of an aldehyde or ketone 1 with a nitroalkane 2 followed by dehydration of the resultant β-nitro alcohol 3. The Henry condensation reaction is routinely effected under mildly basic conditions. Recently, several reagents including dicyclohexylcarbodiimide (DCC) (Knochel and Seebach, 1982), pivaloyl chloride, methanesulfonyl chloride, or phthalic anhydride have been used for the dehydration step. Knochel and Seebach have reported that DCC in the presence of a copper(I) chloride catalyst in diethyl ether or dioxane is a convenient reagent for the conversion of 3 into 4.



2. Reduction of unsaturated carbon-carbon double bonds

Catalytic hydrogenation: Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents can be catalytically hydrogenated to saturated hydrocarbon. Catalytic hydrogenation on almost 99% known alkenes and hydrogen can be reacted at temperatures between 0 and 257 °C (Morison and Boy, 1983). Many catalysts have been used for example, Raney Nickel, Pt_2O, Rhodium, Ruthenium, Palladium, and Copper chromite. Hydrogenation in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and should be required higher temperatures and under pressures.

Metallic hydrides: Catalytic hydrogenation is most often used. Unsaturated double bond may be reduced by other reagent as well. Among these are sodium in

methanol, chromous ion, zinc and acids, lithium and aliphatic amine. However, metallic hydrides such as lithium aluminium hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) do not in general reduced carbon-carbon double bond, although this can be done in special cases, where double bonds is polar.

The reduction of nitroalkenes to produce a nitroalkane can be achieved by several distinct methods. Reagents such as sodium borohydride, sodium cyano-borohydride, various complex metal hydrides, and catalytic hydrogenation have been employed for this purpose. Of these, perhaps the most widely used method is the reduction using sodium borohydride. Unfortunately, in some case, dimeric products are produced during the borohydride reduction. These arise from Michael addition of the nitronate intermediate with starting nitroalkene. Usually with aliphatic nitroalkenes the formation of these byproducts may be suppressed by reaction at reduced pH. In contrast, sodium borohydride reductions of β-nitrostyrenes often result in significant dimerization even when the reaction is run at pH 3. Some of the more recent reagents developed for nitroalkane production from nitroalkenes have addressed the dimerization problem to demonstrate their synthetic prowess.

It has recently been reported that the use of silica gel in a mixed chloroform-propanol solvent system assists the sodium borohydride reduction of nitroalkenes. The products are obtained in high yield and purity and are largely free of dimeric contaminants. This method is operationally simple and gives pure products under mild conditions. Methanol has also been reported to activate the sodium borohydride reductions of nitroalkenes to give saturated nitro-compounds without dimerization (Varma and Kabalka, 1985). However, the yields are generally inferior to the silica method. Other trialkyl borohydride reagents such as tri-sec-butylborohydride have also been applied with success. Pakrahsi has reported that β-nitrostyrenes may be efficiently reduced to produce nitroalkanes (80-95 %) using sodium borohydride in ethanol-dioxane at 30 °C (Pakrashi *et al.*, 1985). The solvent mixture prevented the production

of dimeric products since the nitronate intermediates were of low solubility in this medium.

3. Reduction of nitro to amine

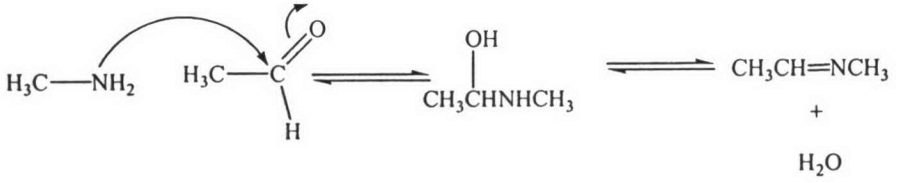
The nitro compounds can be reduced in two general ways: a) by catalytic hydrogenation using molecular hydrogen, or b) by chemical reduction, usually by a metal and acid.

Catalytic hydrogenation: Hydrogenation of a nitro compound to an amine takes place smoothly when the nitro compound in alcohol solution is shaken with catalyst, such as nickel, platinum or palladium carbon under hydrogen gas. This method cannot be used when the molecule also contains some other easily hydrogenation group such as carbon-carbon double bond.

Chemical reduction: This method is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal. In the acidic solution, the amine is obtained as its salts; the free amine is liberated by the addition of base and is separated from the reaction mixture by steam distillation. The crude amine may be contaminated with some nitro compounds, which can be separated by acid-base extraction. Thus, the basic property of the amine is soluble in acid aqueous solution, whereas the nitro compound is insoluble.

4. Schiff base

Schiff bases known as imines (Pine, 1987) are synthesized from the reaction between primary amines and aldehydes or ketones to produce a compound possessing a carbon-nitrogen double bond. Imines are often not very stable, yet it may be important intermediates in some reactions.



The reaction is activated at pH of 3.5 and retarded at pH > 5. In the reaction, dehydration from the carbinolamine, the rate-controlling step, can be accelerated by acid catalysis.

5. Oxidation of glycol to carbonyl compound

Glycol (1,2-diol) is oxidized with periodic acid (HIO_4) or lead tetraacetate by cleavage of carbon-carbon single bond between the hydroxyl groups. Two carbonyl groups are formed in the process. The reaction has been formulated as proceeding through cyclic ester, which undergoes 1,2-elimination illustrated in Figure 13 (Pine, 1987).

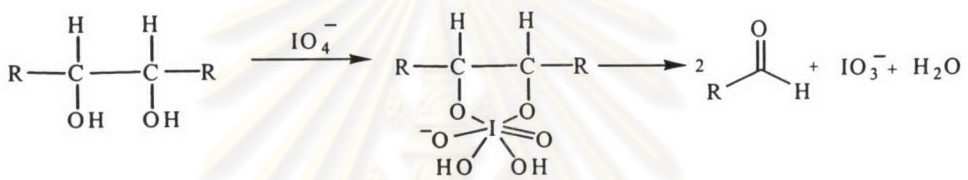


Figure 13 The oxidation reaction of the glycol by periodic acid

Structural features, which retard formation of the cyclic intermediate, decrease the reaction rate. For example, *cis*-1,2-dihydroxycyclohexane is substantially more reactive than the *trans*-isomer. Glycols for which the geometry of the molecule precludes the possibility of a cyclic intermediate are essentially inert to periodate.

6. Electrophilic substitution: Halogenation

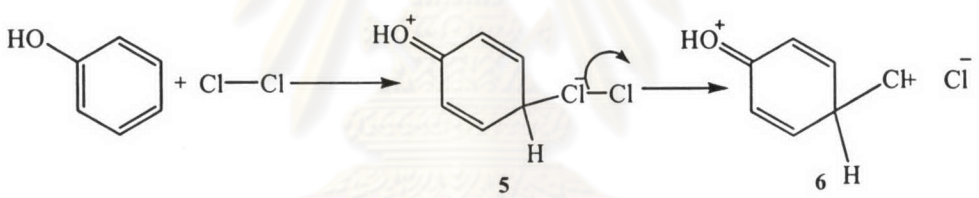
The introduction of the halogens onto aromatic rings by electrophilic substitution is an important synthetic procedure. Chlorine and bromine are reactive toward aromatic hydrocarbons, but Lewis acid catalysts are normally used to achieve desirable rates. Elemental fluorine reacts very exothermically and very careful control of condition is required. Iodine can effect substitution only on very reactive aromatics, but a number of useful iodination reagents have been developed.

A. Chlorine and bromine

Aromatic compounds may be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real

catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. For active substrates such as amines or phenols, no catalyst is needed and indeed the reaction is so rapid that it is carried out with a dilute solution of bromine or chlorine in water at room temperature. Even so, it is not possible with amines to stop the reaction before all of the available *ortho-* and *para-* positions are substituted. With phenols it is possible to stop after one group has entered. The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 which has been polarized by the ring.



Although the equation as written shows an intermediate, which has two chlorines, the Cl-Cl bond may also be broken in the course of the attack so that the only intermediate is 6.

If 5 is present (note that the central chlorine has 10 electrons in its outer shell), then its stability may be such that an outside entity, such as the solvent, may be required to remove Cl^-. If this is the rate-determinating step in these cases, then the rate should be different in different solvents. This has been shown to be the case. Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, including especially chloride ion, accelerate the rate about equally, although if chlorine were dissociating in Cl^+ and Cl^-, the addition of chlorides should decrease the rate, and acids should increase it.

When a Lewis acid catalyst is used along with chlorine or bromine, then the attacking entity is possibly Cl^+ or Br^+, formed in this manner.

$$AlCl_3 + Br_2 \longrightarrow AlCl_3Br^- + Br^+$$

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400 °C), *ortho-para*-directing groups direct *meta*, and vice versa. A different mechanism is operating here, which is not completely understood.

B. Iodine

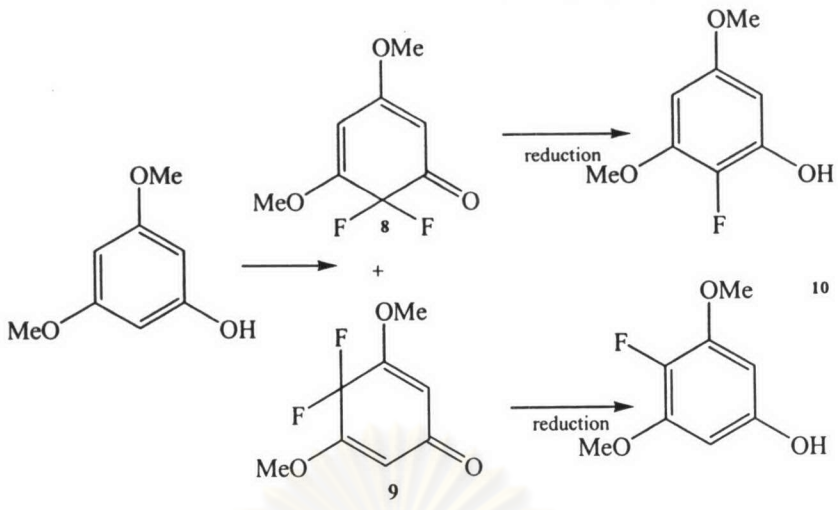
Iodine is the least reactive of the halogens in aromatic substitution, and reversibility is important enough so that iodination is seldom feasible unless some species is present to remove iodide ion as soon as it is formed. When the substrate is an aromatic amine, the reaction occurs because the iodide precipitates as the salt. Otherwise an oxidizing agent must be added. Examples are HNO_3, HIO_3 and H_2O_2, which oxidize the iodide ion to iodine. ICl is a better iodinating agent than iodine itself.

The actual attacking species is less clear in this case than with bromine or chlorine. There are good reasons for believing that I^+ is the electrophile in most situations. Iodine itself is probably too unreactive, except for active species such as phenols, where there is good evidence that I_2 is the attacking entity. There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the catalyst.

C. Fluorine.

Fluorine is too reactive for the fluorination of aromatic rings. However, ClO_3F attacks phenols to give *gem*-difluoro products, which can be reduced to give what amounts to overall substitution of fluorine for hydrogen.

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$



7. Suzuki Coupling Reaction: The palladium–catalyzed cross-coupling reaction of phenylboronic acid with haloarenes

The cross-coupling reaction now accessible via a variety of organometallic reagents may provide a fundamentally common synthetic methodology (equation 1) (Suzuki and Miyaura, 1995).

$$RM + R'\text{-}X \xrightarrow{\text{Pd-catalyst}} R\text{-}R' \qquad \text{eq. 1}$$

In 1972, Kumada and Tamao and Corriu reported independently that the reaction of organomagnesium reagents with alkenyl or aryl halides could be markedly catalyzed by Ni(II) complex. Kochi found the efficiency of Fe(III) catalyst for the cross-coupling of Grignard reagents with 1-halo-1-alkenes and Li_2CuCl_4 catalyst for haloalkanes (Kumada *et al.*, 1972; Tamao *et al.*, 1973; Corriu and Masse, 1972). The palladium catalyzed reaction of Grignard reagents was first reported by Murahashi (Murahashi *et al.*, 1975), the synthetic utility of which was then amply demonstrated by Negishi on the reactions of organoaluminium, zinc, and zirconium reagents (Negishi and Baba, 1976). After those discoveries, many other organometallic reagents have proven to be highly useful as nucleophiles for the cross-coupling reaction, e.g. organolithiums by Murahashi (Murahashi, 1979), organostannans by Migira and Stille (Migita *et al.*, 1983; Milstein and Stille, 1979), 1-alkenylcopper(I) by Normant

(Alexakis and Normant, 1981), organosilicon compounds by Hiyama (Hatanaka and Hiyama, 1988). These reactions are mechanically and synthetically closely related to the present article; however, the reactions mechanism, and their synthetic utility have been extensively review elsewhere.

Organoboron compounds are highly electrophilic, but the organic groups on boron are weakly nucleophilic, thus limiting the use of organoboron reagents for the ionic reactions. The coordination of a negatively charge base to the boron atom has been recognized to be an efficient method of increasing its nucleophilicity to transfer the organic group on boron to the adjacent positive center (1,2-migration reaction). However, intermolecular transfer reaction such as the Grignard-like reaction is relatively rare. Fortunately, organoboron compounds even organoboronic acids and esters, have sufficiently enough reactivity for the transmetalation to other metals. Transmetalations to silver(I), magnesium(II), zinc(II), aluminum(II), tin(IV), copper (I), mercury(II) halides have been extensively studied. In 1987, Negishi reported that iodobenzene selectively couples with the 1-alkynyl group on lithium 1-hexynyl (tributyl) borate through a palladium-catalyzed addition-elimination sequence (Heck-type process); however, the cross-coupling reaction of organoboron compounds, which involves the transmetalation to palladium(II) halides as key step, was found to proceed smoothly when these were activated with suitable bases and have proven to be a quite general technique for a wide range of selective carbon-carbon bond formation. Many organometallic reagents undergo similar cross-coupling reactions, but much attention has recently been focused on the use of organoboronic acids in laboratories and industries since they are convenient reagents, which are generally thermally stable and inert to water and oxygen, thus allow their handling without special precaution. This review summarizes the palladium-catalyzed cross-coupling reaction of organoboron compounds with organic halides or triflates, the reaction mechanism, the scope of synthetic applications, and other related catalytic processes with transition-metal complexes are discussed (Suzuki and Miyaura, 1995).

Palladium-catalyzed Reactions of Organoboron Compounds and Their Mechanism

I. Cross-Coupling Reaction

A. Introduction

A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition-transmetalation-reductive elimination sequences, is shown in Figure 15. Although each step involves further knotty processes including ligand exchanges there is no doubt about the presence of those intermediates (11 and 12) which have been characterized by isolation or spectroscopic analyses. It is significant that the great majority of cross-coupling reactions catalyzed by Ni(0), Pd(0), and Fe(I) are rationalized in terms of this common catalytic cycle.

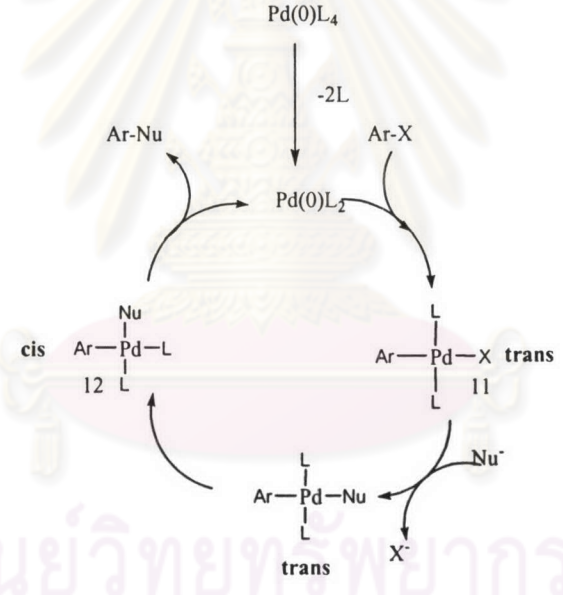


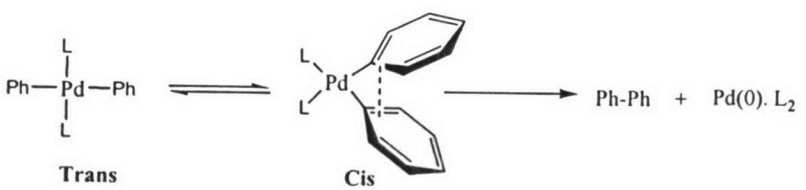
Figure 15 A general catalytic cycle for cross-coupling

Oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable *trans*-σ-palladium(II) complex (11). The reaction proceeds with complete retention of configuration for alkenyl halides and with inversion for allylic and benzylic halides. Alkyl halides having β-hydrogen are rarely useful because the oxidative addition step is very slow and may complete with β-hydride elimination from the σ-organopalladium(II) species. However, it has been

recently shown that iodoalkanes undergo the cross-coupling reaction with organoboron compounds.

Oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in the order of I > OTf > Br >> Cl. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups thus allowing the use of chlorides such as 3-chloroenone for cross-coupling reaction. A very wide range of palladium(0) catalysts or precursors can be used for cross-coupling reaction. $Pd(PPh_3)_4$ is most commonly used, but $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ plus PPh_3 or other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complexes with organometallics or phosphines used for the cross-coupling. Palladium complexes that contain fewer than four phosphine ligands or bulky phosphines such as tris(2,4,6-trimethoxyphenyl) phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinate unsaturated palladium species.

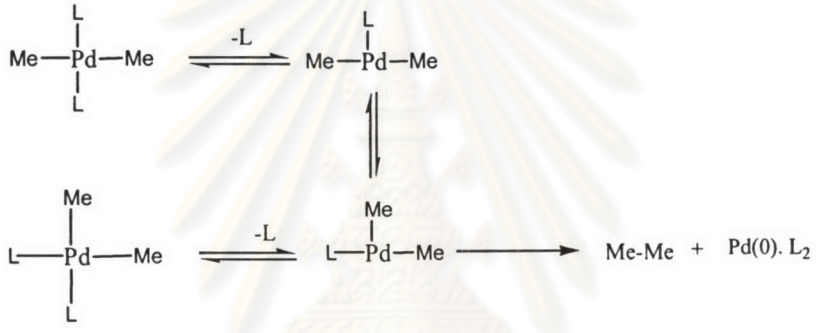
Reductive elimination of organic partners from 12 reproduces the palladium(0) complex. The reaction takes place directly form *cis*-12, and the *trans*-11 reacts after its isomerization to the corresponding *cis*-complex (eq. 2 and 3). The order of reactivity is diaryl- > (alkyl) aryl- > dipropyl- > diethyl- > dimethylpalladium(II), suggesting participation by the π-orbital of aryl group during the bond formation (equation 2). Although the step of 1-alkenyl-or 1-alkynylpalladium(II) complexes is not studied, the similar effect is observed in the reductive elimination of related platinum(II) complexes.



eq. 2

The thermolysis of *cis*–(dialkyl)palladium (II) L_2, which is an intermediate on the alkyl-alkyl coupling, is inhibited by excess phosphine (L), hence it is considered to be initiated by the rate-determining dissociation of phosphine ligand (L) producing a three-coordinated *cis*-(dialkyl)palladium(II) L complex (dissociative mechanism, equation 3). Thus, the effect of phosphine ligands is comparable to the order of ease of their dissociation: dppe << PEt_3 < PEt_2Ph < $PMePh_2$ <$PEtPh_2$ <PPh_3.

On the other hand, *cis*-alkenyl- and *cis*-arylpalladium(II) complexes, which are intermediates in most of cross-coupling reactions discussed here, directly eliminate organic partners from the four-coordinated complex (nondissociative-nonassociative mechanism, equation 2).



eq. 3

Although the mechanism of oxidative addition and reductive elimination sequences are reasonably well understood and are presumably fundamentally common processes for all cross-coupling reactions of organometallics, less is known about the transmetalation step because the mechanism is highly dependent on organometallics or reaction conditions used for the couplings.

In spite of these previous reports, organoboron compounds are quite unlikely to participate in the catalytic cycle of cross-coupling reaction since they are inert to the organopalladium(II) halides (11) such as $PdCl_2$, $PdCl_2(PPh_3)_2$, or $PhPdI(PPh_3)_2$. There is some experimental evidence for the transmetalation to the transition metals. The reaction of organoboranes with organomercurials proceeds under neutral conditions when $Hg(OAc)_2$, $Hg(OR)_2$ or HgO is used. It has also been reported that the addition of sodium hydroxide or other bases exerts a remarkable effect on the transmetalation rate of organoboron reagents with metallic halides, such

as mercuric, silver, auric, and platinic halides. Thus, the transmetalation with transition–metal complexes appears to proceed well indeed, but the choice of suitable bases and ligands on transition-metal complexes is essential.

Preliminary successful results have reported that (*E*)-1-hexenyl-1,3,2-benzodioxaborole couples with iodobenzene in the presence of $Pd(PPh_3)_4$ and bases to produce a mixture of desired and undesired coupling products depending on the base and the catalyst used (equation 4).

3a **13** **14** eq. 4

The formation of normal coupling product 13 predominates when sodium hydroxide or alkoxides are used, whereas a combination of triethylamine and a palladium catalyst without phosphine ligands leads almost exclusively to an abnormal head-to-tail coupling product 14 (Table 3).

Table 3 Reaction Conditions for Head-to-Tail Cross-Coupling.

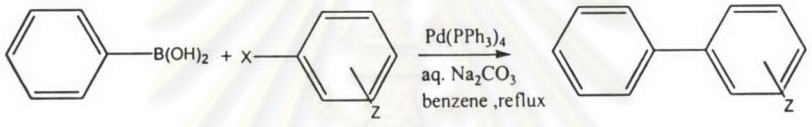
catalyst	*solvent*	*Base (equiv)*	*Time, h*	*Yield, %*
$Pd(PPh_3)_4$	Benzene	None	6	0
$Pd(PPh_3)_4$	Benzene	NaOEt (2)	2	99 (100/0)
$Pd(PPh_3)_4$	Benzene	NaOH (2)	2	99 (100/0)
$Pd(PPh_3)_4$	DMF	Et_3N (5)	20	54 (10/90)
$PdCl_2(PPh_3)_2$	DMF	Et_3N (5)	20	66 (8/92)
Pd black	DMF	Et_3N (5)	20	94 (4/96)
Pd black	DMF	NaOH (2)	6	86 (56/44)

[a]All reactions were carried out at 80 °C by using Pd catalyst (3 mol%), PhI, base and 3a (1.1 equiv).

The formation of the abnormal coupling product 14 can be best understood by the mechanism of Heck reaction (Heck, 1982) for vinylic metal compounds, that often predominates on the cross-coupling reaction of weakly nucleophilic organo-metallics, such as 1-alkenylmercurials, -silanes, and –tin compounds.

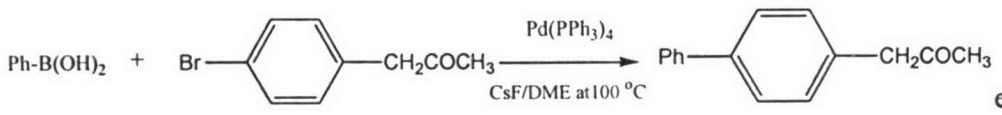
B. Coupling of Arylboron Derivatives: Synthesis of Biaryls

The first observed method to prepare biaryls is shown in equation 5. After this discovery, various modifications have been made for the reaction conditions. A combination of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and aqueous Na_2CO_3 in dimethoxyethane (DME) works satisfactorily in most case.



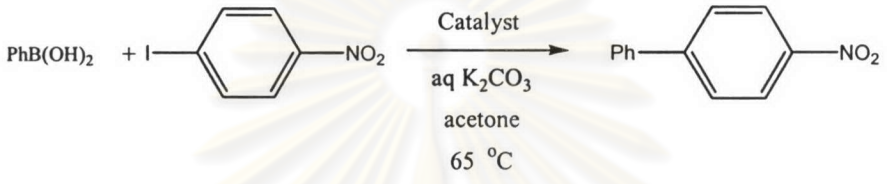
eq. 5

The combination with other bases such as Et_3N, $NaHCO_3$, Cs_2CO_3, Tl_2CO_3, and K_3PO_4 with or without Bu_4NCl and 8-Crown-6 also have been used. The reaction is successful for aryl triflates and iodo- and bromoarenes. Chlorobenzene derivatives are generally quite inert to oxidative addition, but some of π-deficient heteroaryl chlorides gives coupling products. The reaction proceeds more rapidly in homogeneous conditions (aqueous base in DME), but the reasonable yields are also obtained under heterogeneous conditions. For example, K_2CO_3 suspended in toluene works well for base-sensitive reactants. The coupling is also carried out in an aqueous medium by using water-soluble phosphine ligand (*m*-$NaO_3SC_6H_4PPh_2$). Although the conditions using such bases are not entirely compatible with the functional groups present in the desired reactants, the extremely mild conditions using CsF or Bu_4NF allow the synthesis of various functionalized biaryls (equation 6).



eq. 6

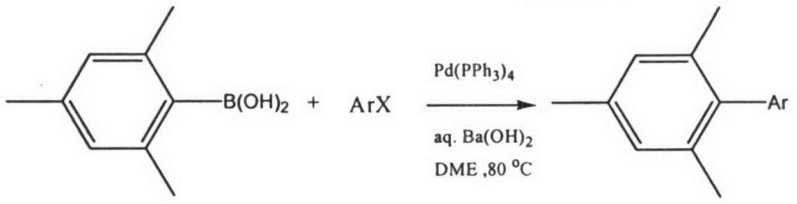
Phosphine-based palladium catalysts are generally used since they are stable on prolonged heating; however, extremely high coupling reaction rate can be sometimes achieved by using palladium catalysts without a phosphine ligand such as $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and $Pd_2(dba)_3.C_6H_6$. Phosphine free palladiums are approximately 1 order of magnitude more active than $ArPd^{II}I\cdot PPh_3)_2$, both of which are in turn markedly more active than $Pd(PPh_3)_4$ (equation 7).



eq. 7

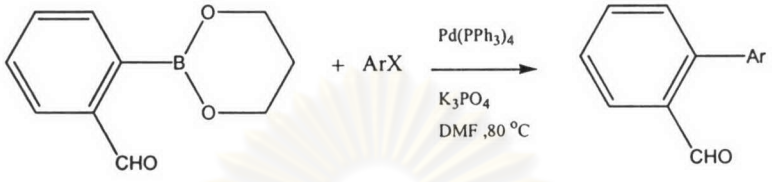
catalyst: $Pd(PPh_3)_4$ (8 h, 23 %); $PhPdI(PPh_3)_2$ (0.33 h, 53 %); $Pd(OAc)_2$ (0.75 h, 98 %)

Although steric hindrance of aryl halides not a major factor for the formation of substituted biaryls, low yields are resulted in when using ortho-disubstituted arylboronic acids. For example, the reaction with mesitylboronic acid proceeds only slowly because of steric hindrance during the transmetalation to palladium(II) halide. The addition of strong bases, e.g. aqueous NaOH or $Ba(OH)_2$, both in benzene and DME exerts a remarkable effect on the acceleration of the coupling rate (equation 8). Although weak give better results for less hindered arylboronic acids, the order of reactivity for mesitylboronic acids corresponds to the basic strength: $Ba(OH)_2 > NaOH > K_3PO_4 > Na_2CO_3 > NaHCO_3$.



eq. 8

ArX: 2-$MeOC_6H_4I$ (80 %), 2-ClC_6H_4I (94%), 2-bromonapthalene (86 %)

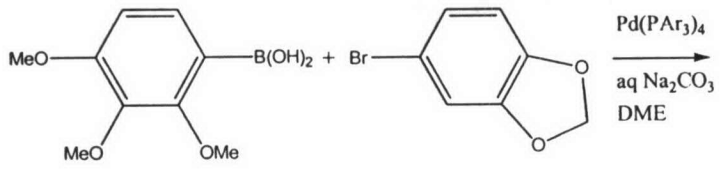


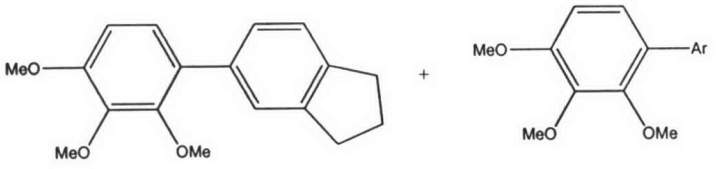
eq.9

ArX: iodomesitylene (73%), 2-$MOMOC_6H_4I$ (85%) , 2-$MeO_2CC_6H_4Br$ (63 %)

Even if here is no great steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive hydrolytic deboronation. The rate for the cleavage of $XC_6H_4B(OH)_2$ with water at pH 6.7 is shown as follows: (relative to phenylboronic acid) 2,6-dimethoxy (125), 2-F (77), 2-Cl (59), 2-MeO (11), 4-MeO (4.2), 2-Me (2.5), 3-F (2.3), 3-Me (2), 4-F (1.7). For example, the coupling of 2-formylphenylboronic acid with 2-iodotoluene at 80 °C using an aqueous Na_2CO_3 in DME gives only 54 % of biaryl with benzaldehyde (39 %). The yield can be improved to 89 % by using the corresponding ester of boronic acid and anhydrous K_3PO_4 suspended in DMF (equation 9). However, Negishi's coupling using corresponding arylzincs or Stille's coupling using arylstannanes is perhaps a more general alternative in such cases.

An aryl-aryl exchange between the palladium center and phosphine ligands in palladium(II) complexes I enhance by electron-donating substituents(Segelstein *et al.*, 1995). The synthesis of biaryls substituted with electron donating groups results in contamination of the coupling product with the aryl group on phosphine ligand. Tris(2-methoxyphenyl) phosphine is effective in reducing the formation of such by-product while maintaining a high yield of the desire product (equation 10) (O'Keefe, Dannock and Marcuccio, 1992).

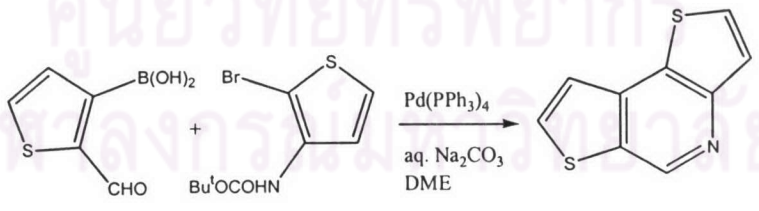




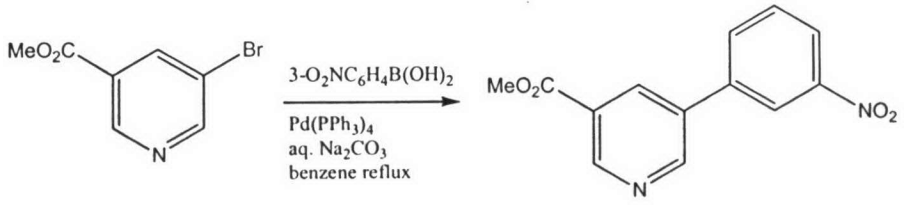
Ar = Ph 54 % 27 %

Ar = *o*-$MeOC_6H_5$ 79 % 3 % eq. 10

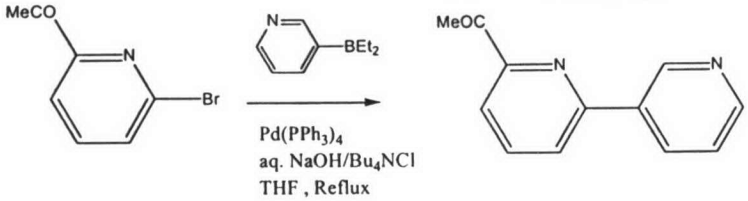
The cross-coupling reaction of arylboronic acids is largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding nontoxic by-products. The reaction offers an additional great advantage of be insensitive to the presence of *ortho*-functional groups or heteroaromatic rings. Gronowthz has shown that unsymmetrical substituted bithienyls and thienylpyridines can be regioselectively synthesized by the cross-coupling reaction of thienylboronic acids (equation 11) (Gronowitz *et al.*, 1988). Arylation of 5-bromonicotinates is demonstrated by Thompson (equation 12) (Thompson, 1984). Diethyl (3-pyridyl) borane synthesized by Terashima is a unique air-stable reagent for the heteroarylation (equation 13) (Terashima and Kamada, 1984).



81 % eq.11

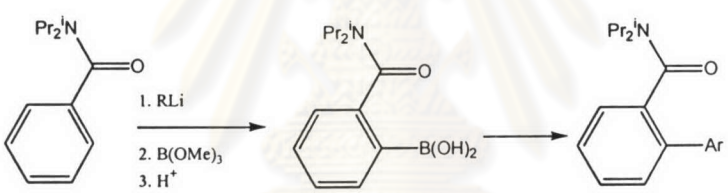


73 % eq. 12

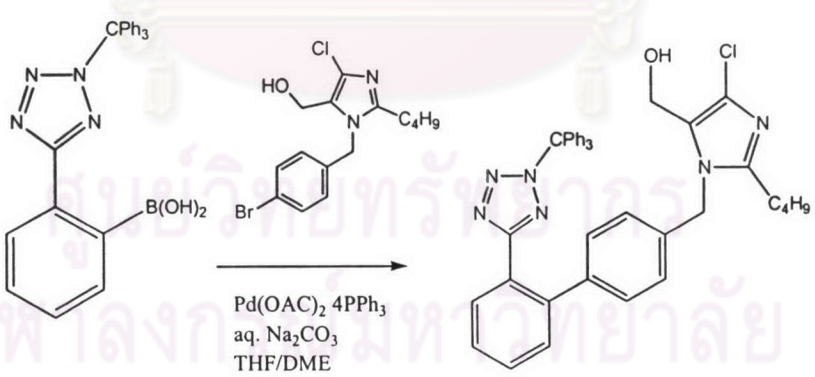


77 % eq. 13

The ready availability of *ortho*-functionalized aryl-boronic acids by directed *ortho*-metalation-boronation sequence provides a synthetic link to the cross-coupling protocol. Snieckus has amply demonstrated that the sequence has considerable scope for the synthesis of unsymmetrical biaryls, heterobiarys, and terphenyls (equation 14) (Sharp and Snieckus, 1985). The utility of the sequence has recently shown by the industrial-scale synthesis of a nonpeptide angiotensin II receptor antagonist (equation 15).



eq. 14



eq. 15