CHAPTER – I

A REVIEW ON HECK REACTION

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1. INTRODUCTION

The palladium-catalysed coupling of haloarenes and haloalkenes with alkenes or alkynes to form new C-C bonds was discovered by Richard F. Heck in the late sixties[1]. The careful choice of substrates and appropriate reaction conditions lead to impressive sequences consisting of even different reaction types that occur not only in a consecutive mode, but also in a single operation.

The Heck reaction opens the door to a tremendous variety of elegant and highly convergent routes to structurally complex molecules. The reaction is not disturbed by heteroatoms such as oxygen and nitrogen nor by sulphur and phosphorus (with some limitations).

The spectrum of recent achievements starts with a range of chemoselective and regioselective monocouplings of highly functionalised substrates with unsymmetrical and multisubstituted reaction partners. The other advantages include cascade reaction in which three, four, five and even eight new C-C bonds are formed to yield oligofunctional and oligocyclic products with impressive molecular complexity. The enantioselective construction of complex natural products with quaternary stereocentres has been achieved[2] with Heck reaction in key steps, such as the synthesis of crinan, picrotoxinin, morphine, epibatidine etc.

The Heck reaction presents one of the simplest ways to obtain variously substituted olefins, dienes and other unsaturated compounds, many of which are useful as dyes, UV screens, pharmaceuticals and optoelectronic devices.

Today, the Heck reaction is indispensable in the arsenal of synthetic methods available to organic chemists. It has already found many applications in industry. In view of our work on Heck reaction, a brief review is presented in the following pages. Several recent reviews[3-5] on various aspects of Heck reaction are available which indicate the growing interest in this reaction.

2. MECHANISM

A reasonable concept for the mechanism of the Heck reaction which has emerged is given in a simplified manner (Chart-I, Scheme-1). The mechanism consists of five important steps, (A) preactivation, (B) oxidative addition, (C) migratory insertion, (D) termination and (E) reductive elimination.
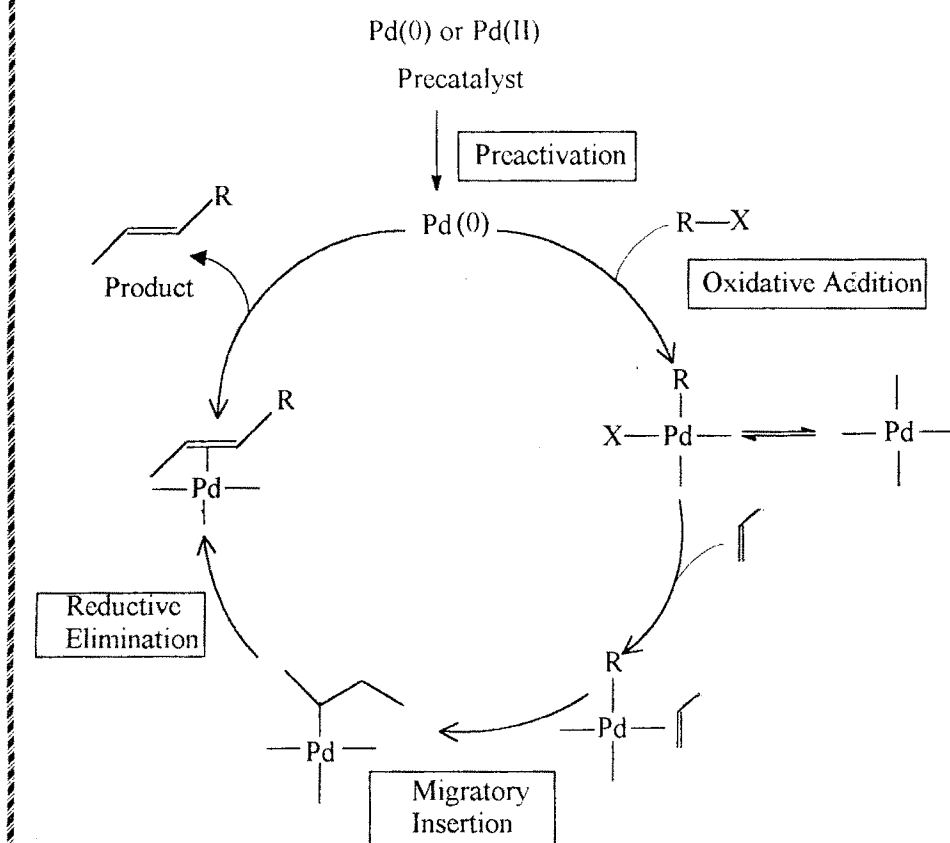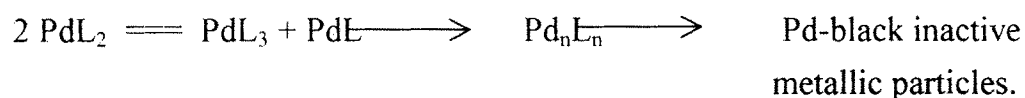
A) Preactivation step

The preactivation step has been extensively studied by Amatore et al.[6] for phosphine-assisted reactions. This step includes reduction of Pd(II) complexes to Pd(0) and the generation of active species through multiple ligand exchange equilibria.

The primary reduction of Pd(II) to Pd(0) is most likely accomplished by phosphine in the phosphine-assisted catalytic cycles[7]. The reduction is assisted by hard nucleophiles, of which the most common are hydroxides[8], alkoxide ions[9], water[10], water and acetate ion[11] etc. Most probably, the nucleophile either attacks the coordinated phosphine in a way that can be viewed as a nucleophilic substitution at phosphorus atom. An inner-shell mechanism involving the reductive elimination of phosphonium species, which is transformed into phosphine oxide is also possible (Chart-II, Scheme-2). In the presence of excess ligand, the concentration of active species is strongly decreased, which leads to the inhibition of catalytic process.

CHART – I

Scheme – I

$$2 \ PdL_2 \ \rightleftharpoons \ PdL_3 + PdL \longrightarrow \quad Pd_nL_n \longrightarrow \quad \text{Pd-black inactive}$$

metallic particles.

This problem arises in all methods of the generation of catalytically active Pd complexes, either by reduction of PdL_2X_2 by means of chemical reductants or by reaction of $Pd(OAc)_2$ with 3 equivalents of phosphine[7].

B) Oxidative addition

The oxidative addition proceeds as a concerted process in which C-X bond rupture is more or less perfectly synchronized with the formation of M-C and M-X bonds. The oxidative addition is much less sensitive to the substituents in the unsaturated system but much more sensitive to the nature of nucleophile and the strength of C-X and M-X bonds. The order of reactivity for common oxidative addition is $I \gg OTf > Br \gg Cl$ [12]

The stepwise addition-elimination mechanism of nucleophilic aromatic or vinylic substitution, in which the addition to the unsaturated system is the primary and often rate limiting stage.
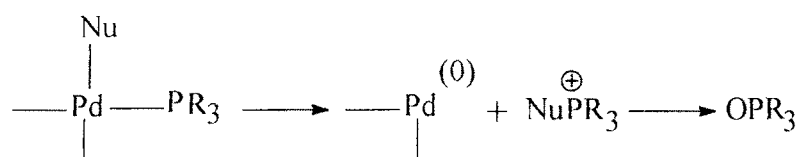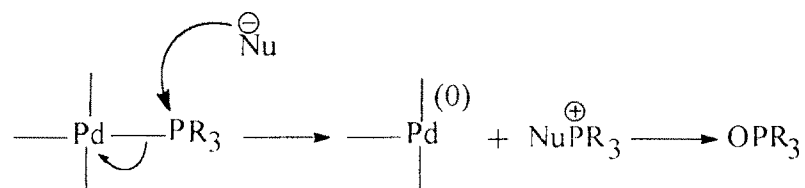
In most cases except for the complexes with chelating ligands, the isolable product of the oxidative addition possesses trans-geometry, the cis-complex being formed first. Moreover, the cis-complex enters the next stage of catalytic cycle. Recent studies have indicated the formation of cis-adduct and cis-trans isomerisation. The latter process can proceed through dissociation – isomerisation – addition and through association – pseudorotation – dissociation.
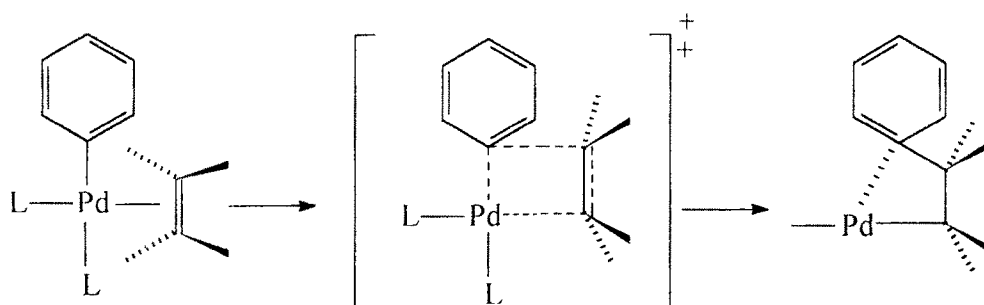
C) Migratory Insertion

Migratory insertion is the product forming step of the Heck cycle, in which a new C-C bond is formed. It is the step which is responsible for regio- and
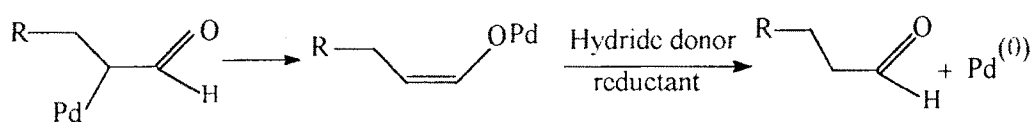
CHART – II

Scheme -2

$$\begin{array}{c} \text{—Pd—PR}_3 \xrightarrow{\quad} \text{—Pd}^{(0)} + \text{NuPR}_3^{\oplus} \xrightarrow{\quad} \text{OPR}_3 \end{array}$$

with $\overset{\ominus}{\text{Nu}}$

$$\begin{array}{c} \text{Nu} \\ | \\ \text{—Pd—PR}_3 \xrightarrow{\quad} \text{—Pd}^{(0)} + \text{NuPR}_3^{\oplus} \xrightarrow{\quad} \text{OPR}_3 \end{array}$$

Scheme - 3

Scheme - 4

Scheme - 5

stereo discrimination as well as the substrate selectivity. The understanding of this step is realized by three possibilities.

i) RPdX intermediate behaves, similar to organometallic derivatives of nontransition and early transition metals, as a carbanion and the insertion is a nucleophilic addition similar to found in vinylic nucleophilic substitution mechanism. A well-known high reactivity of typical Michael donors (acrylates, acrylonitriles etc.) in the Heck reaction is the only evidence.

ii) RPdX and particularly RPd^+ intermediates are metal-centered electrophiles attacking the double bond in a sort of classical electrophilic addition process.

iii) RPdX and RPd^+ intermediates add to the double bond in a concerted process.

The data gathered for the reactivity and selectivity of the migratory insertion step showed that the electrophilicity of aryl-Palladium species has nothing or atleast little to do with positive charge, and both $ArPd^+$ and ArPdX may behave as a tacit electrophile with donor olefins or a tacit nucleophile with acceptor olefins (Chart-II, Scheme-3).

D) Termination

After the migratory insertion the palladium(0) is released and launches the next turn of the Heck cycle. There are several possibilities of termination which are discussed below.

i) Palladium hydride is eliminated to release the double bond (Chart-II, Scheme-4). This is the most common termination of the Heck-Mizoroki reaction[13].

ii)   Elimination of other Palladium-metal complex occurs with the same outcome.

iii)   Palladotropic shift may occur giving a new intermediate. The evidence for this process is the arylation of enones which gives the product of Michael addition instead of Heck arylation (Chart-II, Scheme-5).

iv)   The PdH elimination cannot occur and hence the termination occurs by nucleophilic attack at Pd, which either by nucleophilic substitution or by reductive elimination of coordinated nucleophilic leads to the release of Pd(0).

v)   The alkylpalladium intermediate goes into a subordinate catalytic process – a cascade of Pd-catalysed transformation (Chart-III, Scheme-6).

E) Palladium Hydride Elimination

After elimination, PdH is coordinated to alkene. If PdH is not scavenged fast by base, the readdition to the double bond may occur. As PdH is smaller than hydrocarbyl palladium, it adds to either end of the double bond, giving a new intermediate which can pass Pd further along the chain (Chart-III, Scheme-7). PdH can also be scavenged by starting alkene, which is always more reactive than the Heck product, due to its smaller size. This process leads to the isomerisation of alkenes, which results in the formation of isomeric Heck product with the wrong stereochemistry[14] (Chart-III, Scheme-8).
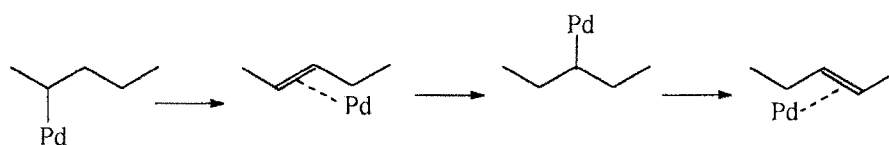
The selectivity of the Heck reaction can be explained by a concerted syn-elimination of PdH. This process is opposite to the addition of PdH to the double bond. Hence syn-elimination defines the stereochemistry of the Heck reaction.
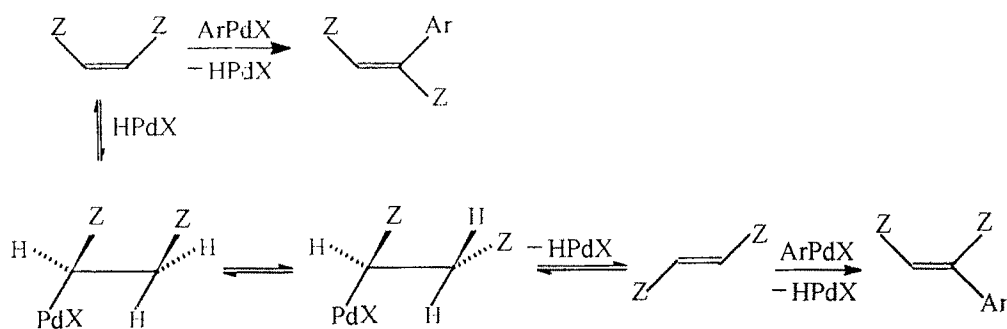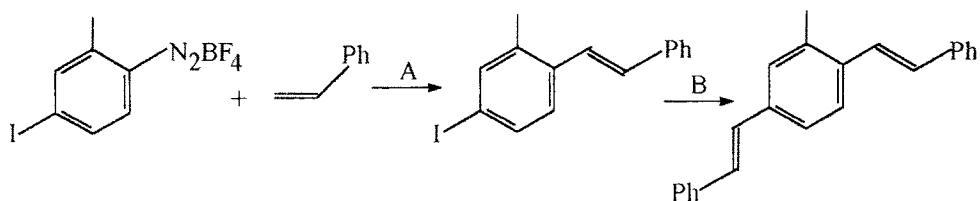
CHART - III

Scheme - 6
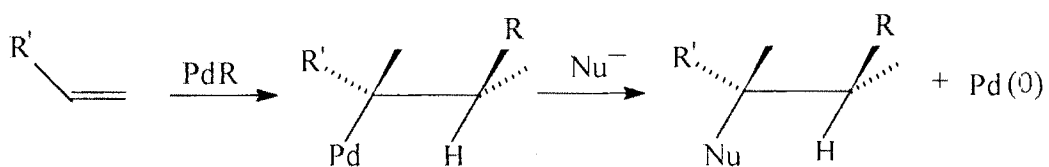
Scheme - 7

Scheme - 8

Scheme - 9

A : $Pd(OAc)_2$ (2 mol %), EtOH, 80^0 C.

B : $Pd(OAc)_2$ (2 mol %), $NaHCO_3$, Bu_4NCl, DMF, 100^0 C.

3. INFLUENCING PARAMTERS OF HECK REACTION :

The important parameters such as leaving group, temperature, solvent, base and ligands play important role in reactivity and selectivity of Heck reaction.

3.1 Effect of Leaving Group

The nature of the leaving group 'X' affects the rate of addition. The order of reactivity is ArI > ArBr >> ArCl [15]. The oxidative addition of haloarenes to Pd(0) is in many cases the rate determining step. Many successful reactions with alkenyl triflates have demonstrated the advantages of this leaving group. Addition of metal halides or tetrabutylammonium halides can also facilitate Heck couplings. Similarly in many cases the Heck reaction is also accelerated by silver(I) [16] and thallium(I) salts [17].

Besides halides and triflates, other electrophiles such as diazonium iodonium salts [18] have been tested for Heck-type reactions. The reaction with diazonium salts does not require the presence of base and phosphines, the addition of which leads to uncontrolled decomposition of diazonium salts (Chart-III, Scheme-9). The most common solvents used are alcohols, the basicity of which may be enough for the deprotonation, which may lead to the transesterification of esters or esterification of carboxylic acids [19].

Due to mild conditions and high reactivity, diazonium salts are a valuable arylating reagents for cyclic olefins such as camphene, 2,5-dihydrofuran [20] etc.

Iodonium salts show a similar behaviour as diazonium salts, the reaction occurs at low temperature with high rates, if diaryliodonium salts are taken as arylating agents in water. At room temperature, only one aryl group of iodonium salt is transferred to the product, while at 100°C, both aryl groups are utilized (Chart-IV, Scheme-10).
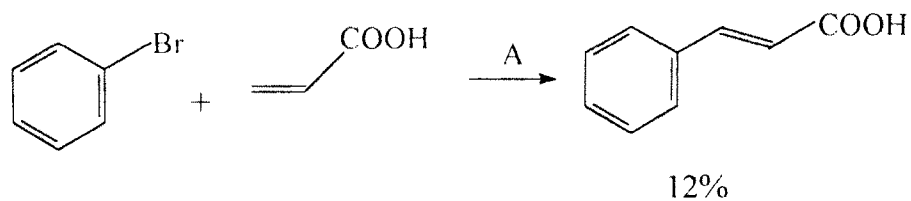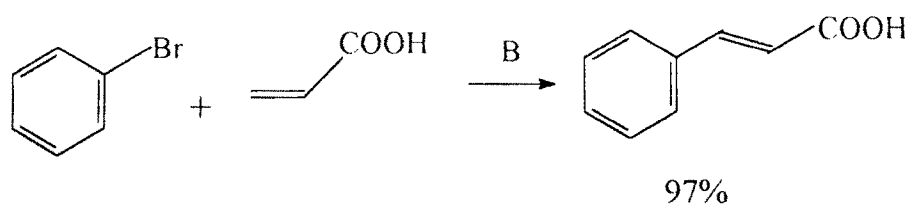
CHART – IV

Scheme - 10
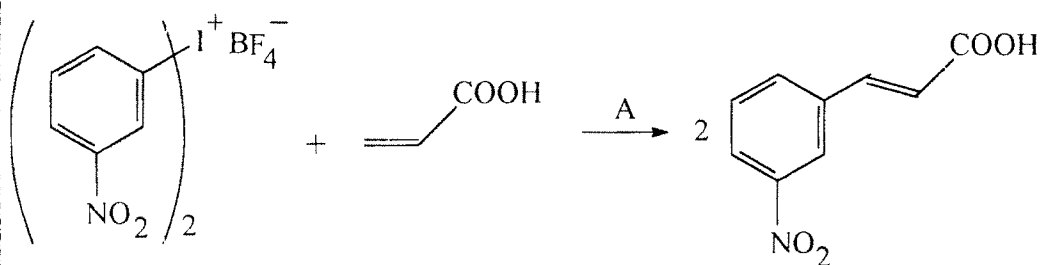
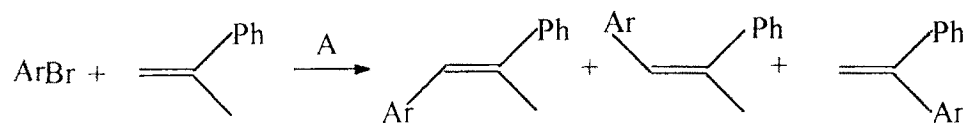A : $Pd(OAc)_2$, Na_2CO_3, H_2O, r.t. 1hour.

Scheme -11

12%

A : $Pd(OAc)_2$, $P(o - Tol)_3$, K_2CO_3, DMF, 80^0 C.

97%

B : $Pd(OAc)_2$, $P(o - Tol)_3$, K_2CO_3, $DMF - H_2O$, 100^0 C.

Scheme - 12

A : hc (0.1 mol %), base, DMA, 140^0 C.

3.2 Effect of Temperature

The Heck reaction is carried out normally in the range of 70° to 100°C, though chloroarenes are practically unreactive under these conditions. It has been shown that Heck reaction can be performed at room temperature with aryl diazonium salts[18],N-nitroso-N-arylacetamides[21] and iodocompounds, even haloarenes and haloalkenes reacts at room temperature when high pressure[22] is applied or phase transfer catalysts such as tetrabutylammonium salts[23] are added.

Additional improvement of Heck procedure can be sought in ultrafast heating and pressure effects. Very fast heating by means of microwaves leads to shortening of the reaction time, while the yields and selectivity do not greatly differ from the same reactions carried out using conventional heating. Most probably, the influence of microwave heating is associated with direct and uniform input of energy to the reaction media. Uniform transfer of heat directly to the reacting molecules by means of absorption of microwave energy by polar solvent effectively affords higher temperature than those achievable through conventional heating.

High pressure can also have a beneficial effect on Heck reactions. The key steps of the Heck cycle – oxidative addition and migratory insertion are likely to be accelerated by pressure[22]. Pressure extends the lifetime of Pd catalyst. High pressure is also likely to favour association – dissociation ligand exchange mechanisms involving five –coordinate intermediates.

3.3 Effect of Solvents

Initially, dipolar aprotic solvents such as dimethyl formamide (DMF), N-methyl pyrrolidone (NMP), Dimethyl sulfoxide (DMSO) and acetonitrile were common solvents used in Heck reactions. But the pioneering work by Beletskaya

et al.[23] many alkene arylation are also known to proceed superbly in aqueous solution. Thus, excellent results were achieved with water soluble triaryl phosphine ligands in water containing acetonitrile[24]. In fact, water accelerates the reaction, especially in the presence of quaternary ammonium salts[25].

Now a days, the search for alternative media for Heck chemistry is targeted at the development of highly productive, environmentally safe, recyclable techniques, which can be promoted to large scale applications. The use of aqueous solvents pursues the development of environmentally and technologically safe processes, but also brings a new dimension into the chemistry of Pd-catalysed reactions.

Water is one of the most polar solvents. It must have an accelerating influence on the Heck reaction as it promotes the migratory insertion to follow the cationic mechanism. Water acts as a good ligand for palladium-catalysed reactions, particularly effective in phosphine-free reactions. Due to its high concentration it is able to displace the other labile ligands from the coordination shell of palladium, particularly iodide which poisons the catalyst and blocks the cationic path. Water and aqueous organic solvents can be successfully used for carrying out the Heck reaction in the aqueous phase catalysed by simple palladium salts in presence of inorganic bases such as K_2CO_3, Na_2CO_3, KOH or $NaHCO_3$. The presence of water in the solvent has a definite positive influence on the reaction rate and efficiency of the catalytic system (Chart-IV, Scheme-11).

Other than water, molten salts (ionic liquids) are used as media. It allows for both easy recycling of catalytic systems and possible activation of catalyst[26]. Molten salts are highly polar, thus facilitating the cationic mechanism of Heck

reactions. The following molten salts have been used : nBu_4NBr, ph_3MePCl, ph_3MePBr etc.

Similarly supercritical and subcritical fluids can also be used as media[27]. Supercritical CO_2 is considered as one of the most perfect environmentally friendly solvents. Liquid CO_2 is a good solvent for organic compounds but very poor solvent for inorganic salts and complexes. Solvent properties of CO_2 resemble those of fluorinated liquids so called fluorus systems.

3.4 Effect of Base

The nature of base plays an important role in Heck reaction. Depending on the nature of base the process leads to a mixture of internal and terminal olefins with different ratio (Chart-IV, Scheme-12). The ratio of internal and terminal olefins in presence of different bases are tabulated below :

Table – 1 :

Base	Internal/Terminal	Internal E/Z
NaOAC	39/61	17
$(iPr)_2NEt$	95/05	2.5

The reaction in the presence of inorganic base such as NaOAc gives the mixture of internal and terminal olefins with a ratio apparently equal to the ratio of the number of protons at the respective sites, which has been interpreted as a result of conventional base independent syn-elimination.

If base catalysed elimination can occur, it would have a strong influence both on the reactivity and stereochemistry of Heck reaction. The stronger base can start the process to base-catalysed elimination giving a more stable internal olefin.

The strength of base affects the elimination of terminal and internal hydrogen. Bulky amine probably is less efficient in the abstraction of proton from PdH, thus giving the addition-elimination reactions more time to settle down to the equilibrium.

Both internal and terminal olefins equilibrate through reversible addition and elimination of PdH, which stays bonded with olefin. The preferred conformation of the terminal olefin complex is likely to be the one with the double bond bearing a bulky palladium pendant remove the aryl group. Readdition from this complex leads to the σ-Pd complexes with configurations ready for the elimination to give the Z-isomer of internal olefin. The E/Z ratio of internal olefin undergoes significant change, thus revealing the isomerisation route.

3.5 Effect of Ligand

To increase the catalytic activity and productivity in the Heck reaction different ligands have been used. The ligands used in Heck reactions are phosphine, palladacycles; carbene complexes, phase-transfer agents and palladium nanoparticles etc.

i) Phosphine

The phosphine assisted Heck process was made in the early 1980's by Spencer[28], who showed that the arylation of olefins with activated aryl bromides can be carried out in less amount of catalyst in presence of polar aprotic solvents with high yield. Spencer modified phosphine ligands into different varieties which became a basic technique successfully used until today for all kinds of reactions belonging to Heck chemistry with Bromo- and Iodo derivatives.

The phosphine assisted reactions were targeted at increasing the activity of catalytic system. The increase of the steric bulk in the phosphine gave the

infinitely stable Pd(0) complex, which is totally inactive in Heck reaction even with bromobenzene[29]. Quite recently, tris (tert-butyl) phosphine has been shown to be a good catalyst for the Heck reaction with arylchlorides, including not only the activated ones, but also chlorobenzene itself and even deactivated p-methoxychlorobenzene and o-chlorotoluene (Chart-V, Scheme-13). Following table indicates the effect of ligand on productivity in Heck reactions.

Table 2 : Comparison of phosphine ligands in Reactions of Bromo- and chloroarenes with n–butylacrylate (2.5 mol % Pd (dba)$_2$, 2L, NaOAc, DMF)[30].

Substrate	Conditions	Ligand			
		P(o-Tol)$_3$	tBu$_2$PFc	tBu$_2$PPh	tBu$_3$P
p-BrC$_6$H$_4$COOMe	2h, 75°C	97	82	n/a	94
p-BrC$_6$H$_4$Me	2h, 75°C	31	100	n/a	100
p-Cl-C$_6$H$_4$COOMe	4h, 110°C	9	97	77	96
p-ClC$_6$H$_4$Me	22h, 110°C	0	67	16	51

This indicates that tBu$_2$PFc and tBu$_3$P are the better ligands for Bromo- and chloroarenes.

ii) Palladacycles

The arylation of disubstituted olefins has been investigated in presence of Herrmann's pallodacycle catalyst (hc) (Chart-V, Scheme-14). It is an ingenious catalyst which breeds a new generation of catalytic systems. It has been shown to be highly effective catalyst for the Heck reaction with arylbromides, particularly those with electron withdrawing groups (CN, CHO, COOMe) in presence of NaOAc in DMF.
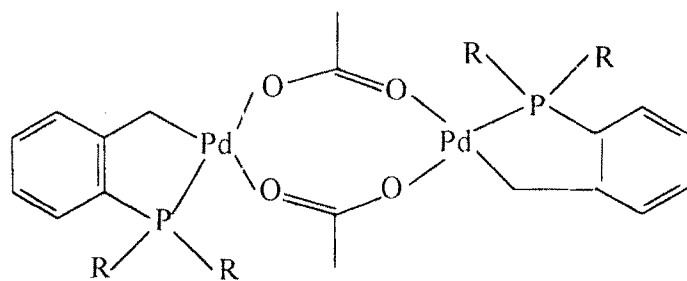
CHART - V

Scheme - 13
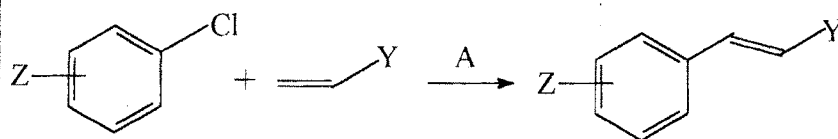
A : Pd(OAc)$_2$ (2 mol %), 4P(tBu)$_3$, Cs$_2$CO$_3$, dioxane, 100 – 120^0 C.
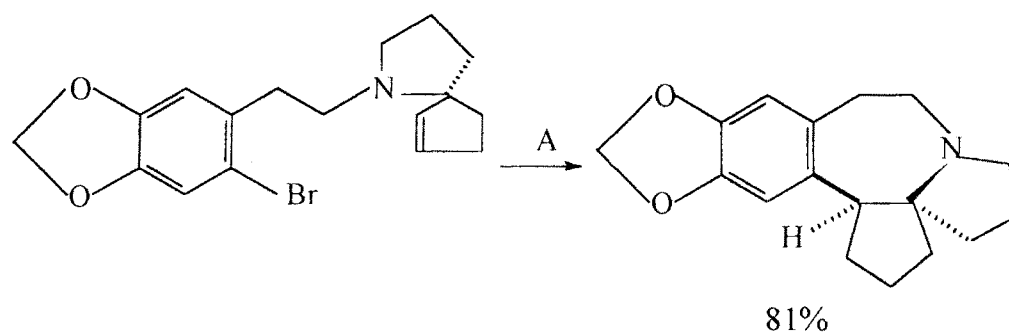Z = OMe, Me, COOMe.
y = COOEt, CN.

Scheme -14

R = o – Tol.

Herrmann catalyst (hc)

Scheme - 15

81%

A : hc (4 mol %), Bu$_4$NOAc, DMF / MeCN / H$_2$O, 110-120^0 C

Apart from model Heck reactions, the application of palladcycles for more complex synthetic purposes has been so far limited to Herrmann's palladaycycle (hc), which is used in those cases where high reactivity and smaller steric demands are in need. Herrmann palladacycle has been successfully applied in the synthesis of several complex molecules[31]. The intramolecular exo-cyclization was catalysed by palladacycle in high yield and stereoselectivity (Chart-V, Scheme-15). The palladacycle showed spectacular efficiency for the enantioselective synthesis of estrone by intramolecular cyclization. The reaction in aqueous solvent was very fast and gave a quantitative yield of desired estrone precursor. Other catalysts such as $Pd(OAC)_2/Ph_3P$ gave yields not exceeding 63-85% after 15 times longer reaction time[32] (Chart-VI, Scheme-16).

Herrmann catalyst has also been used for the production of naproxen, an anti-inflammatory drug via the Heck arylation of ethylene by 2-bromo-6-methoxy naphthalene[33].
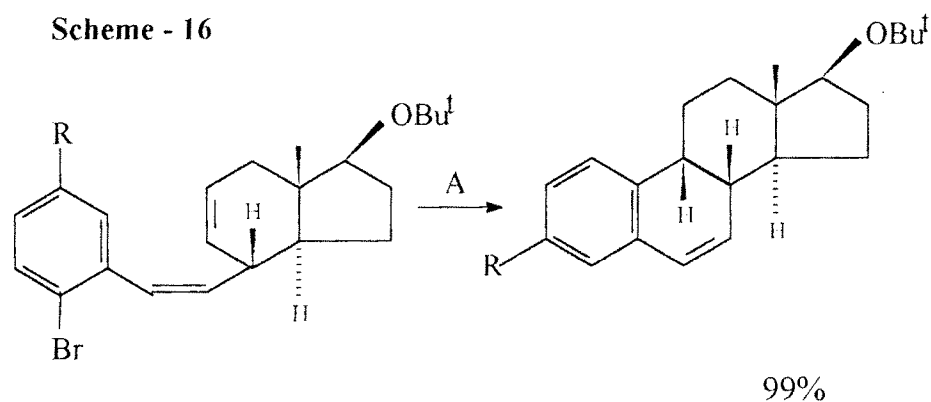
iii) Carbene complexes

A new principle for designing catalysts for palladium-catalysed reactions has been proposed by Herrmann et al.[34]. Stable heterocyclic carbenes, the derivatives of imidazole and 1,2,4-triazole, turned out to be excellent ligands forming a wide range of complexes. Carbene ligands are strong σ-donors which lack any appreciable ability for π-acceptor back bonding, and in this respect these ligands resembles donor phosphines.

Bis-carbene complexes are obtained by electrophilic palladation of imidazolium salts[35,36].Bis-carbene complexes are capable of cis-trans isomerism, the process required for some steps of catalytic cycle[37] (Chart-VI, Scheme-17).
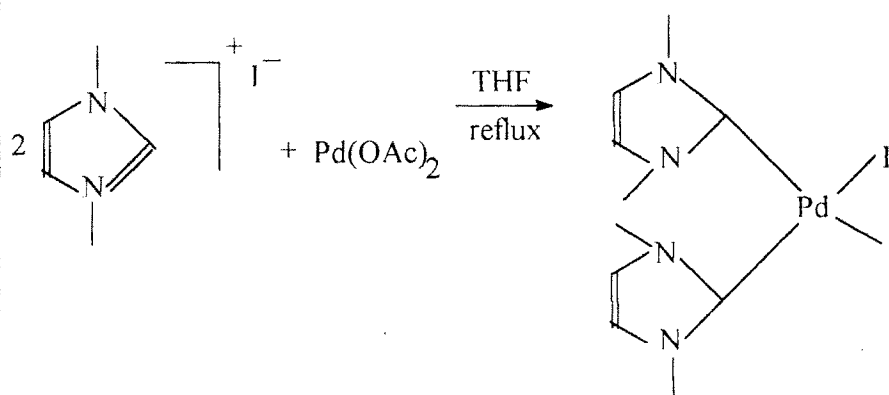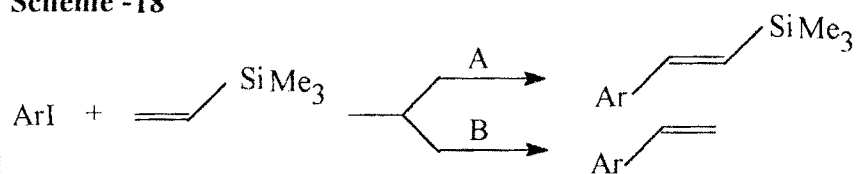
CHART - VI

Scheme - 16

99%

A : hc (2.5 mol %). Bu$_4$NOAc, DMF / MeCN / H$_2$O, 115^{0}C, 4.5 hours.

Scheme - 17

Scheme -18

A : Pd(OAc)$_2$ (3.5 mol %), Bu$_4$NOAc, DMF, r.t.

B : Pd(OAc)$_2$ (3.5 mol %), KF, Bu$_4$NCl, DMF, r.t.

Mixed carbene-phosphine complexes are also available and have been tested in Heck and other palladium-catalysed reactions[38]. Nevertheless, under catalytic conditions, mono-, bis- and chelated carbene complexes showed excellent stability and reaction rates. The performance of carbene palladated complexes are shown below.

Table-3. Performance of carbene-palladium-complexes in the reaction of p-bromoacetophenone with n-butylacrylate (NaOAC,DMA, 120-125°C)

Complex (mol%)	Time(h)	Conversion(%)
cis-(dimy)$_2$PdI$_2$ (0.5%)	10	99
(dmmdiy)PdI$_2$ (0.5%)	10	99
(dimy)Pd^b (2x10^{-4}%)	96	66

Pd^b = Generated insitu.

dimy = 1,3-dimethylimidazol-2-ylidene.

dmmdiy = 3,3'-dimethyl-1,1'-methylenediimidazol-2,2' diylidene.

iv) Underligated and phosphine-free systems

In the mechanism of Heck reaction, steps like oxidative addition, migratory insertion and hydride elimination do not require the assistance of specific ligands. The inherent reactivity of non-ligated palladium is sufficient for oxidative addition to most kinds of C-X bonds.

The most serious drawback of phosphine-free systems is the inherent instability of catalytic cycles driven by palladium complexes with an undefined coordination shell. Mismatch of reaction rates of individual stages leading to the deactivation of catalyst can be caused by many factors including temperature,

variation of concentration, change of the composition of reaction mixture in the course of reaction etc.

Due to lack of strongly bound neutral ligands, phosphine-free systems are bound to proceed via the cationic route via the de-ligation of anionic ligands. Therefore, phosphine-free systems are realized in polar solvents, particularly in aqueous media.

A phosphine-free system has been shown to be quite suitable for the reactions with activated bromoarenes showing almost identical yields to the system supported by 4 equivalents of Ph_3P ligand[39].

v) Phase-Transfer Agents

As in any reaction requiring basic catalysis, the Heck reaction is responsive to phase-transfer phenomena. The beneficial effect of quaternary ammonium salts was first noted by Jeffery[40]. The quaternary ammonium salts may play the following roles.

a) It can acts as a solid-liquid phase-transfer agent in the reaction catalysed by solid salts such as sodium or potassium acetates, carbonates, phosphates, hydrocarbonates etc.

b) It can serve as liquid-liquid phase-transfer agents in the reaction in aqueous solvents, in which the base is soluble while the substrate is not.

c) Halide, acetate and possibly other anions can serve as promoters to increase the rate of some steps of the catalytic cycles.

d) It can act as a stabilizing additive to increase the lifetime of underligated Pd(0) species to match slower oxidative addition rates with less reactive substrates.

e) It can act as an ion exchanger that is particularly important for the reactions with iodides.

Under all conditions, tetrabutylammonium salts exerted a dramatic positive change depending on the nature of base, solvent and catalytic mode. On the other hand, amines as base do not require phase-transfer agent. In presence of base phase-transfer agents show inferior performance.

Mild reaction conditions assisted by tetrabutyl ammonium salts in phosphine-free mode helped to realize a highly chemoselective process of the arylation of vinyltrimethyl-silane[41]. The use of tetrabutylammonium acetate in polar solvent enables a selective formation of β-trimethylsilylstyrenes, while the use of KF assisted by tetrabutylammonium chloride leads to an introduction of vinyl group. This method is convenient for the preparation of styrenes at room temperature (Chart-VI, Scheme-18).

Phase-transfer methods are useful for all sorts of phosphine-assisted, underligated and phosphine-free catalytic systems. The phosphine-free phase-transfer method was found to be advantageous for application of the Heck reaction, with resin-bound (polymer supported) iodobenzyl alcohol and a wide range of olefins (Chart-VII, Scheme-19).

Heck reactions under phase-transfer conditions were applied to the construction of large highly conjugated molecules such as the derivatives of paracyclophane[42] or benzocyclobutenoacenaphthylene[43].

A good choice of stabilizing ligands may have a strong effect on the stability of the catalytic system. N,N-Dimethylglycine (DMG)[44] acts as a good stabilizing ligand and increases the rate of conversion in Heck reaction.
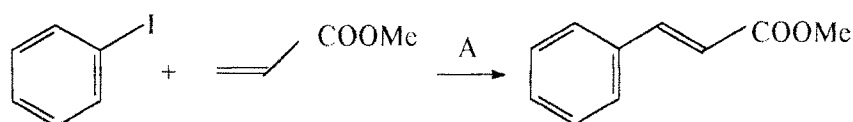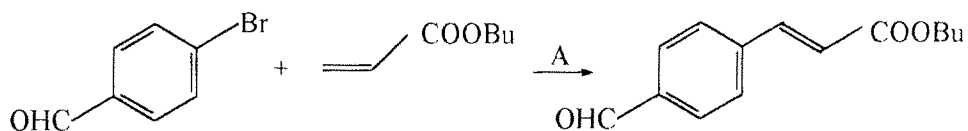
CHART – VII

Scheme - 19
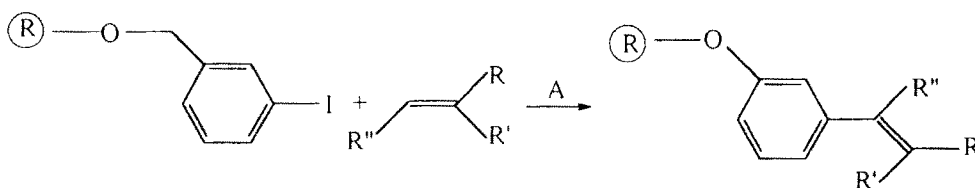
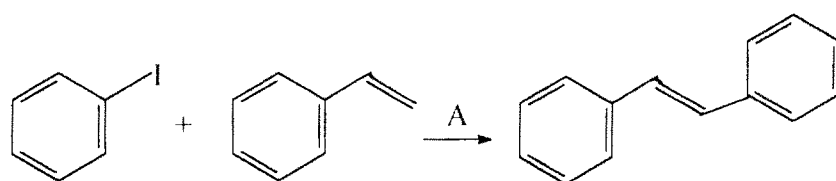A : Pd(OAc)$_2$ (2.5 mol %), NaOAc, Bu$_4$NCl, DMA, 100^{0}C.

Scheme -20

100%

A : hc (0.001mol %), NaOAc, Bu$_4$NBr, DMA, 130^{0}C, 24 hours.

100%

A : hc (0.001 mol%), NaOAc, DMA, 135^{0}C, 12 hours.

93%

A : Pd(OAc)$_2$ (O.007 mol %), Na$_2$CO$_3$, DMF, 80^{0}C, 12 hours.

4. Applications of Heck reaction

Heck reaction has been employed in chemoselective, regioselective and enantioselective couplings of aryl or vinyl halides with alkenes.

4.1 Synthesis of unsaturated systems

The Heck reaction is extensively used for the synthesis of useful unsaturated compounds with high yields (Chart-VII, Scheme-20).

4.2 In Natural Product Synthesis

Application of the Heck reaction in natural product synthesis were limited[25], despite the potential of this reaction for the arylation and alkenylation of alkenes. This is due to the lack of regioselectivity in couplings with unsymmetrical alkenes and isomerisation of products after β-elimination. Many complex natural products have been synthesized by Heck reaction, such as the synthesis of crinan, picrotoxinin, morphine,strychnos alkaloids[46,47] etc.

The alkaloid epibatidine[48] has been synthesised by the arylation of Norbornene and related bicyclic structures in the presence of formate hydride donor for reductive trapping of organopalladium intermediate (Chart-VIII, Scheme-21).

The Heck reaction using nickel bromide was successfully applied to a simple synthesis of the pheromone of *Damaliscus dorcas dorcas* by arylation or vinylation of electron-acceptor substituted alkenes in a reductive mode in a electrochemical cell using iron cathode[49] (Chart-VIII, Scheme-22).

4.3 Industrial application

The Heck coupling reactions are of major importance in organic synthesis and are finding wide application in manufacture of fine chemicals. The first
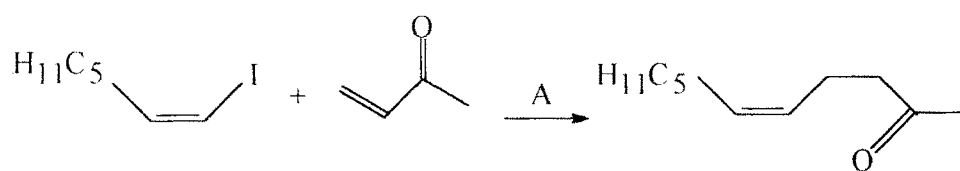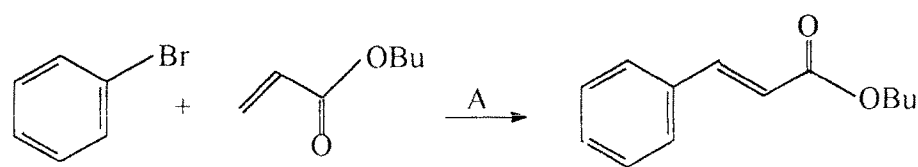
CHART – VIII

Scheme - 21

92%
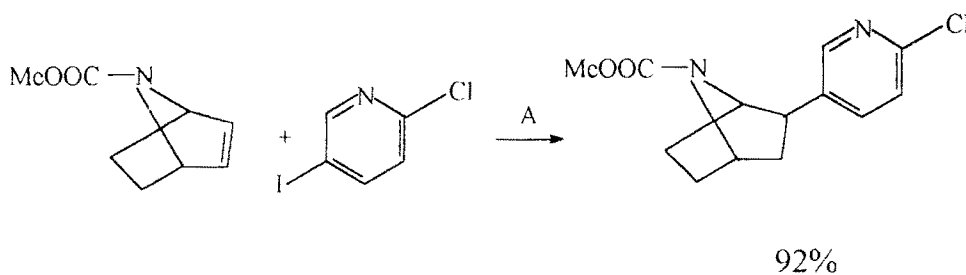
A : Pd(OAc)$_2$, Ph$_3$As, NEt$_3$, HCOOH, DMSO, 1hours.

Scheme -22

A : NiBr$_2$ 3H$_2$O, Fe-cathode, DMF / MeCN (1:1), 60 – 80^0 C.

Scheme - 23

A : (Ph$_3$P)$_2$ PdCl$_2$, Et$_3$N, C$_{16}$H$_{33}$ (Bu)$_3$PBr.

example of a Heck coupling in an ionic liquid was reported by Kaufmann et al.[50] Butyl trans-cinnamate was produced in high yield by reaction of bromobenzene with butyl acrylate in molten tetraalkyl ammonium and tetraalkyl phosphonium salt. The product was isolated by distillation from the ionic liquid (Chart-VIII, Scheme-23).

Similarly, the Heck reaction was applied for a single step synthesis of a nonsteroid anti-inflammatory drug Nabumethone, Naproxen etc. (Chart-IX, Scheme-24).

4.4 In Asymmetric synthesis

Asymmetric synthesis has been reported by Overman et al.[51] and Shibasaki et al.[52] using intramolecular asymmetric Heck reaction as well as by intermolecular asymmetric Heck reaction. Hayashi et al. systematically investigated the ligand induced asymmetric arylation of dihydrofurans[53]. The regioselectivity and enantioselectivity was better in reactions of alkenyltriflates than iodoarenes with 2,3-dihydrofuran (Chart-IX, Scheme-25).

Rawal et al.[46,47] have reported the stereo controlled asymmetric synthesis of strychnos alkaloid dehydrotubifoline (Chart-IX, Scheme-26).

4.5 Heteroannelation

The palladium-catalysed Heck reaction leads to the development of elegant and efficient synthetic routes to heterocycles. In palladium-catalysed annelation reaction the ortho-heterosubstituted iodoarene can undergo reaction with 1,2- 1,3[54] and 1,4-[55] dienes, which leads to a variety of naturally occurring heterocyclic compounds (Chart-X, Scheme-27).
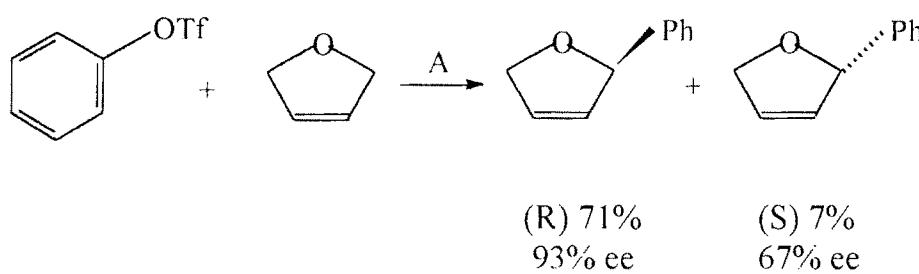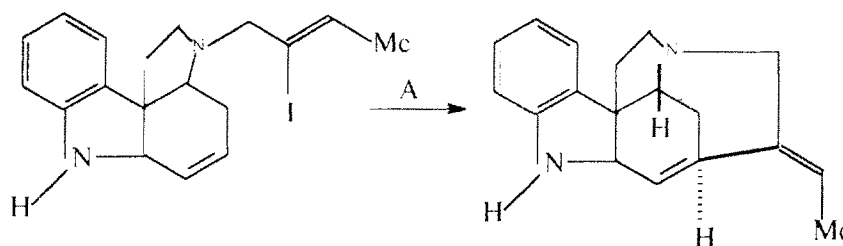
CHART – IX

Scheme - 24
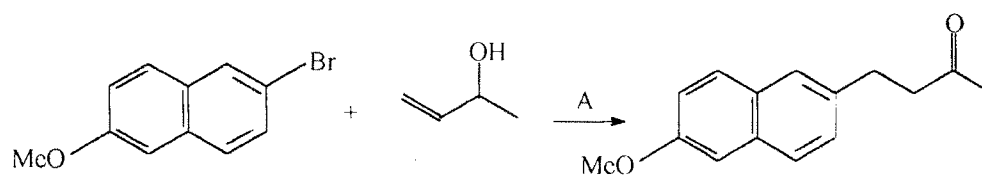
A : Pd(OAc)$_2$, P(OC$_6$H$_3$Bu$^t_2$ – 2, 4)$_3$, Na$_2$CO$_3$, DMA, 160^0 C.

Scheme - 25

(R) 71%   (S) 7%
93% ee   67% ee

A : [Pd(OAc)$_2$, (R)- BINAP]$_2$. C$_6$H$_6$.

Scheme -26

79%

A : Pd(OAc)$_2$ (5 mol %), K$_2$CO$_3$, Bu$_4$NCl, DMF, 60^0 C.

27
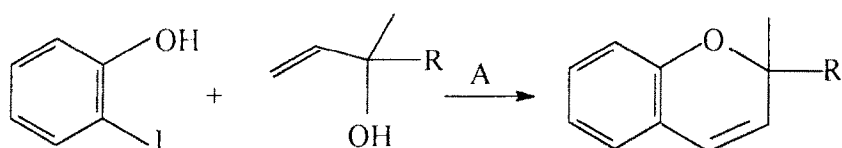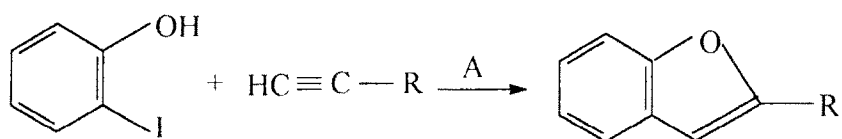
CHART – X

Scheme - 27

A : Pd(OAc)$_2$, LiCl, NEt$_3$, DMF, 100^0 C.
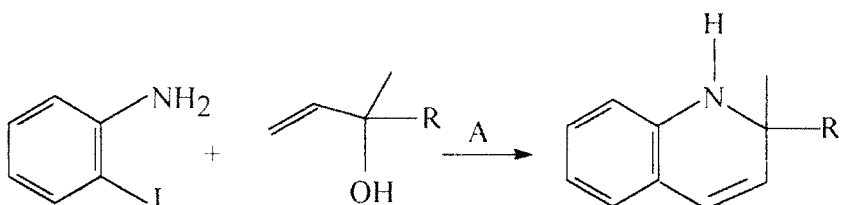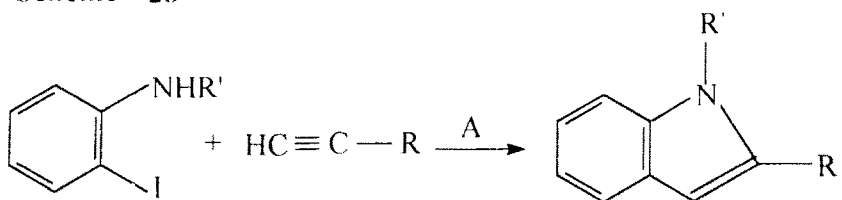
Scheme - 28

A : Pd(OAc)$_2$, LiCl, NEt$_3$, DMF, 100^0 C.
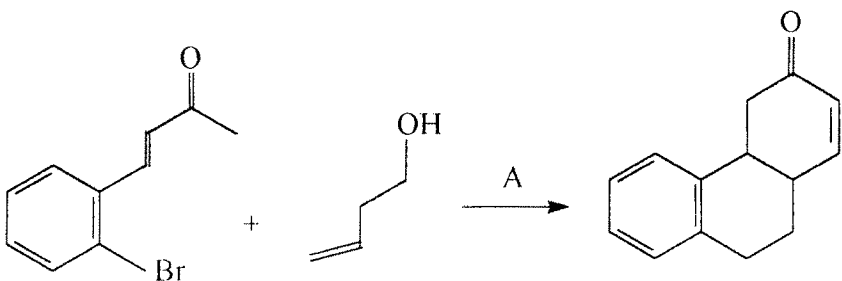
Scheme - 29

A : Pd(OAc)$_2$, LiCl, iPr$_2$NEt, DMF, 80^0 C.

Similarly, o-iodoaniline gave nitrogen heterocycles (Chart-X, Scheme-28). Annelation of the following type has been carried out by Heck reaction (Chart-X, Scheme-29).

4.6 Arylation of Aldehydes and Ketones

Arylation of carbonyl compounds is likely to proceed as a Heck type attack of aryl palladium intermediates on enols or enolates. Several methods of direct arylation of carbonyl compounds were explained such as phenylation of benzyl ketones by iodobenzene in a phosphine-free system[56] (Chart-XI, Scheme-30).

The conjugate addition may compete with regular Heck arylation. Conjugate addition is usually observed for arylation of α, β-unsaturated enones and enols in the presence of Et_3N as a base[57], while inorganic bases favour regular Heck arylation (Chart-XI, Scheme-31).
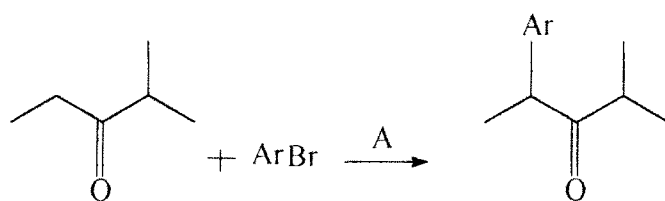
CHART – XI

Scheme - 30

Ph⟶CH₂–CO–CH₂⟶Ph + 2 Ph I $\xrightarrow{A}$ (product)
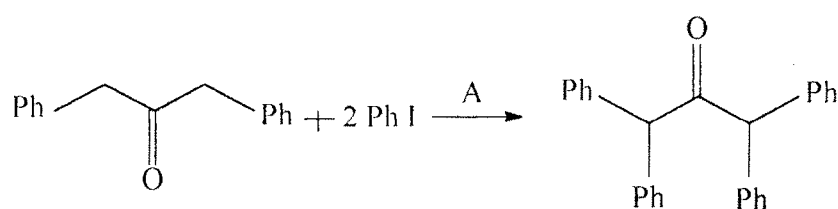
48%

A : PdCl$_2$, (5 mol %), CsCO$_3$, LiCl, DMF, 100^0 C 5 hours.

+ ArBr $\xrightarrow{A}$ (product)

93%

A : Pd$_2$(dba)$_3$.(1.5 mol %), 2 Tol BINAP, t BuONa, THF, 70^{0}C

Scheme - 31
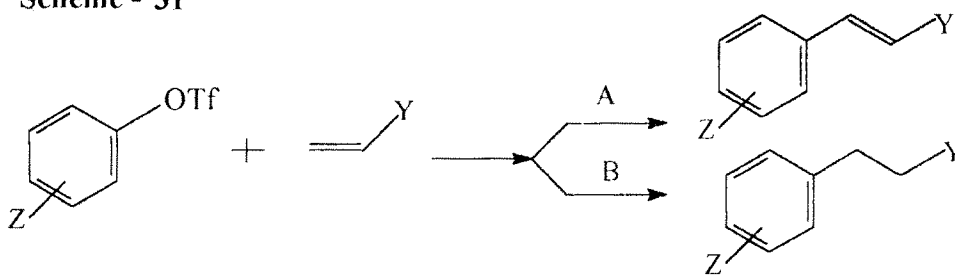
A : PdCl$_2$ (PPh$_3$)$_2$ (5 mol %), dppp, NaHCO$_3$,LiBr, DMF, 150^{0}C, 6.5 hours

B : PdCl$_2$ (PPh$_3$)$_2$ (5 mol %), dppp, Et$_3$N, DMF, 150^0 C, 6 hours.

Y = COOMe, COEt, COMe, CN.

Z = 4-Cl, 4-OMe.

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