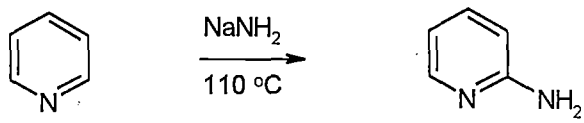
Part I: Palladium-Catalyzed Amination of Halopyridines Mediated on KF-Alumina Surface

I.1: Introduction

The Russian scientist Betekov once compared heterocyclic molecules as setting of several carbon atoms in a molecular ring studded with jewels. In general, it is the heteroatom, which imparts to a heterocycle its distinctive and sometimes striking properties. For example, if we change one carbon atom in benzene for one nitrogen atom, we obtain a heterocyclic ring, pyridine from a homocyclic molecule. A large number of heteroaromatic compounds are known. All biological processes in nature are based on chemical reactions involving the participation of many heterocyclic and heteroaromatic compounds.

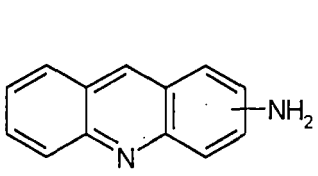
The nitrogen atom in pyridine induces π–electron withdrawal from the carbon atoms. Because of this electronic shift the pyridine-like heterocycles, which are often referred to as π–deficient heterocycles, undergoes facile interaction with negatively charged nucleophilic reagents. A typical example is:



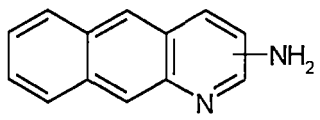
Heterocyclic compounds as a group dominate modern organic chemistry, with at least 55% of organic chemistry publications dedicated to this field. Different substituents on the heterocyclic rings impart diverse applications in biological chemistry as well as in industries. Since the present work is directed towards the development of a new reaction conditions for palladium-catalyzed amination of halopyridines, we confine our discussion in the following few pages on the numerous applications of heterocycles containing at least one amino group.

Natural products containing heterocyclic units or molecules such as alkaloids and glycosides have been used as medicine since ancient times. Substituted heterocycles are widely common in life and society. As for example, aminopyridines are important compounds with a variety of applications. The heteroaromatic amines are often

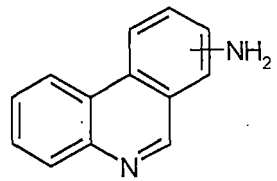
present as subunits in various alkaloids, DNA bases (purine, adenine etc.), antibiotics and in many other natural products. A few examples are given below.



Aminoacridine

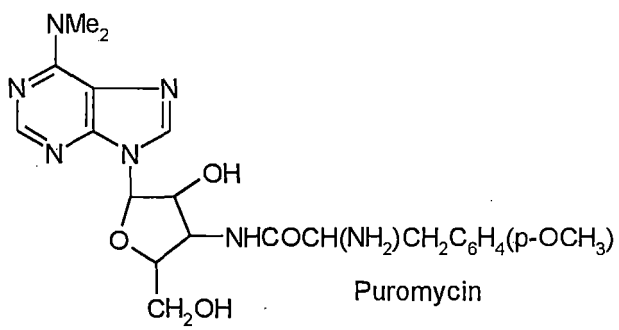


Aminobenzoquinoline



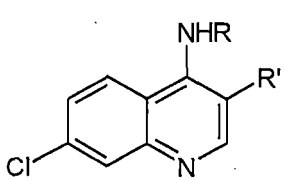
Aminophenanthredine

Puromycin, aminopurine-containing antibiotics derived from *Str. Alboniger.*, which biologically acts as a competitive analogue of aminoacyl tRNA to replace the latter in the reaction with peptidyl tRNA.[1]



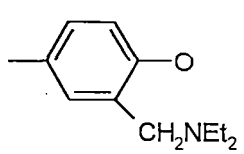
Puromycin

Aminopyridine-based phenazopyrine was introduced in 1926 for the treatment of infections of urinary tract. During the World War II, the sontonin and chloroquine were the choice for treating overt-attack of malaria, i.e. the stage in which the blood cells are attacked. Unfortunately, chloroquine-resistant strains of the parasite have now emerged and an alternative side chain is found in amodiaquine.[2]

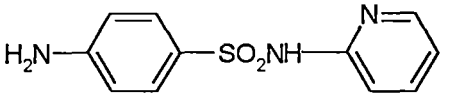


Sontonin; R = $CHMe(CH_2)_3NEt_2$; R' = Me

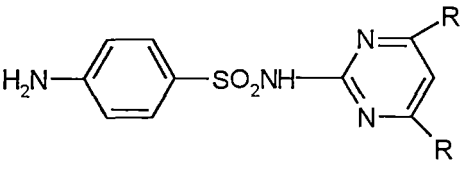
Chloroquine; R = $CHMe(CH_2)_3NEt_2$; R' = H

Amodiaquine =  R' =

p-Aminobenzenesulfonamide structure containing heterocyclic substitutents into the amine markedly enhanced the biological activity and derivatives of 4-aminopyridine, 4-aminopyrimidine have been introduced into clinical treatment. All the heterocyclic sulfa- drugs contain pyridine-like nitrogen and the heterocycles are rather strong electron-accepting moieties, which increase the acidity of the sulfamide N–H linkages making it close to that of *p*-aminobenzoic acid. The anion form by dissociation of the N–H bond is likely to be delivered to the target infection more quickly owing to its increased solubility in blood compared with the neutral molecule. Furthermore, the enhanced NH acidity may favour the conversion of sulfanilamide into its tautomeric imino form, which is stabilized by intramolecular hydrogen bonding and that may succeed in binding to and thus inhibiting the enzyme (Scheme 1).[3]

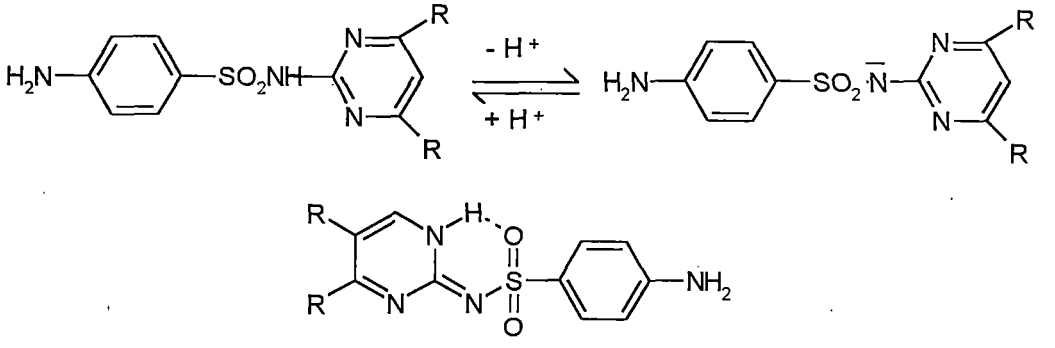


Sulfapyridine



R = H; Sulfapyrimidine
R = Me; Sulfamethazine
R = OMe; Sulfadimethoxine

Scheme 1

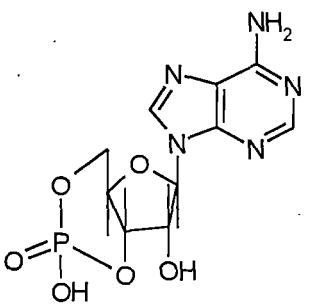


Tautomeric form of sulfadimidine

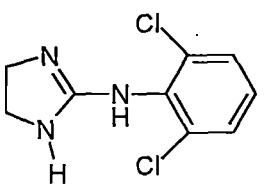
The mechanisms of nervous processes in human beings are extremely complicated. The transmission of nervous impulses is always accompanied by a release of neuromediators, which are chemical substances and that affects receptors and induces a particular biochemical response. Where a drug mimics a mediator, the drug can be either an antagonist or an agonist of the mediator. Among the many known nervous system drugs, the heterocyclic compounds predominate. Cyclodenylic acid plays the

role of a secondary mediator (hormone) by activating phosphorylase, an enzyme that stimulates physiological processes such as cardiac activity and glycogenosis in the liver. Aminopyridines are biologically important as central nervous system (CNS) stimulant.[4]

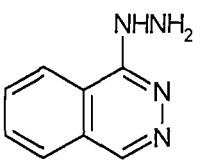
High arterial blood pressure (hypertension), coronary spasms (stenocardia) and cardiac arrhythmia are typical manifestations of cardiovascular disorders. Clonidine and hydralazine are derivatives of imidazoline and phthalazine respectively that exhibit marked hypotensive activity.[5]



Cyclodenylic acid

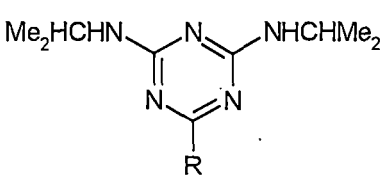


Clonidine



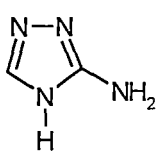
Hydralazine

As the heterocyclic compounds participate in many biological systems, it is not surprising that many pesticides are heterocyclic derivatives. Today, more than 200 different types of herbicides are utilized in agriculture. Heterocyclic compounds, especially azines and azoles, are frequently employed as herbicides. 3-Amino1, 2, 4-triazole, a herbicide of the azole series, has been in use for a relatively long time. All such herbicides are antiphotosynthetics, which interact with photosystem II. Some of the heterocycles with amino group are mentioned as examples of herbicides.[6]

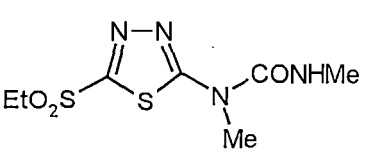


R = SMe; Prometryn

R = Cl; Propazine



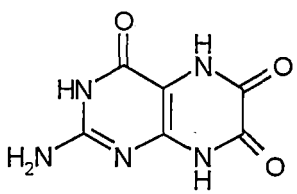
3-Amino-1,2,4-triazole



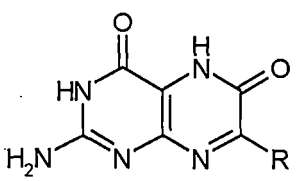
Ethidimuron

The human eye perceives the surrounding world as a multicolored picture. The heterocycles remain enormously important in traditional branches of industry such as

in the dye industry. The manufacture of synthetic dyes began in the second half of the nineteenth century and heterocycles immediately achieved preeminence. Pterin pigments such as Leucopterin, Xanthopterin, Chrysopterin are frequently found in butterflies and other insects.[7] The synthetic dye, Mauveine, an ionic derivative of phenazine is red in color and is characterized by high stability to light, washing and mechanical agitation.[8] The heterocyclic amines can also act as chromophores, which help to fasten the colour to the fibre. Highly π-deficient azines, pyrimidine, quinoxaline etc. act as electron acceptor thereby activating the nucleophilic displacement of halides during interaction of a reactive dye with a fibre. Luminophores have proven to be irreplaceable as components for a multitude of applications, including geological, hydrological and medical fields. For instance, the luminescent dye, acridine orange, 'marks' healthy and cancerous cells differently and therefore has been used in the diagnosis of malignant tumours.[9]

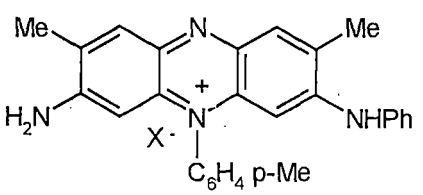


Leucopterin

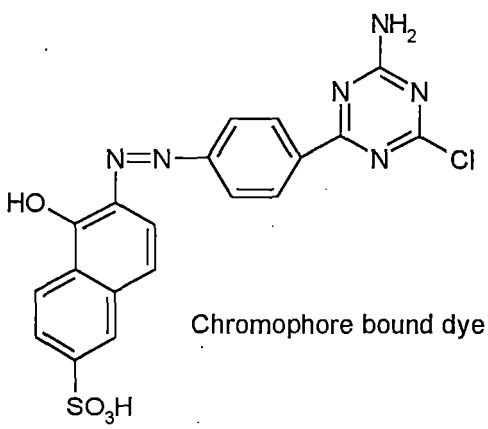


R = H; Xanthopterin

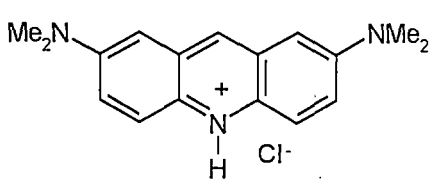
R = Me; Chrysopterin



Mauveine



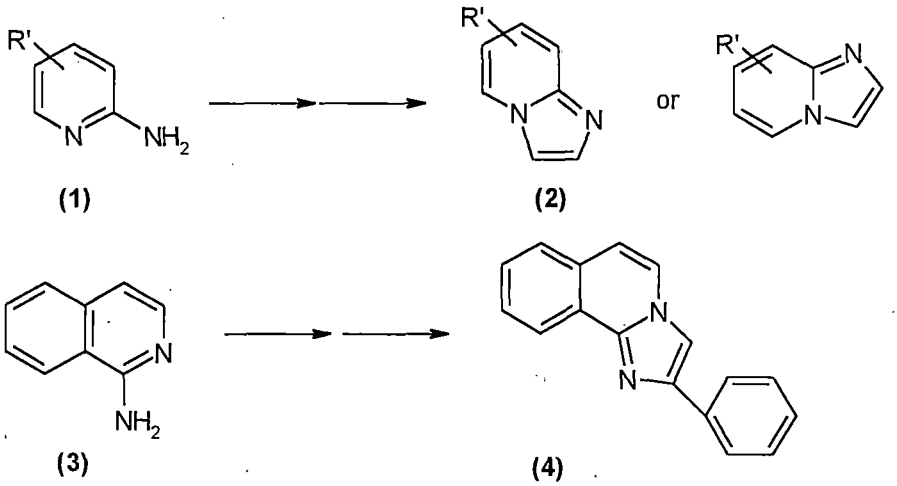
Chromophore bound dye



Acridine orange

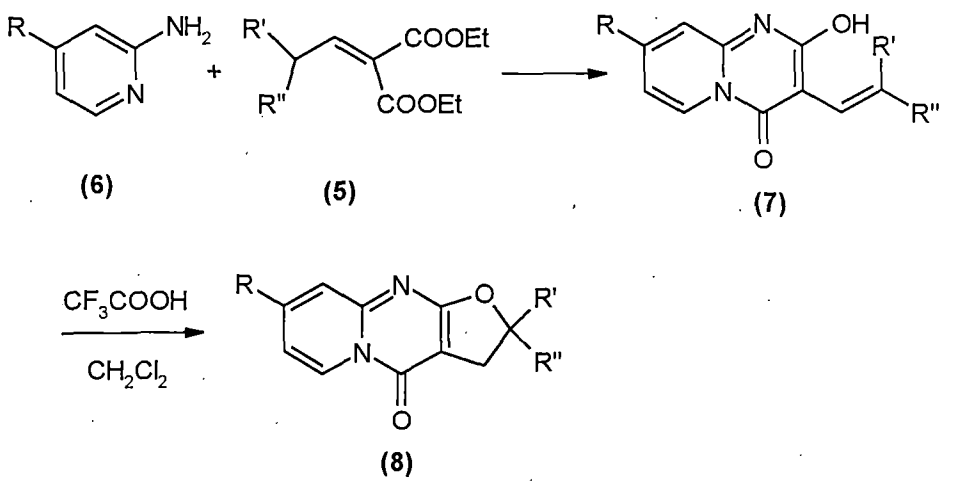
Since the discovery in 1985 that doped polyaniline is capable of conducting electricity in the metallic regime,[10] research has focused on using this material in application such as electrodes in lightweight batteries,[11] and as flexible, hole-transport layers in electroluminescent devices.[12] The derivatives of aminopyridines are often used as

ligands in coordination and organometallic chemistry.[13] The coordination complexes derived from the heteroatom donors both on the aromatic nucleus as well as the substituent amino group have attracted considerable interests in the fields of coordination and organometallic chemistry. Aminopyridines are also important starting materials for the synthesis of several heterocyclic compounds of potential drug activities. Recently, Katritzky *et al.*[14] utilized substituted 2-aminopyridine (**1**) and 1-aminoisoquinoline (**2**) for the synthesis of imidazolo[1,2-α]pyridines (**3**) and imidazolo[2,1-α]isoquinolines (**4**), which are of interest due to their antiinflamatory,[15] antirhinoviral,[16] long-acting anesthetic,[17] antiulcer[18] and anthelmintic or bacteriostetic activities.[19]



Furo[2,3-*d*]pyrido[1,2-a]pyrimidines are novel tricylic pyrimidine derivatives and were synthesised for the first time from 3-alkenylpyrido[1,2-*a*]pyrimidines.[20] The thermal reaction of alkylidinemalonate ester (**5**) with 2-aminopyridines (**6**) gave 3-(2-alkenyl)-pyrido[1,2-*a*]pyrimidines (**7**) in good yields. The cyclization of in trifluoroacetic acid/ dichloromethane produced 4H-5,6-dihydrofuro[2,3-*d*]pyrido[1,2-*a*]pyrimidines (**8**), as outlined in Scheme 2.

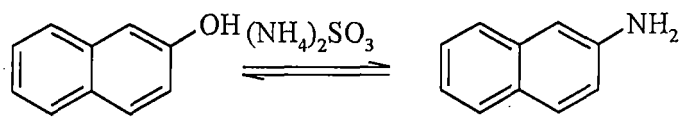
Scheme 2



The applications of aminopyridines are well diversified. Because of their wide prevalence in the nature as well as industrial relevance, aminopyridines are attractive targets for chemical synthesis. Despite its structural simplicity, the synthesis of aminopyridines is often difficult. The early preparative processes of aminopyridines are primarily based on the methods applicable to its benzene counterpart. The formal replacement of a CH in benzene, by N, leads to, however, far reaching changes in typical reactivity: pyridines are much less susceptible to electrophilic substitution than benzene, and much more susceptible to nucleophilic attack. However, pyridine undergoes a range of simple electrophilic additions, some reversible, some forming isolable products, each involving donation of the nitrogen lone pair to an electrophile, and thence the formation of 'pyridinium' salts which, of course, do not have a counterpart in benzene chemistry at all. Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[21]These methods suffer either from a nucleophilic regiocontrol problem, the need for very high temperature or the presence of specific functionality on the heterocyclic ring.

Replacement of a halogen atom attached to aromatic nucleus is difficult to achieve, unless there is an electron withdrawing substituent such as $-NO_2$ group present in the *ortho*- or *para*-position. Transformations of phenols to corresponding anilines, i.e. for replacement of aromatic hydroxyl substituents by an amino group in the same

position, are very few.[22] The reaction of naphthols with ammonia and sodium bisulfite is called Bucherer reacion.[22, 23] Primary amines can be used instead of ammonia, in which case N-substituted naphthylamines are obtained.



Phenol (**9**) can be converted to a diethyl phosphate ester (**10**) and the reaction of ester with KNH_2 and potassium in liq. NH_3 gives aniline (**11**).[24] The mechanism of the second step probably occurs via $S_{RN}1$mechanism.[25]

$$\underset{\textbf{(9)}}{ArOH} + NaOH + (EtO)_2POCl \longrightarrow \underset{\textbf{(10)}}{ArOPO(OEt)_2}$$

$$ArOPO(OEt)_2 + KNH_2 + K \xrightarrow[NH_3]{\text{liq.}} \underset{\textbf{(11)}}{ArNH_2}$$

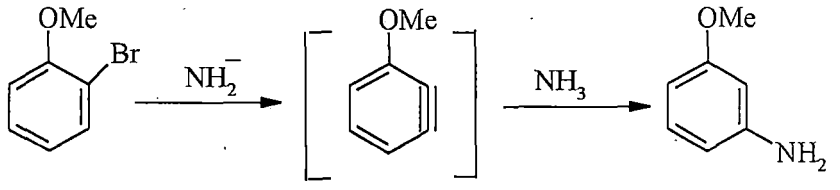
Aniline is prepared directly from phenol on an industrial scale. The amination is carried out in the vapour phase at high temperature and pressure over a SiO_2/ Al_2O_3 catalyst to give aniline in high yield. Direct amination of benzene with anhydrous NH_3 is known in presence of catalyst consisting of Mo, W, or chromium- salt with Cu or Ni oxide.

Halobenzene can be converted to aniline by the action of $NaNH_2$ or KNH_2 at low

$$ArX + NaNH_2 \xrightarrow[NH_3]{\text{liq.}} ArNH_2 + NaX$$

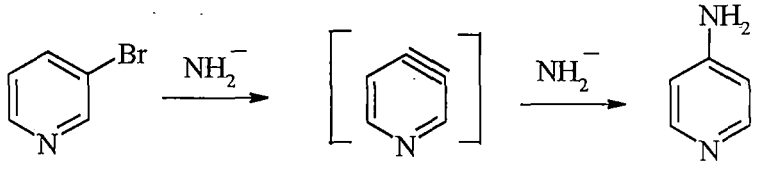
temperature in liq. NH_3.[26] The occurrence of cine along with normal substitution is explained by benzyne mechanism (Scheme 3). It is clearly different those occurred by S_NAr or S_N1 mechanism.[21]

Scheme 3



The existence of a γ-pyridine intermediate has been postulated to account for the formation of 4-amino pyridine (**13**) when 3-bromopyridine (**12**) is treated with sodamide in liquid ammonia as outlined in (Scheme 3).[27]

Scheme 4



(12) (13)

Reactions of benzyne with a variety of nucleophiles in competition with amide ions generally show a considerable lack of selectivity in its addition reactions. Further, base strength is not the only factor of importance in determining the attack of the nucleophiles on benzyne. Although several other strong bases, such as triphenylmethide, anilide, flourenyl and thiophenate have been widely used in lieu of alkali metal amides, the functional group tolerance along with formation of other products are the major drawbacks for this method.[28]

I.1.1: Copper-assisted nucleophilic substitution of aryl halide

The halogen atom in aryl halides is relatively inert to nucleophilic substitution unless it is activated by the presence of electron withdrawing groups.[29] Metal and metals complexes may participate in these reactions in a variety of ways as illustrated by the following examples.

(i)The metal may form a σ-complex with the lone pair of electrons of the halogen atom, this leads to polarization of the carbon to halogen bond and subsequent attack by nucleophile may occur intermolecularly or intramolecularly (Scheme 5).

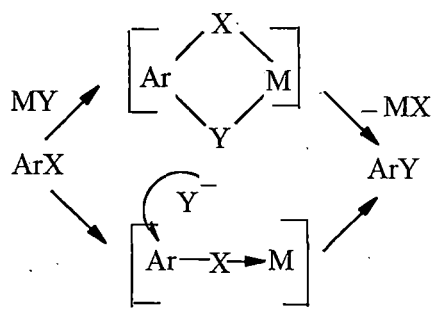
(ii) The metal may form a π-complex in which the metal is equivalent to a strong electron-withdrawing group in the aryl ring (Scheme 6). Reactions of this type are particularly favoured with cationic π-complexes.[30] A synthetically equivalent result may be achieved by nucleophilic addition to coordinated cyclohexadienyl cations followed by demetallation and dehydrogenation of the resulting diene (Scheme 7).[31]

(iii) The metal may function as a one electron donor as in the $S_{RN}1$ reaction (Scheme 8).[32]

(iv) The metal may function as an electron acceptor as in the $S_{ON}2$ reaction (Scheme 9),[33] or as in the S_HAr reaction [34] (Scheme 10) *ipso*-substitution in the S_HAr reaction is most common with nucleophilic radicals.

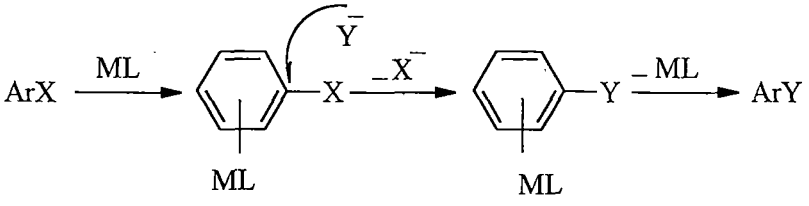
(v) The metal may undergo oxidative addition of the aryl halide, followed by reductive elimination of exchanged product [35] (Scheme 11). The mechanism of oxidative addition may involve either successive one-electron transfers or electron pair processes.[36]

Scheme 5

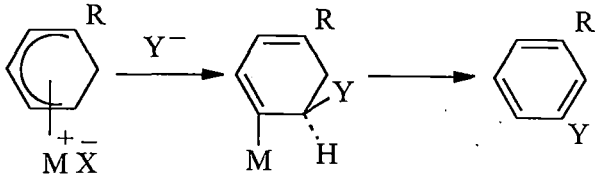


X=hal. Y=nucleophile

Scheme 6



Scheme 7



Scheme 8

$$M^{n+} + ArX \longrightarrow M^{(n+1)+} + ArX^{\cdot-}$$

$$ArX^{\cdot-} \longrightarrow Ar^{\cdot} + X^{-}$$

$$Ar^{\cdot} + Y^{-} \longrightarrow ArY^{\cdot-}$$

$$ArY^{\cdot-} + ArX \longrightarrow ArY + ArX^{\cdot-}$$

etc.

Scheme 9

$$M^{n+} + ArX \longrightarrow M^{(n-1)+} + ArX^{\cdot-}$$

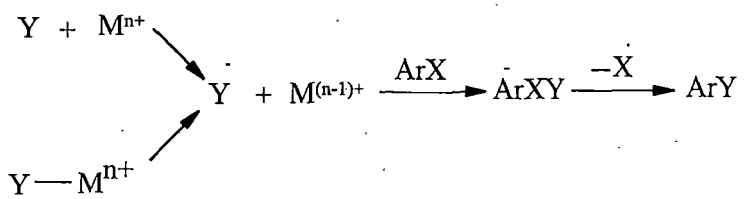
$$ArX^{\cdot-} + Y^{-} \longrightarrow \dot{A}rXY$$

$$\dot{A}rXY \longrightarrow ArY^{\cdot-} + X^{-}$$

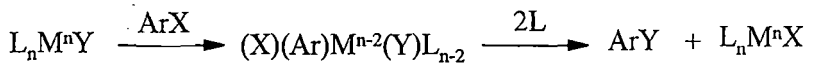
$$ArY^{\cdot-} + ArX \longrightarrow ArY + ArX^{\cdot-}$$

etc.

Scheme 10



Scheme 11

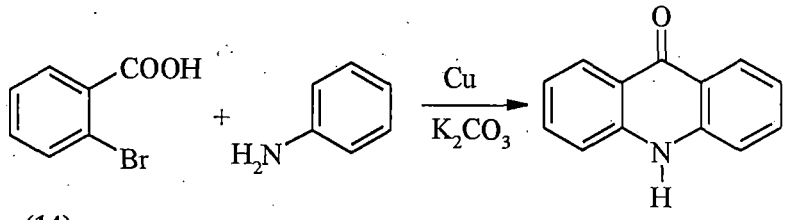


The *ipso*-substitution of aryl halide promoted by copper compounds was first reported by Ullmann in 1901,[37] and has since been used on a widespread basis. Although many of the reactions outlined in Schemes 4 - 10 occur under much milder conditions than with copper compounds, there may be limitations to their utilization in large-scale synthesis. For example, reactions based on π-complexes invariably involve toxic co-ligands such as carbon monoxide or phosphines, which are themselves nucleophilic and may promote side reactions. $S_{RN}1$ reactions[38] require solvents with a low affinity for the aryl radical and of low acidity; liquid ammonia is commonly used, or the reaction may require photostimulation. For these and other reasons copper promoted *ipso*-nucleophilic reactions seem to be favoured for reactions carried out on an industrial scale.

Ammonation of aryl halides catalyzed by copper is well known and is carried out extensively on an industrial scale.[37] A wide variety of copper catalysts have been used, with copper in the 0, +1 or +2 oxidations states. For unsubstituted aryl halides the reaction is generally carried out at room temperatures in excess of 150 °C in aqueous solution. Activated aryl halides can be ammonated at much lower temperatures, for example the industrially important ammonation of 1-bromoanthraquinones occurs in high yield at 80 °C.[39] A kinetic study of the ammonation of chlorobenzene shows that the activation energy for the copper (II) catalyzed reactions is twice that for the copper (I) catalyzed reaction.[40]

The Ullmann condensation of amines with aryl halides is similar in many respects to the ammonation. The reaction of *o*-halobenzoic acids (**14**) with phenylamines (**15**) is a key step in the synthesis of acridenes (**16**) as outlined below (Scheme 12).[41]

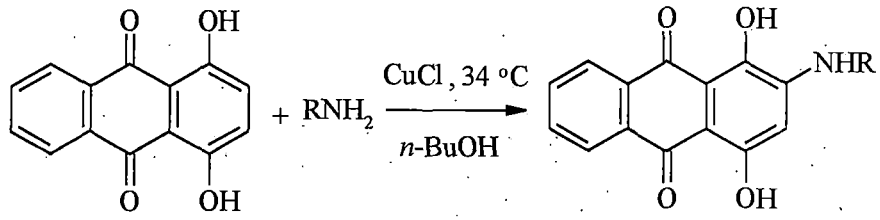
Scheme 12



(**14**) (**15**) (**16**)

The direct displacement of aromatic hydrogen by alkylamines promoted by Cu (I) chloride form α-substituted anthraquinones (**17**) (Scheme 13).[42]

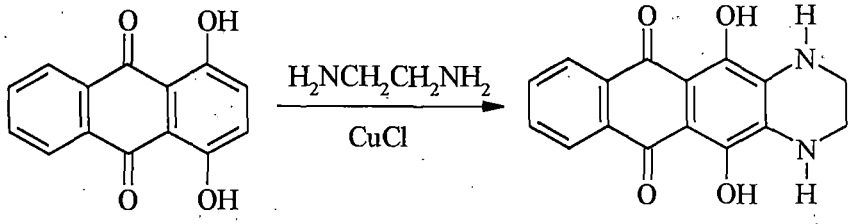
Scheme 13



R=alkyl group (**17**)

Use of 1,2-diamine gave rise to cyclized product (**18**) as outlined below (Scheme 14).[43]

Scheme14



(**18**)

The Ullmann condensation of aryl halides with amines is traditionally carried by heating with copper powder in the presence of bases such as Na_2CO_3 or NaOH.[44]

The condensation of 1-bromoanthraquinones with aniline in aqueous solution is catalyzed by Cu (II) salts, however, kinetic and ESR studies indicate that the effective catalyst is a Cu (I) species.[45] This condensation is accelerated by an increase in concentration of hydroxide ion, which deprotonate the amine and facilitate the reduction of Cu (II):

$$LnCu^{II}NH_2Ph \overset{OH^-}{\rightleftharpoons} LnCu^{II}NHPh^- \rightleftharpoons LnCu^{I}NHPh$$

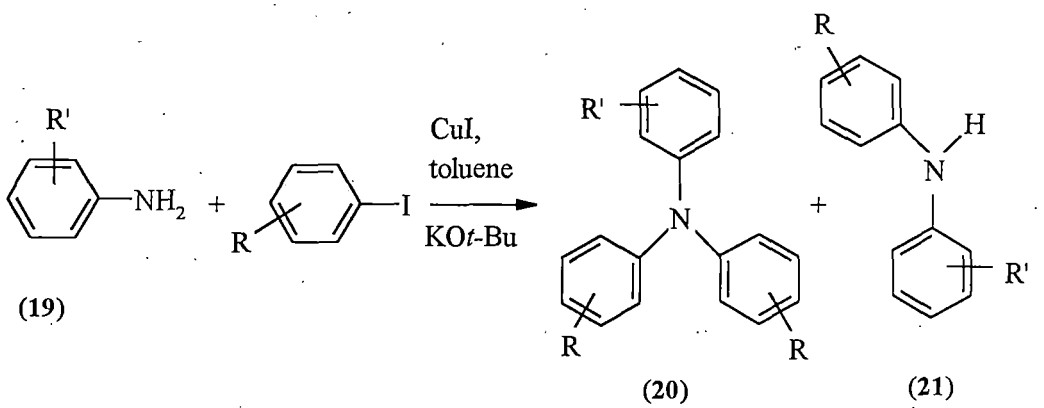
Major drawbacks of these methods are the requirement of high temperature (>200 °C), sensitivity of the catalyst type and low to moderate yield of amines [46] along with varied quantities of biaryl products.

Recently, milder Ullmann type methodologies for the *N*-arylation of anilines,[47] imidazoles, [48] amides [49] and nitrogen heterocycles [50] have been reported. Gujadhur *et al.*[51] have found that the copper complex $Cu(PPh_3)_3Br$, is active for amination of mono- and diarylamines to di- and triarylamines, respectively, using Cs_2CO_3 as a base at 120 °C. However, CuI and CuBr with or without PPh_3 as a ligand were not active for this reaction. Similarly, Goodbrand and Hu[46] have reported ligand-accelerated single-step catalytic synthesis of triarylamines with high selectivity using CuCl / 1,10-phenanthroline catalyst system and KOH as a base at 125 °C. However, in this case also, CuCl alone (in the absence of 1,10-phenanthroline as a ligand) produced very low yields of triaryl-amines. Thus, copper salts in the absence of ligands such as triphenylphosphine or 1,10-phenanthroline exhibit poor catalytic activity and selectivity for the synthesis of triarylamines at lower temperatures such as 110-125 °C.

Chaudhari and coworkers reported a simple and efficient methodology in copper-catalyzed amination. Anilines (**19**) were converted to triarylamines [52] (**20**) along with

7–15% diaryl amines (**21**) in presence of CuI and KO*t*-Bu at 135 °C (Scheme 15). A variety of N- or P-containing ligands were examined and they observed high catalytic activity using chelating bidentate ligands.

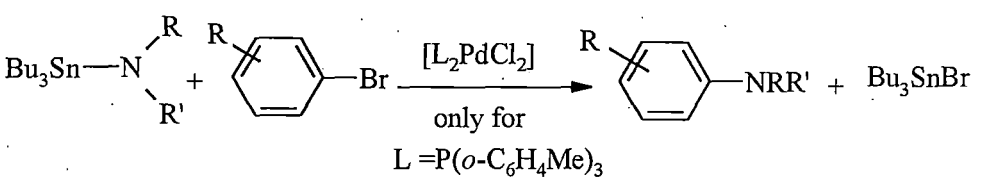
Scheme 15



I.1.2: Palladium-catalyzed Amination

In the 1980s a few results suggested that a general metal-catalyzed method to form arylamines from aryl halides would be possible.[53] In 1983, Kosugi *et al.* published a short paper on the reaction of tributyltin amides with aryl bromides catalyzed by $[PdCl_2\{P(o\text{-}C_6H_4Me)_3\}_2]$ (Scheme 16).[54]

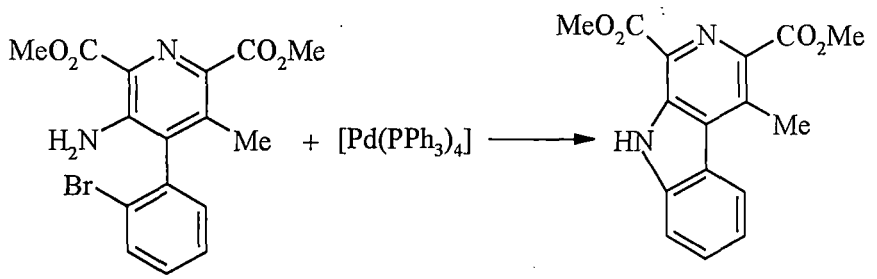
Scheme 16



The scope of this reaction appeared to be limited to dialkylamides and electron-neutral aryl halides. For example, the use of aryl halides with nitro, acyl, methoxy, and dimethylamino substituents gave poor yields upon palladium-catalyzed reaction with tributyltin diethylamide. The mechanism did not appear to involve radicals or benzyne intermediates.

Boger *et al.* reported studies on palladium-mediated cyclization to form the CDE ring system of lavendamycin (**22**) [55] as outlined below (Scheme 17).

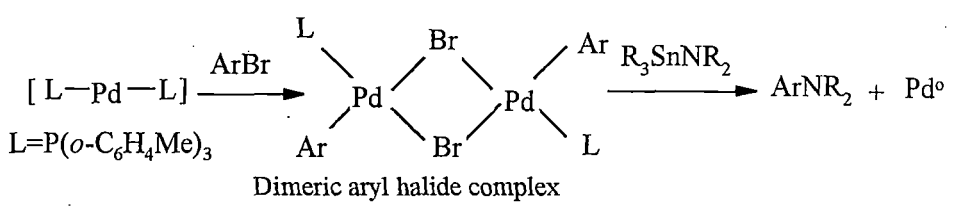
Scheme 17



(**22**)

These reactions were conducted with stoichiometric amounts of $[Pd(PPh_3)_4]$. When used in a 1 mol % quantity, $[Pd(PPh_3)]_4$ failed to catalyze these reactions, presumably because of the absence of a base. Until almost ten years latter, Paul, Patt, and Hartwig revealed the reactions involved in the amination chemistry with tin reagents.[56] They showed that

Scheme 18

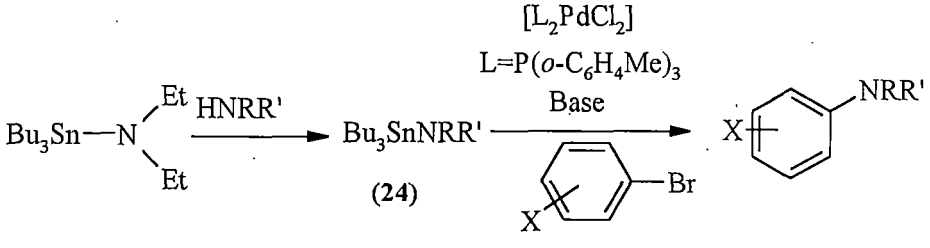


(**23**)

the active catalyst was $[Pd\{P(o\text{-}C_6H_4Me)_3\}_2]$ which oxidatively added aryl halides to give dimeric aryl halide complexes (**23**). These aryl halide complexes reacted directly with tin amides to form arylamines (Scheme 18). Thus, this chemistry could accurately be viewed as a rough parallel to stille coupling.

Guram and Buchwald showed that the chemistry could be extended beyond electron-neutral aryl halides[57]. With tin amides (**24**) derived in situ, this chemistry was extended to arylhalides bearing alkoxycarbonyl, amino, and alkoxo groups. However, reactions that proceeded with 80% yield or greater were still limited to tin amides derived from secondary amines (Scheme 19).

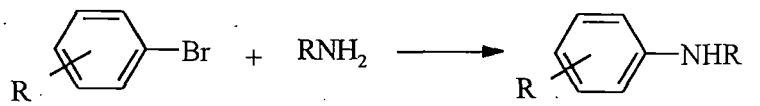
Scheme 19



In their earlier studies, Buchwald and Hartwig had shown that primary amines could be coupled with a limited number of aromatic bromides using the Pd(0)/P(*o*-tolyl)$_3$ catalyst system. However, this was not a general reaction and in the absence of a *para*- electron- withdrawing substituent or an *ortho*-substituent on the aryl bromide, only a low conversion of starting materials to products was observed. A general aromatic carbon- nitrogen bond forming reaction employing primary amines and aryl bromides as coupling partners was realized independently by both the Buchwald and Hartwig research groups when they switched to certain bis(phosphine) palladium complexes.

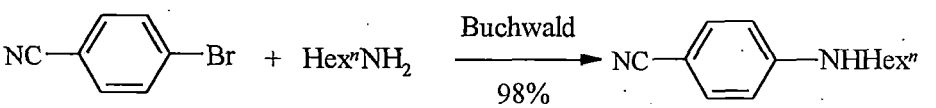
The Buchwald group found that a combination of $Pd_2(dba)_3$ and BINAP in the presence of *tert*-BuONa performed as a superior catalyst for the cross coupling of amines with aryl bromides (**25**) to afford aniline derivatives (**26**).[58] The efficiency of BINAP as a ligand may be attributed to its ability to inhibit the formation of catalytically inactive palladium bis(amine) aryl halide complexes. This remarkable protocol is illustrated by the catalytic cross coupling of 4-bromo benzonitrile (**27**) with *n*-hexylamine to give the amino product (**28**) in 98% yield using only 0.05 mol% of catalyst.

Scheme 20

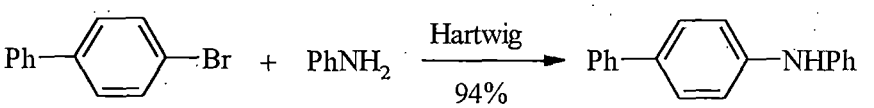


(25) Buchwald
cat. $Pd_2(dba)_3$
BINAP
NaO*t*-Bu
toluene, 80 °C

Hartwig (26)
cat. (DPPF)$PdCl_2$
DPPF
NaO*t*-Bu
THF, 100 °C



(27) (28)



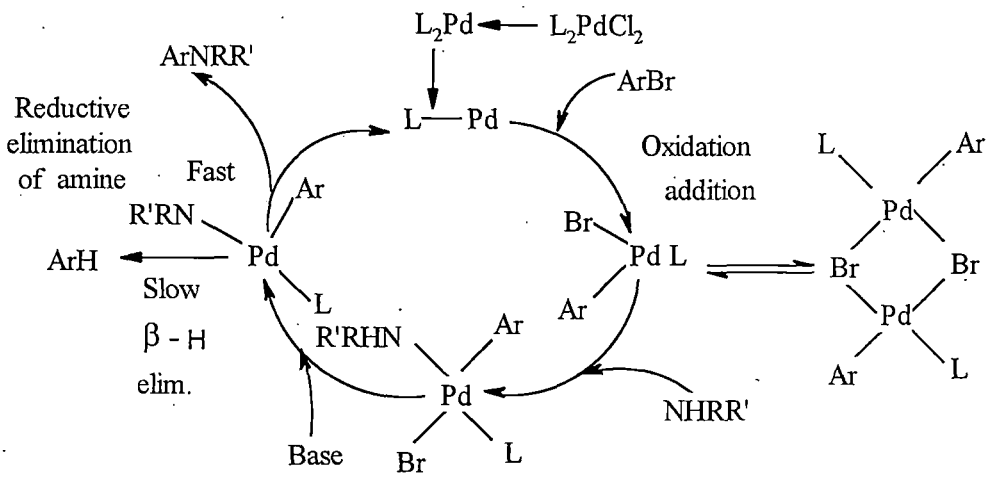
(29) (30)

The Hartwig group discovered that (DPPF) $PdCl_2$ catalyst provide high yields of mixed, secondary arylamines from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(*o*-tolyl)$_3$ catalyst system.[59] This study revealed several important concepts; firstly, the catalytic cycle involves bis(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high-yielding, intermolecular amination of aryl halides. For example, Hartwig reports the catalytic cross coupling of 4-bromo biphenyl (**29**) with aniline to afford the product (**30**) in 94% yield (Scheme 20). Finally, the observed favourable selectivity for reductive elimination over β-hydrogen elimination results from chelation and large bite angle, rather than from steric effects.

Mechanism of Pd-catalyzed amination:

The possible mechanism of Pd-catalyzed amination involves oxidative addition of aryl halide to a phosphines-based Pd(0) complex,[60] and subsequent generation of amido aryl intermediates by coordination of an amine to the aryl halide complex and deprotonation of the amine N-H (Scheme 21).[61]

Scheme 21



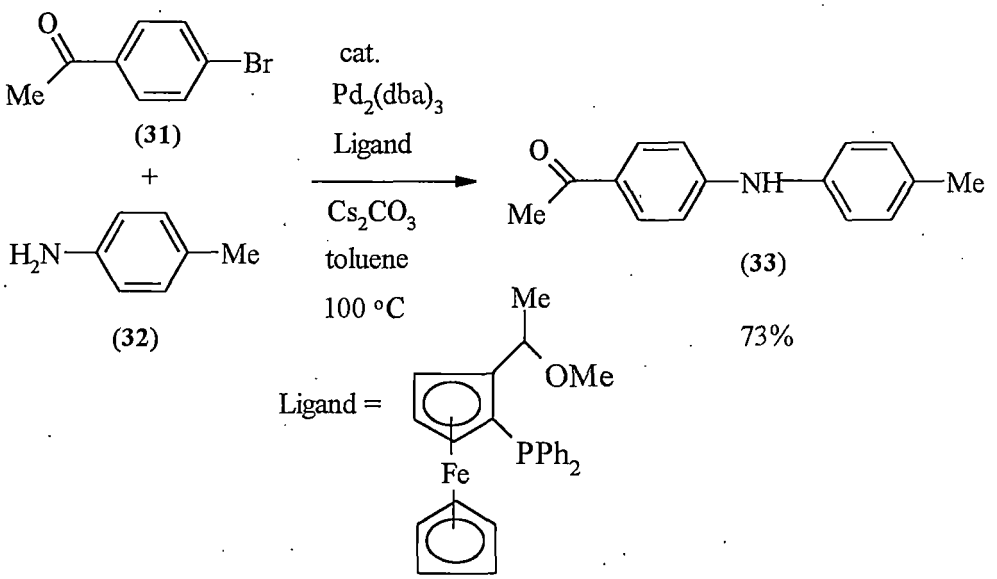
The formation of a palladium dialkylamido complex is unusual, and productive catalytic chemistry of such intermediates is rare. Indeed the dialkylamido complex involved in the catalytic amination chemistry is unstable at room temperature. Experiments directed at generating the complex at low temperatures by methods that were independent of the catalytic reactions showed that such complexes provided arylamine products below room temperature.[62] Further, it is remarkable that this intermediate would undergo the rare reductive elimination of amine, since β-hydrogen elimination of alkylamido complexes has been thought to be a rapid route to their decomposition.

Although a general protocol had been developed for the palladium-catalyzed cross coupling of primary and secondary amines with aryl bromides, the use of sodium *tert*-butoxide as base presented problems with a number of common functional groups. Buchwald discovered that the ligand (rac)-PPF-OMe was superior for effecting aminations with acyclic secondary amines. [63]

Furthermore, it was noted that the combination of $Pd_2(dba)_3$ and (rac)-PPF-OMe allowed the reaction to proceed with weaker base cesium carbonate. These new reaction conditions are sufficiently mild to tolerate the presence of methyl ethyl esters, aldehydes, enolisable ketones and nitro groups, which are incompatible with reaction conditions, which employ sodium *tert*-butoxide as the stoichiometric base.[64]

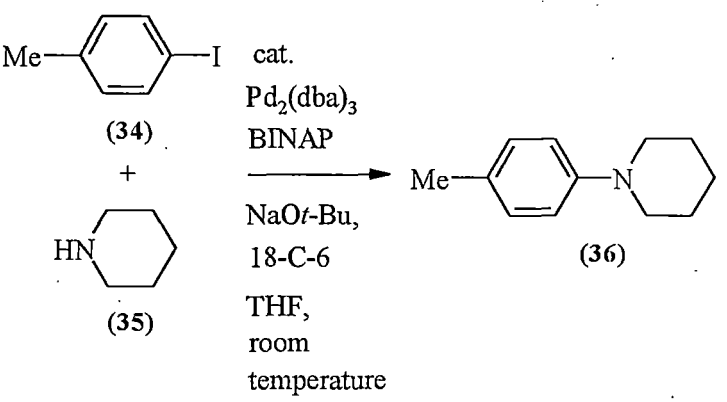
Thus, the reaction of *p*-bromo acetophenone (**31**) with *p*-toluedine (**32**) proceeds efficiently to afford a 73% yield of amino product (**33**) (Scheme 22).

Scheme 22



A further improvement in procedure has been reported by Buchwald, which allows the catalytic amination of aryl iodides at room temperature.[65] For example, the reaction of *p*-iodotoluene (**34**) with piperidine (**35**) in the presence of stoichiometric quantities of sodium *tert*-butoxide and 18-crown-6 and a catalytic amount of $Pd_2(dba)_3$/BINAP proceeds to completion in 6 hours at room temperature. The product (**36**) is isolated in 85% yield (Scheme 23). This is a significant advance for reactions involving thermally sensitive molecules or where it may be inconvenient to heat reactions such as large parallel syntheses or applications in combinatorial chemistry.

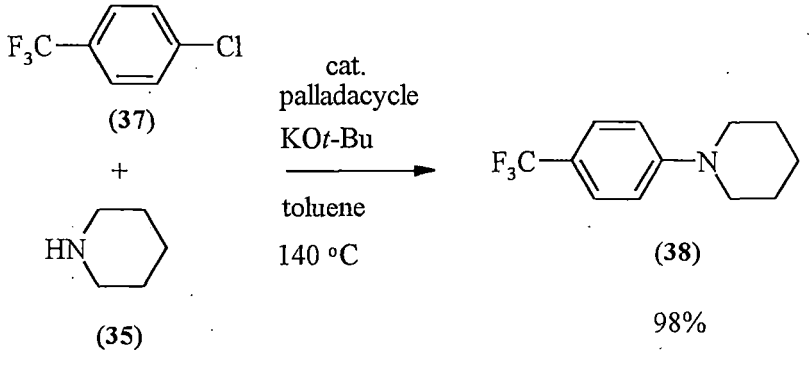
Scheme 23

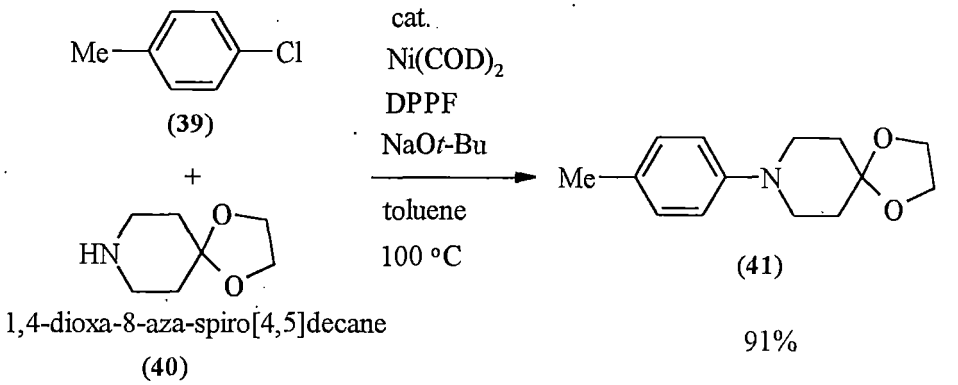


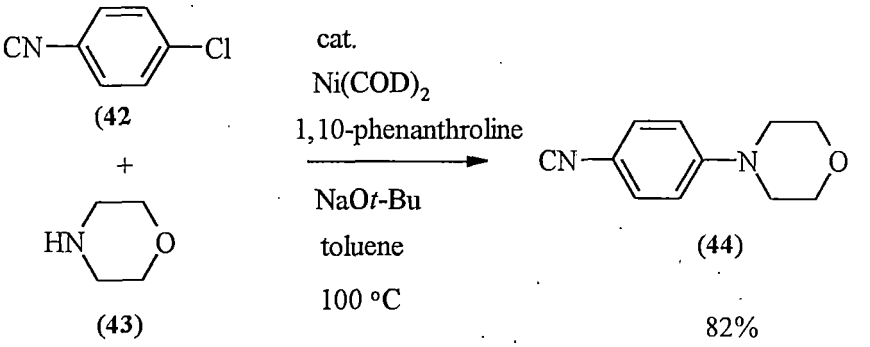
The first palladium-catalyzed coupling reaction of aryl chlorides with amines was reported by Beller.[66] Crucial to the success of the reaction was the use of potassium *tert*-butoxide as base. The coupling of aryl chloride (**37**) and piperidine (**35**) was catalyzed by *trans*-di(μ-aceto)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II)-(palladacycle) to give the product (**38**) in 98% yield. Further amination of aryl chlorides have reported by Buchwald.[67]The mild nickel catalyzed procedure tolerates a variety of functional groups including ethers, nitriles, acetals, and non-enolisable ketones. For example, 4-chlorotoluene (**39**) and 1,4-Dioxa-8-aza-spiro[4,5]decane (**40**) gave the desired tertiary amine (**41**) in 91% yield by employing a $Ni(COD)_2$/DPPF catalyst. Interestingly, the chelating nitrogen ligand 1,10-phenanthroline, which is not effective in palladium catalyzed aminations, proved useful in the nickel-catalyzed reaction. This is demonstrated in the preparation of (**44**) by a nickel-catalyzed cross coupling of 4-chloro-benzonitrile (**42**) with morpholine (**43**) (Scheme 24).

The conversion of phenols to aryl amines clearly has considerable synthetic value. Given the simple conversion of phenols to aryl triflates, and the application of aryl triflates in Stille and Suzuki couplings, it was no surprise that Hartwig and Buchwald independently extended their amination chemistry to include aryl triflates as coupling partners. Under the standard conditions, Hartwig reports the conversion of aryl triflates (**45**) into aryl amine (**46**) in 96% yield as an example of the utility of this methodology.[68] Similarly, Buchwald reports that the combination of

Scheme 24

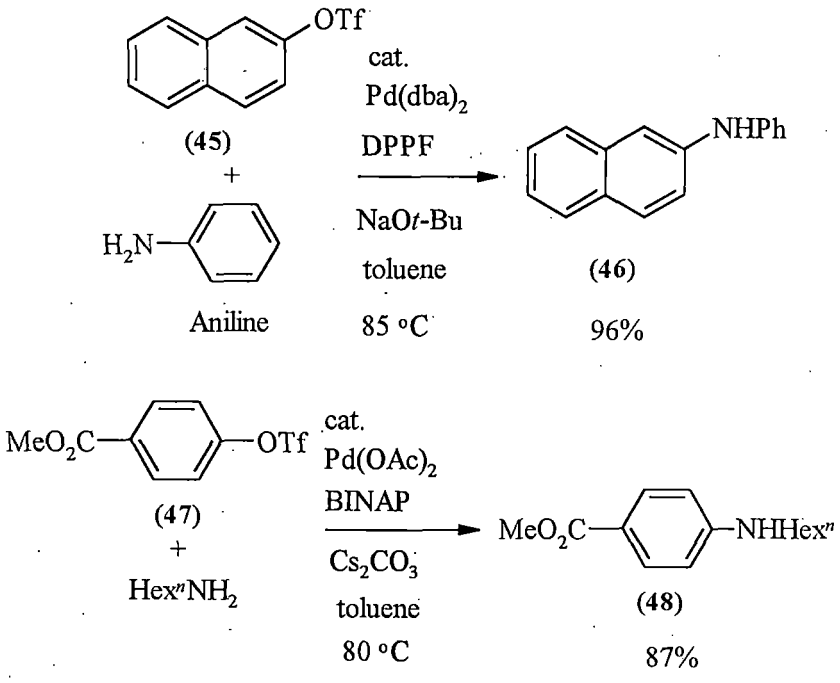






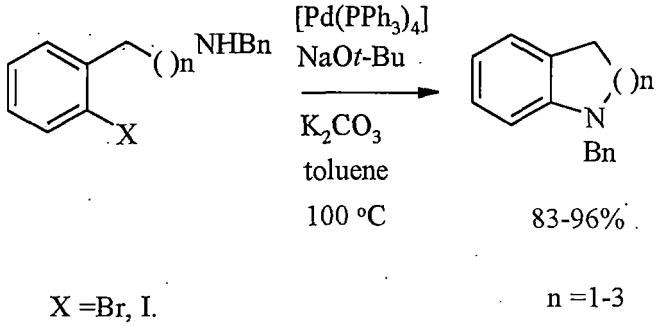
$Pd(OAc)_2$/BINAP is an effective catalyst system for this valuable transformation.[69] Once again, by changing the stoichiometric base from sodium *tert*-butoxide to caesium carbonate, a greater functional group tolerance is exhibited.[70] This is demonstrated by the conversion of the aryl triflates (**47**) and hexylamine into the product (**48**) in 87% yield, the methyl ester is unaffected (Scheme 25).

Scheme 25



Intramolecular aryl halide aminations to form nitrogen heterocycles were included in the initial reports on tin-free aryl halide aminations.[71] For example, the following reactions occurred in greater than 80% yield (Scheme 26). In this case the halide could be iodide or bromide, and $[Pd(PPh_3)_4]$ was a most effective catalyst than $[PdCl_2\{P(o\text{-}C_6H_4CH_3)_3\}_2]$.

Scheme 26



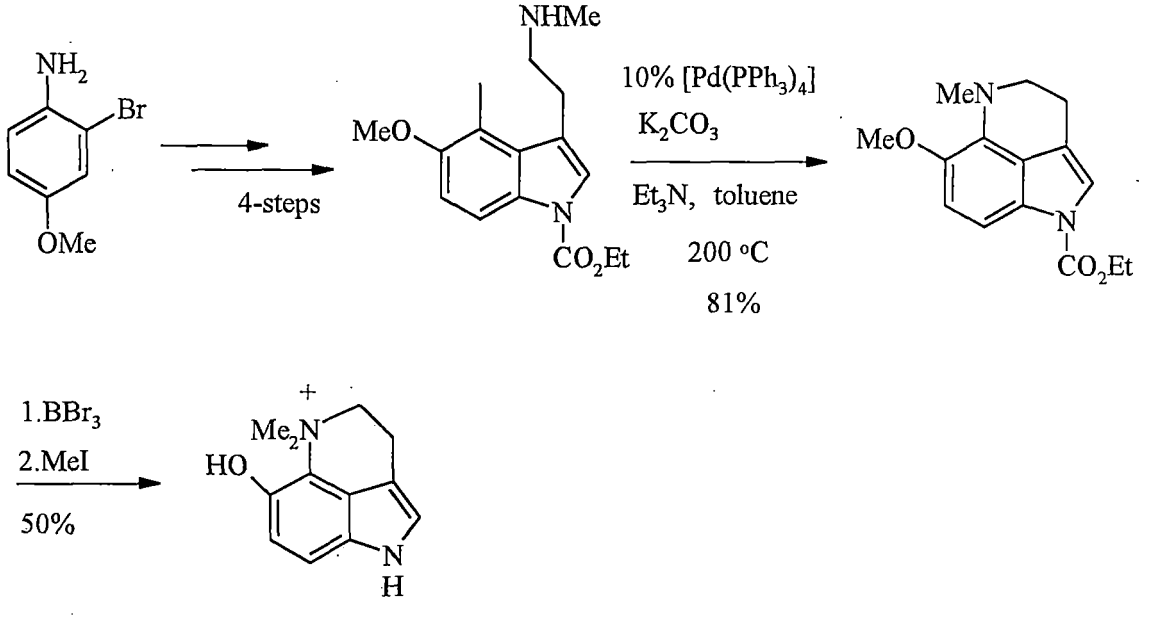
Subsequent to the initial report, Buchwald and co-worker provided an extensive account of the intramolecular amination reactions.[72] K_2CO_3 was an efficient base, but

a combination of NaO*t*-Bu and K_2CO_3 was most effective. Aryl iodide proved to be the preferred substrate under optimization conditions with [Pd $(PPh_3)_4$] as catalyst. Iodide substrates also allowed for the use of triethylamine as base. Screening of a variety of combinations of phosphanes ligands and palladium precursor showed that chelating ligands such as $Ph_2P(CH_2)_nPPh_2$ (n=2-4) or 1,1'-*bis*-(diphenylphosphanyl) ferrocene-(DPPF) give good yields of cyclized product, as did a combination of $Pd_2(dba)_3$ and P(2-furyl)$_3$, but none were better than [$Pd(PPh_3)_4$].

I.1.3: Applications of the Amination Chemistry

Stiochiometric palladium-mediated cyclisation was used in natural product synthesis by Boger *et al.* a number of years ago. More recently, Buchwald and co-workers reported the total synthesis or the formal total synthesis of a tetrahydropyrroloquinolines by palladium-catalyzed amination.[73] A brief description of the methods employed is shown below (Scheme 27). One approach involves formation of the six-membered ring through palladium- catalyzed intramolecular amination. The cyclization was carried out at high temperatures employing K_2CO_3 as base. However, the use of NaO^{t}Bu, which presumably would have allowed for reaction at lower temperatures, led cleavage of the carbamate; the cleavage products apparently inhibited catalyst activity.

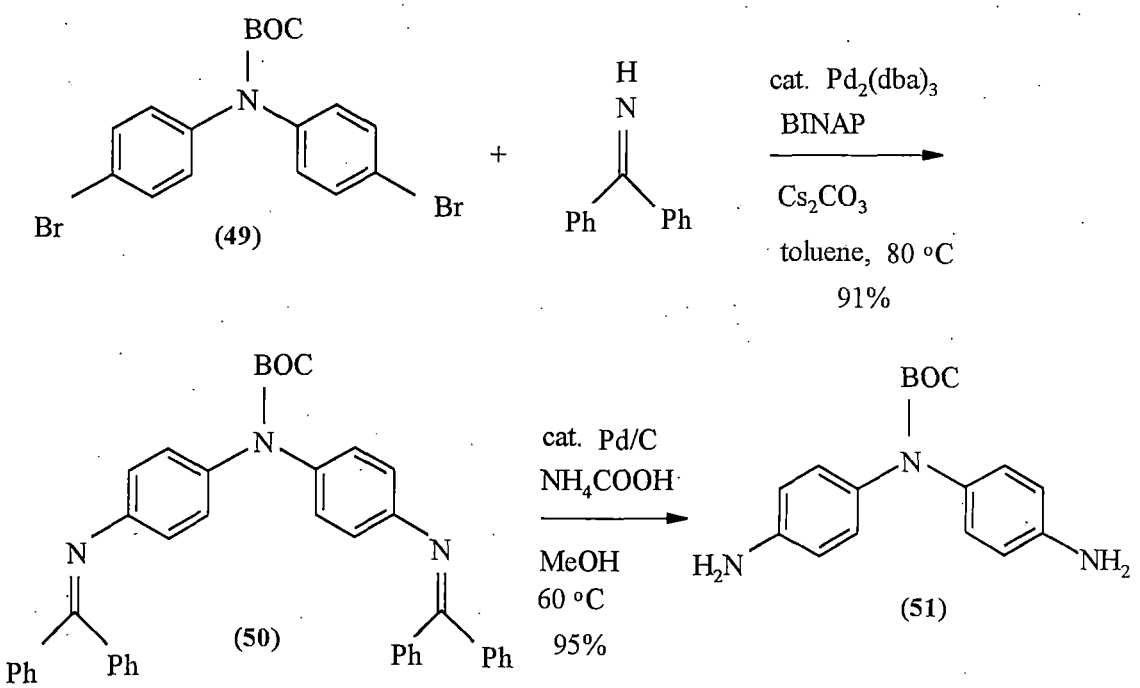
Scheme 27. Palladium catalyzed amination in the synthesis of dehydrobufotenine



The catalytic amination of following bromo-compound (**49**) proceeds in high yield to afford the diphenyl ketimine **(50)** which can be purified and stored as masked amines or the benzophenone imine can be cleaved directly to the primary amine **(51)** by catalytic hydrogenation or treatment with hydroxyl amine hydrochloride or a catalytic amount of HCl in wet THF (Scheme 28).

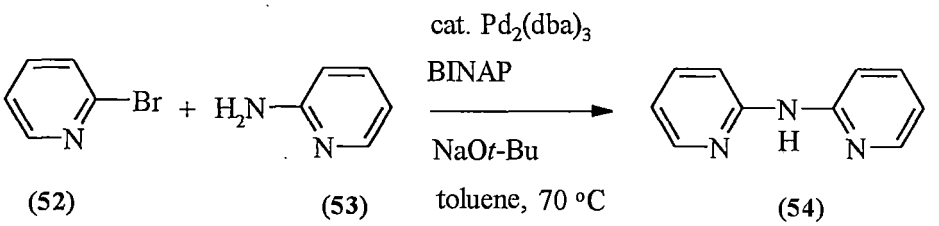
The synthesis of aminopyridines is important to many branches of chemistry, for example, they find applications as ligands, as components of fluorescent dyes, and are stimulants to the central nervous system. The Buchwald groups have revealed that the palladium-catalyzed amination strategy can be effectively applied to the synthesis of amino

Scheme 28



pyridines and this protocol represents a significant improvement relative to existing procedures which often require activated substrates and harsh reaction conditions.[74] The reaction of 2-bromopyridine (**52**) with 2-aminopyridine (**53**) produced the interesting product (**54**) in 87% yield (Scheme 29). This was also an effective strategy for preparing diarylated diamines, as shown by the reaction of four equivalents of 2-bromopyridine with diamine.

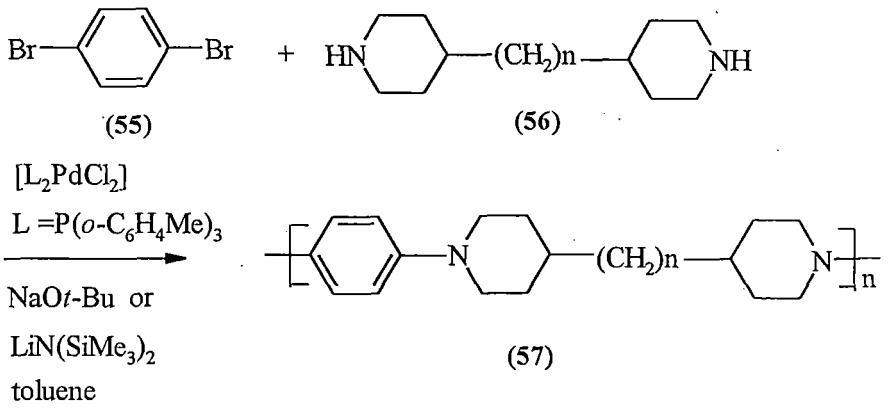
Scheme 29



(52) (53) (54)

Two groups have reported the synthesis of oligomeric or polymeric arylamines by palladium-catalyzed chemistry.[75] One group used the amination of aryl halides with dialkylamines to prepare arylamine polymers. This chemistry is a step-growth polymerization. A bifunctional diamine (**56**) and a dihaloarene (**55**) were used to generate the polymers (**57**) as shown below (Scheme 30). The highest molecular weights achieved were in the range of 5000-6000, indicating an average of 20 monomers in each chain.

Scheme 30

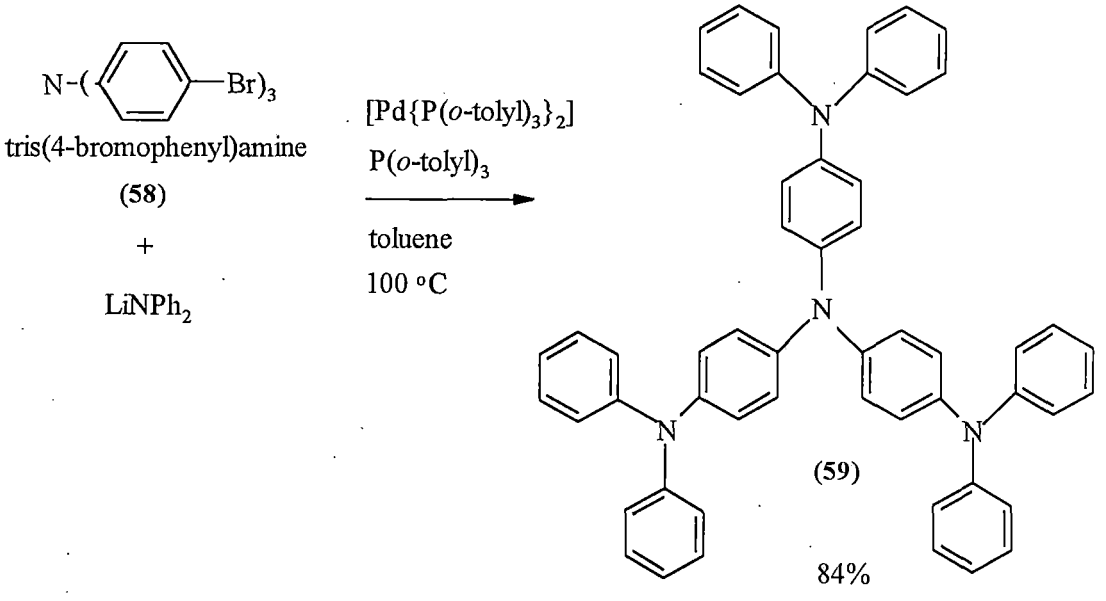


(55) (56) (57)

A second group has prepared highly branched triarylamines.[75] Hartwig further demonstrates the efficiency of the catalytic amination methodology in the preparation of high molecular weight triarylamine dendrimers.[75b] The first generation dendrimers (**59**) is prepared from tris-(4-bromophenyl)amine (**58**) and lithium diphenylamide (Scheme 31). The yield for the reaction is 84%, which is far superior to the modest yields obtained by copper-mediated Ullmann chemistry. The power of the technique

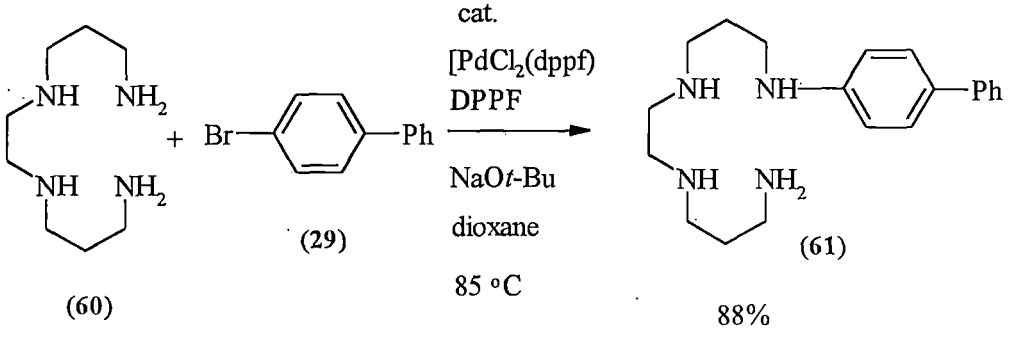
is illustrated by the preparation of the largest reported triarylamine starburst dendrimers.

Scheme 31



In an alternate amination reaction, Beleskaya and Guilard have shown that polyamines such as (**60**) react with 4-bromo biphenyl (29) to afford monoarylated products (**61**) (Scheme 32).[76] This strategy provides a convenient method of arylation of di-, tri-and tetra- amine compounds.

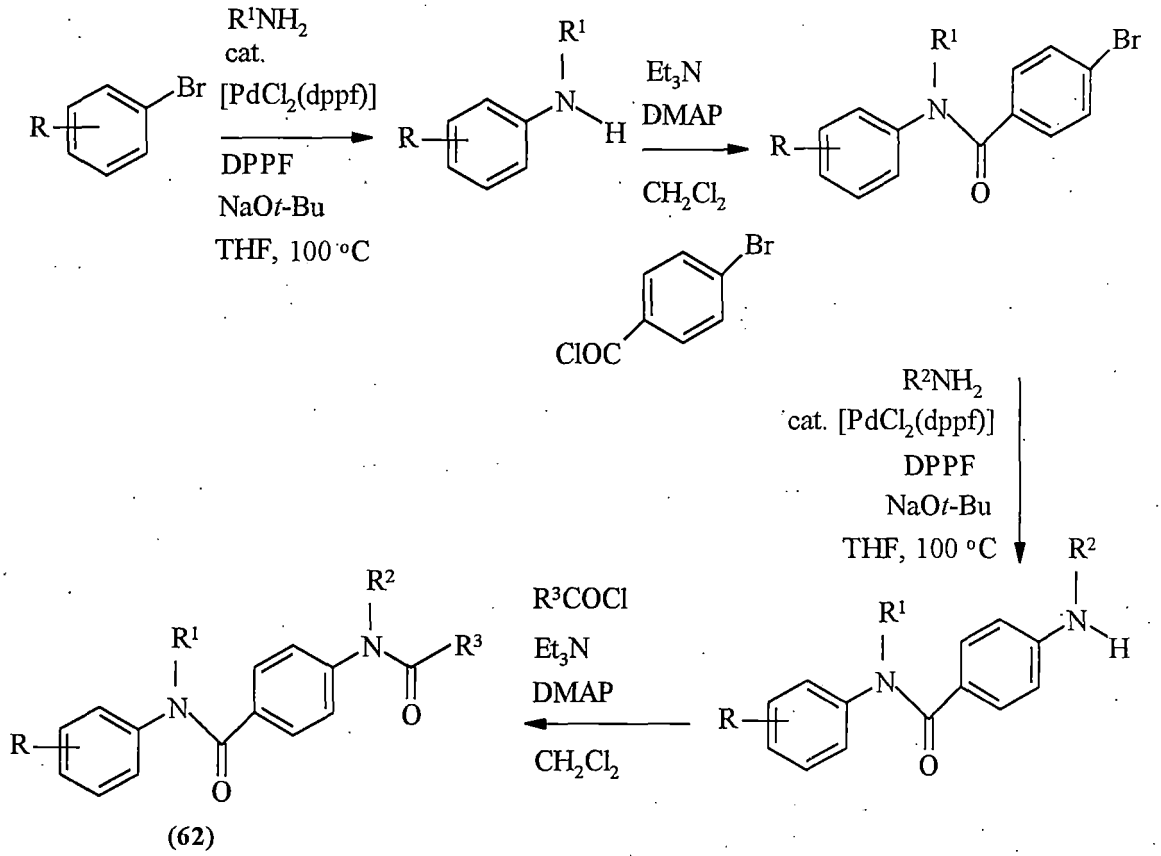
Scheme 32



Frost and Mendonca have reported the successful implementation of an iterative palladium catalyzed amination strategy to prepare an array of peptide analogues (**62**)

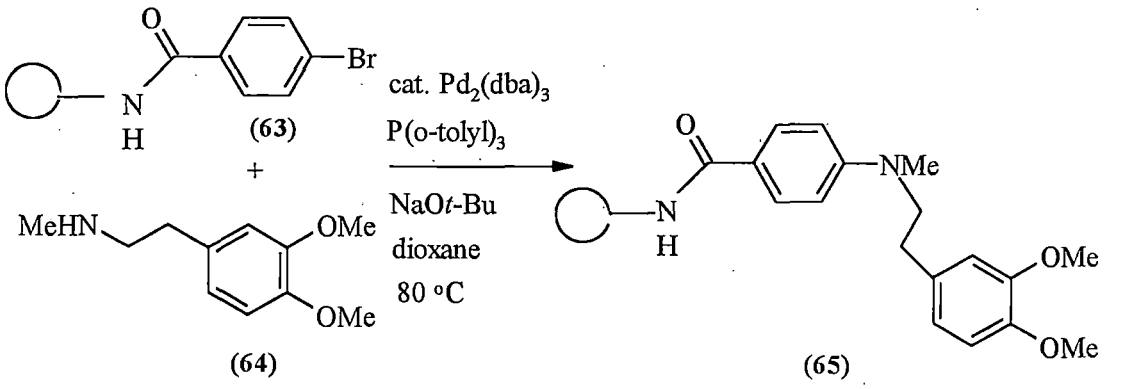
by the parallel synthesis (Scheme 33).[77] The combination of $Pd_2(dba)_3$/DPPF proved to be an effective catalyst for the efficient introduction of nitrogen functionality.

Scheme 33



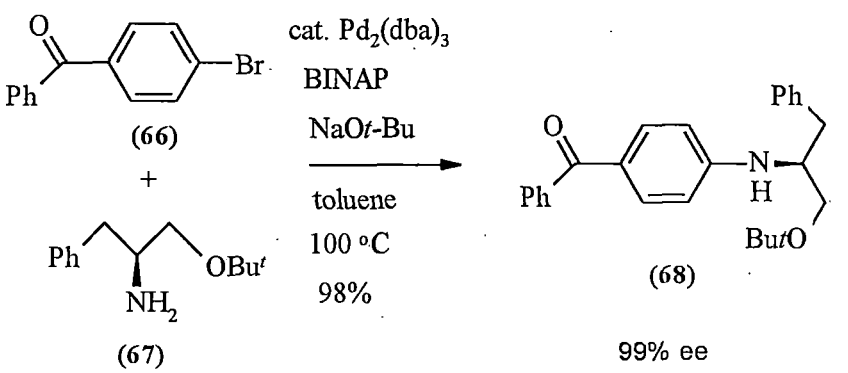
Other groups have reported methods for the solid phase synthesis of aryl amines employing the palladium catalysed amination protocol. Willoughby and Chapman noted that the Pd(0)/P(*o*-tolyl)$_3$ catalyst system is effective in the coupling of secondary amines (**64**) with polymer-bound aryl bromide (**63**) to afford high yields of product (**65**) (Scheme 34).[78] The use of BINAP as a ligand allowed the coupling of primary amines in high yields and with excellent purities. Ward and Farina independently reported similar findings.[79] This methodology would no doubt prove useful for constructing combinatorial libraries of aniline derivatives for biological screening.

Scheme 34



Buchwald reported the palladium-catalyzed coupling of enantiomerically enriched amines with aryl bromides to afford the corresponding *N*-aryl derivatives. The choice of ligand is crucial to the formation of the anilines without racemisation.[80] The Pd(0)/P(*o*-tolyl)$_3$ combination catalyses the intramolecular aryl amination to produce optically pure products, while intermolecular coupling reactions with this catalyst system lead to racemised products. However, intermolecular cross-couplings employing Pd(0)/BINAP afford products in excellent yields with no erosion of enantiopurity. This is illustrated by the reaction of *p*-bromo benzophenone (**66**) with the protected amino alcohol derivative (**67**) to afford the corresponding enantiopure product (**68**) (Scheme 35).

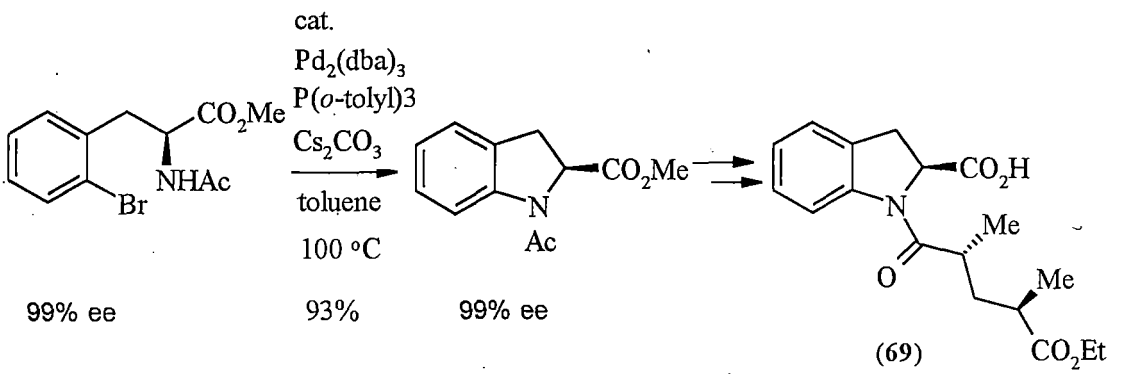
Scheme 35



The application of the intramolecular process to the synthesis of (**69**) a potent ACE inhibitor has been demonstrated (Scheme 36). Further studies by Ma and Yao

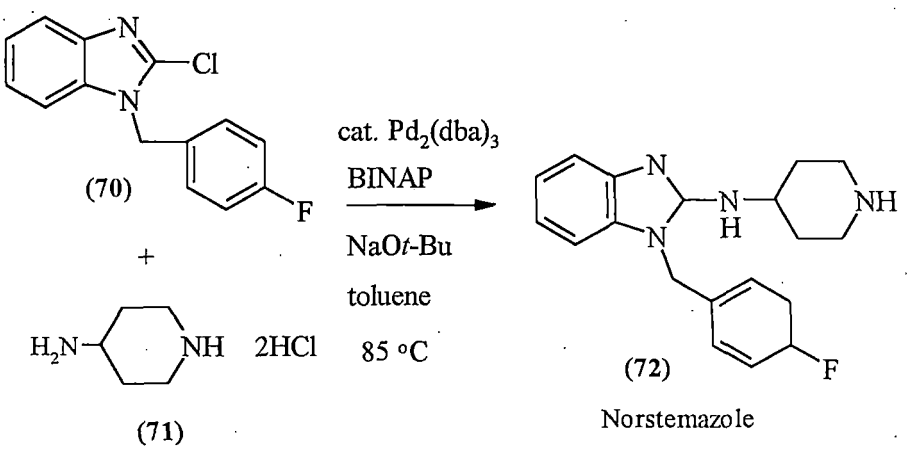
described the Pd-Cu catalyzed couplings of enantiopure α-amino acids and aryl halides.[81]

Scheme 36



The group of Senanayake reported the application of a unique palladium-catalyzed amination reaction in a concise synthesis of the potent H_1-Antihistaminic[82] norstemazole (**72**). Using the standard conditions derived by Buchwald, the amine (**71**) is coupled to the 2-chlorobenzimidazole core (**70**) in 85% yield (Scheme 37). This is a remarkably efficient process considering a primary amine is being selectively coupled in the presence of a secondary amine.

Scheme 37

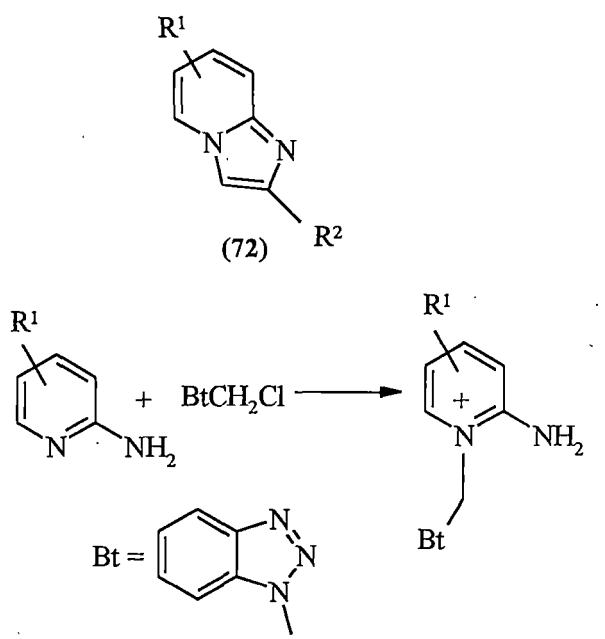


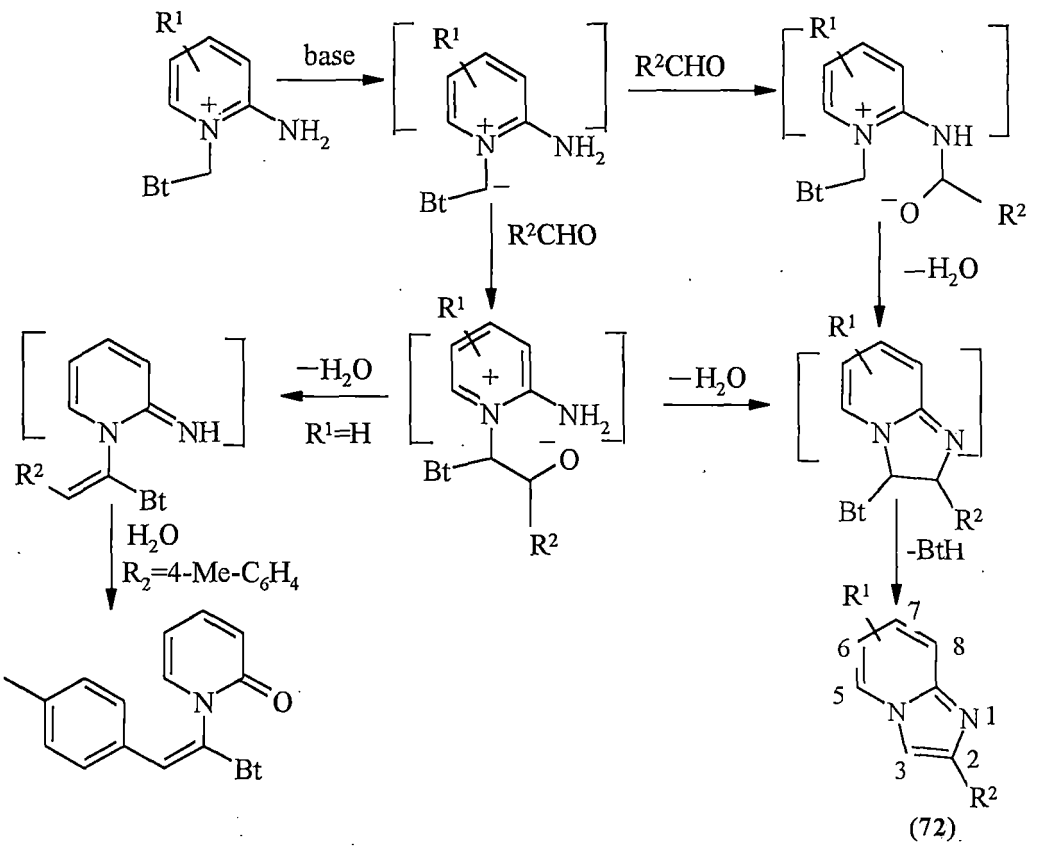
I.2.1: Present work: Background, Objectives and Strategy

Hetero-arylamines form an integral part of numerous natural products[83] and pharmaceuticals[84] and often find various applications. For example, aminopyridines are important in various fields of chemistry. They have been used as acyl transfer reagents in organic chemistry[85] and as ligands in inorganic and organometallic chemistry.[86] Additionally, aminopyridine derivatives have been used as fluorescent dyes[87] and are biologically important as central nervous system stimulants.[88] Aminothiophenes are useful precursors for natural products, pharmaceuticals, conjugated polymers,[89] and other related materials. The aminopyridine nucleus can be found in dopaminergic, serotoninergic, cholinergic and GABA-ergic ligands as well as in monoamine oxidase and acetyl choline esterase inhibitor.[90]

Imidazolo [1,2-α] pyridines (**72**) are generally prepared from 2-aminopyridines. Recently, Kartritzky and co-workers reported synthesis of imidazolo [1,2-α] pyridines, as outlined in (Scheme 38).[14]

Scheme 38



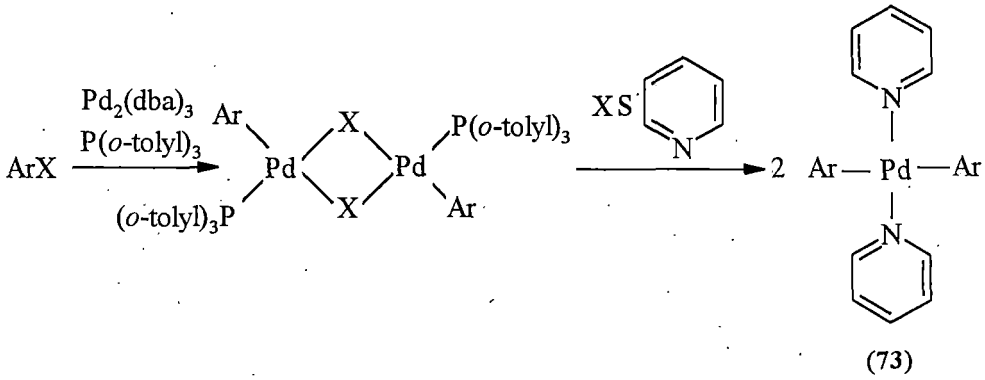


Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[21, 27] These methods either suffer from a nucleophilic regiocontrol problem, the need for very high temperature or the presence of specific functionality on the heterocyclic ring. None of these methods show a combination of good yields and high selectivity.

The palladium-catalyzed aminations of halobenzenes has been extensively investigated over the last decades, primarily by the groups of Buchwald[91] and Hartwig,[92] allowing the coupling of most classes of amine with virtually any halobenzene. Application of this methodology to other heterocyclic aromatics was still relatively unexplored. The protocols for the cross-coupling of arylbromides and aminostannanes and for the cross-coupling of arylhalides and amines using Pd(0)/P(*o*-tolyl)$_3$ complexes and sodium *tert*-butoxide were unsuccessful in the amination of bromopyridines. Buchwald rationalized this unsuccessful observation as being the ability of many nitrogen heterocycles to act as ligands for late transition metals.[53] As a result, heteroaromatic halides with basic nitrogen atoms would displace weakly binding ligands such as P(*o*-tolyl)$_3$, so that the original catalyst system containing P(*o*-

tolyl)$_3$ as ligand was ineffective for amination with heteroaromatic substrates that could bind to palladium. It has been shown in stoichiometric studies that pyridine displaces P(*o*-tolyl)$_3$ to form palladium-pyridine complexes.[93] However, chelating phosphanes are not displaced by pyridine. Thus, the advent of amination reaction with use of chelating ligands now allows for the amination of pyridyl halides.[94] In fact, it was shown by Buchwald that pyridine inhibits the Pd(0)/P(*o*-tolyl)$_3$ catalyzed amination of arylbromides and also displaces a P(*o*-tolyl)$_3$ ligand from key catalytic intermediates (the oxidative addition product) to form complexes such as bis(pyridyl) derivative (**73**) (Scheme 39).[94]

Scheme 39

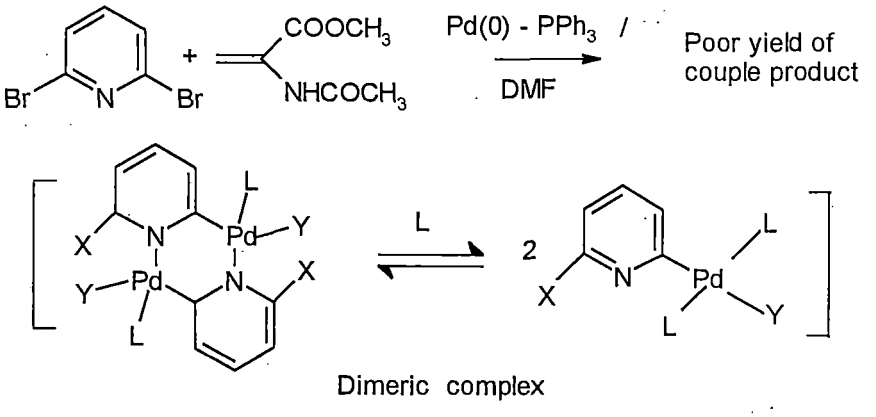


(73)

Similar result was also reported by other group[95] while working with palladium-catalyzed Heck coupling of 2,6-dibromopyridine. Thus, the failure of Heck coupling between 2,6- dibromopyridine and methyl acetamidoacrylate was explained by the formation of a stable dimeric complex (**74**) (Scheme 40).

Buchwald, however, circumvented this problem by using chelating bis-phosphine ligands. They found that the chelating bis-phosphine does not undergo ligand exchanged with excess pyridine, and consequently the formation of bis-pyridine complexes, which terminate the catalytic cycle, is prevented. Thus by using Pd(0)/bis-phosphine ligand such as (±)-BINAP, dppp, they reported amination of halopyridines prepare 2-, 3-, or 4-aminopyridine in good to excellent yields (Scheme 41).

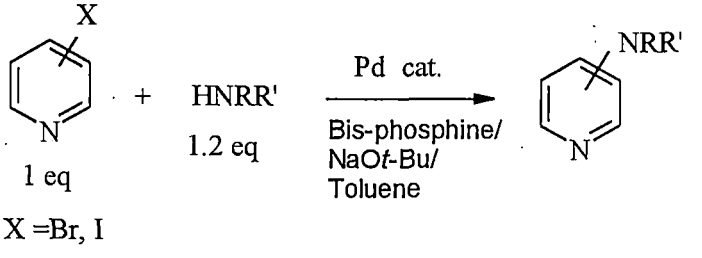
Scheme 40



Dimeric complex

(74)

Scheme 41



The Pd-bis-phosphines are: $Pd_2(dba)_3$-dppp; $Pd_2(dba)_3$-(±)-BINAP; $Pd(OAc)_2$-dppp; $Pd(OAc)_2$-(±)-BINAP.

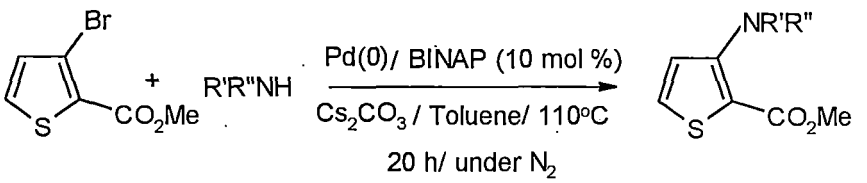
The major limitations of the Pd/(±)-BINAP or dppp-catalyzed amination protocol are the inability of this system to cross-couple halopyridines with acyclic dialkyl-amine. For example, attempts to couple di-n-butylamine with 2-,3-,or 4-bromo-pyridines or 2-chloropyridine using various chelating bis(phosphines) ligands provided only low yields of the di-n-butyl amino pyridine.

Another disadvantage of this amination protocol is the use of strong bases, such as sodium *tert*-butoxide. The use of such strong bases is not desirable and remains associated with problems such as in the case of direct amination using NaNHR or $NANR_2$. [21, 96] Furthermore, the use of strong bases greatly limits the functional group tolerance of the process.[97] For example, methyl and ethyl esters react to form amides

or *tert*-butyl esters (depending on the amine coupling partner), enolizable ketones are deprotonated, and nitroarenes decompose under these reaction conditions. Buchwald and others employed weaker bases such as Cs_2CO_3 to act efficiently in the case of haloaromatics [97] and halothiophenes, [98] but not in the case of halopyridines. However, the use of Cs_2CO_3 is limited due to its high solubility in organic solvents and hygroscopic in nature.

In the case of halothiophenes Luker *et al* [98] and Watanabe *et al* [99] reported Pd-catalyzed amination of electron-deficient halothiophenes using a wide variety of amines (Scheme 42). Luker *et al.* observed that BINAP was a superior ligand to other phosphenes such as DPPF and DPPP. In addition to $Pd_2(dba)_3$, $Pd(OAc)_2$ was also an effective palladium source, crucial in couplings of some of the halothiophenes. They used Cs_2CO_3 as the effective base, and stronger bases such as sodium *tert*-butoxide resulted solely in amide formation when thiophene carboxylate esters were employed.

Scheme 42



Thus the amination of halopyridines under the conditions developed by Buchwald and Hartwig presents two problems.

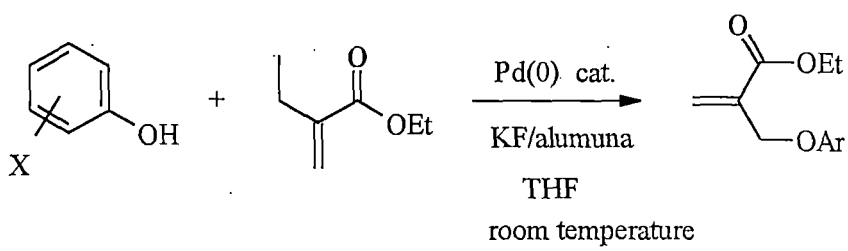
- The amination is specific to the Pd-catalyst and the ligand.
- The use of strong base, such as sodium *tert*-butoxide renders limitation with a variety of base-sensitive functional groups.

In order to address the above two shortcomings of the palladium-catalyzed amination of heteroarylhalides, we were interested to explore some new conditions. Since the use of a base is one of the keys to the success of this coupling reaction, we became

interested to investigate palladium-catalyzed cross coupling of bromo-pyridines and amines on a KF-alumina (basic) surface.

The potential ability of ionic fluorides as bases in a variety of organic reactions is well recognized. Potassium fluoride impregnated on γ-alumina is useful in many base-catalyzed solid surface mediated organic transformations since it was introduced by Clark[100] and Ando *et al.*[101] The basic sites on KF-alumina may be related to a very hard anion F^-, the catalyst exhibits characteristic performance, which differentiate KF on alumina from other alkaline earth metal oxides as base catalysts. On many occasions KF-alumina has appeared as a stronger base than KF itself[102]. In the recent years, several workers have reported carbon-carbon bond formation reactions in the presence of KF-alumina and catalytic amounts of palladium-complexes. As for example, Muzart *et al.*[103] disclosed palladium-catalyzed and KF-alumina mediated Baylis-Hillman reactions (Scheme 43).

Scheme 43

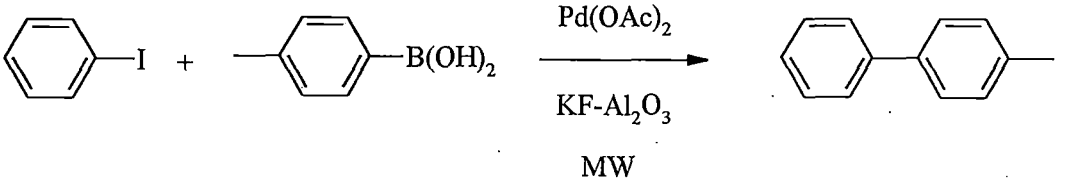


They observed that the use of Pd(0) catalyst and KF-alumina reagent together has a significant beneficial effect on reaction rate and yields of the products.

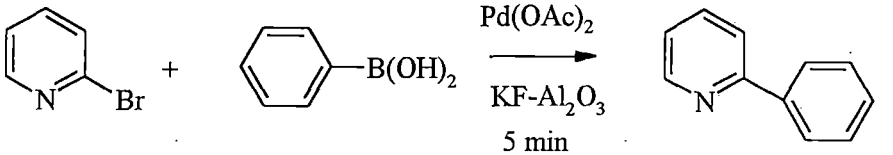
Villemin and his co-workers described palladium-catalyzed Heck, Suzuki, Stille, and Trost-Tsuzi reaction [104] on a surface of KF-alumina without use of solvent. They demonstrated that it is possible to use KF-alumina as a base without solvent in Pd-catalyzed carbon-carbon bond forming reactions. The Suzuki coupling reaction on KF-alumina has also been demonstrated by Kabalka and his co-workers.

Scheme 44

Suzuki Coupling:

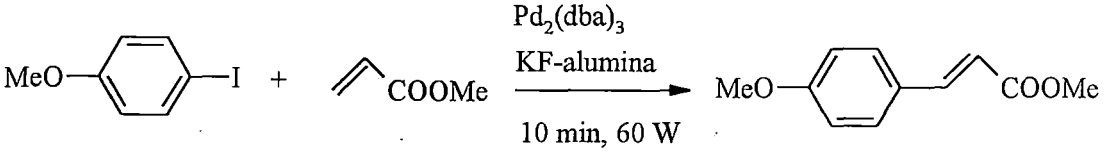


Example



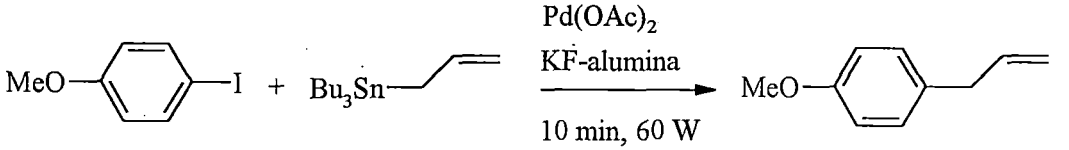
66%

Heck Coupling:



68%

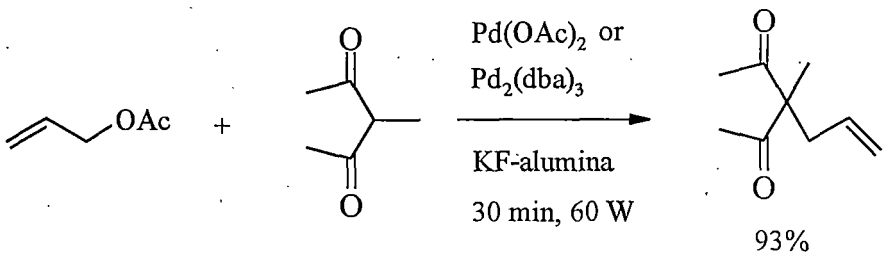
Stille Coupling:



Anethole

68%

Trost-Tsuji reactions:



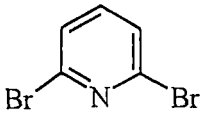
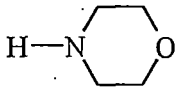
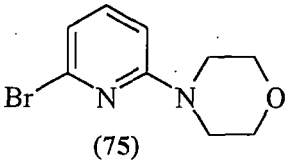
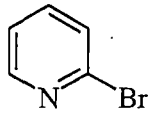
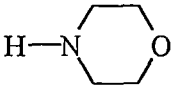
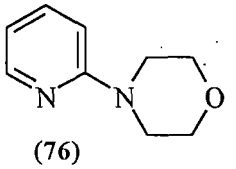
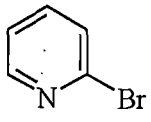
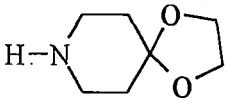
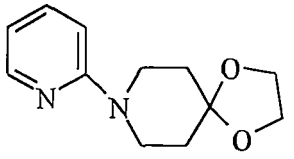
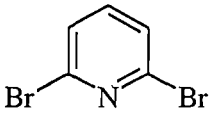
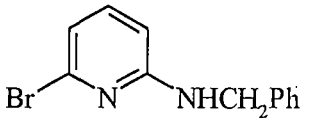
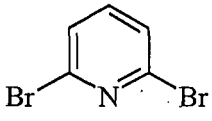
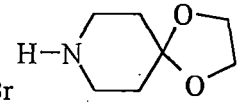
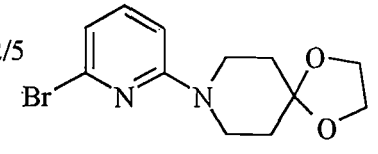
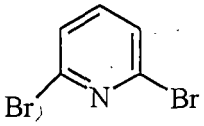
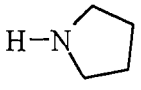
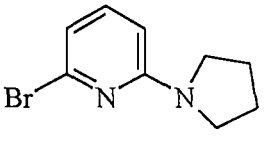
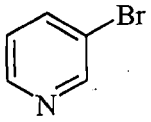
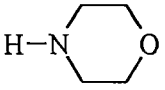
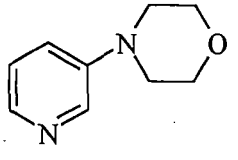
We therefore, studied palladium-catalyzed aminations of halopyridines on a KF-alumina (basic) surface. We also presumed that the formation of bis-(pyridyl) complexes **(73)** using monophosphine ligands as proposed by Buchwald, might possibly be avoided under these conditions.

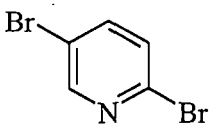
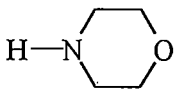
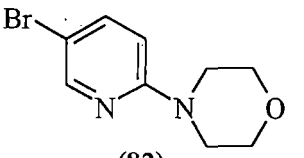
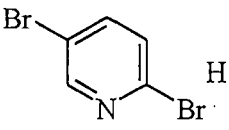
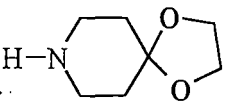
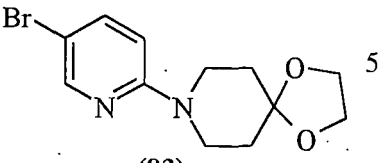
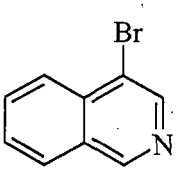
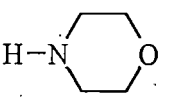
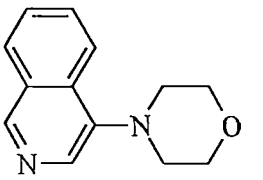
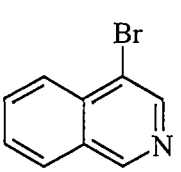
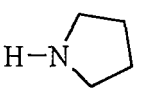
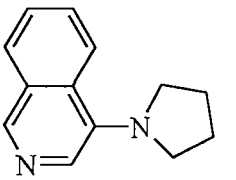
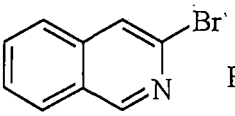
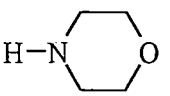
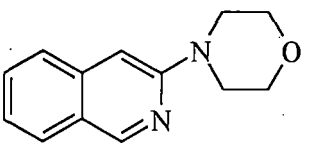
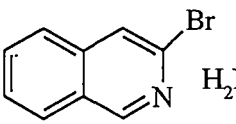
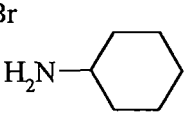
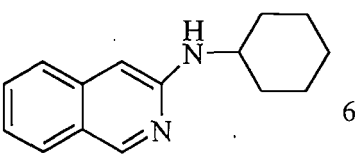
I.2.2: Present work: Results and Discussion

As discussed in the previous section, we attempted amination of 2-bromo pyridine with morpholine using $Pd[P(o\text{-tolyl})_3]_2Cl_2$ as the catalyst on a KF-alumina surface without any solvent. Indeed, the amination proceeded smoothly to produce 2-morpholino pyridine in 70% yield along with 2,2′-bipyridyl (10%), possibly by intermolecular coupling. While carrying out the same reaction in DMF, the formation of cross-couple product was decreased. Similar reaction of 2-bromopyridine with 1,4-dioxa-8-aza-spiro[4,5]decane afforded the corresponding desired product in 58% yield.

The success of the above two reactions prompted us to undertake amination of 3-bromopyridine and dibromopyridines. The reaction of 3-bromopyridine and morpholine was sluggish and we therefore, employed other Pd-sources and phosphines ligands (both mono and bidentate) to optimize the reaction conditions (Entry **7**, Table **1**). After a great deal of experimentation we found $Pd_2(dba)_3$-(±)-BINAP as the suitable catalyst and the reaction conducted without solvent afforded the desired 3-morpholino-pyridine in 48% yield along with the corresponding bipyridyl derivative (15%). In the cases of 2,6-dibromopyridine (Entry **1, 4, 5** and **6,** Table **1**) and 2,5-dibromopyridine (Entry **8** and **9**, Table **1**) the coupling with both primary and secondary amine worked satisfactorily. In all the cases, $Pd[P(o\text{-tolyl})_3]_2Cl_2$ has been found to be suitable catalyst. However, the dibromopyridine

Table 1. Palladium-catalyzed amination of halopyridines on KF-alumina syrface

Entry	Bromoarene	Amine	[a]catalyst	[b]conditions/ times	product	[c]Yield%
1.			[A]	1,2/5	 (75)	78
2.			[A]	2/8	 (76)	70
3.			[A]	2/8	 (77)	58
4.		H_2NCH_2Ph	[H]	2/8	 (78)	90
5.			[A]	2/5	 (79)	62
6.			[A]	2/5	 (80)	91
7.			[F]	1,2/9	 (81)	48

Entry	Bromoarene	Amine	[a]catalyst	[b]conditions/ times	product	[c]Yield%
8.			[A]	1,2/5	 (82)	70
9.			[A]	2/5	 (83)	58
10.			[E],[F]	1,2/6	 (84)	86
11.			[F]	2/6	 (85)	90
12.			[F]	2/6	 (86)	78
13.			[F]	2/8	 (87)	68

[a][A] Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$; [B] Pd$_2$(dba)$_3$-P(*o*-tolyl)$_3$; [C] Pd(PPh$_3$)$_4$; [D] Pd$_2$(dba)$_3$-dppf ; [E] Pd(OAc)$_2$-dppf ; [F] Pd$_2$(dba)$_3$-BINAP ; [G] Pd(acac)$_2$-dppf ; [H] Pd(OAc)$_2$-BINAP [b]1. Alumina-KF in Toluene / 90-100°C; 2. Alumina-KF without solvent at 90-100°C

[c]Yields are reported on the basis of pure isolated products (2-3 runs) and calculated on the basis of recovered starting material (for entries 6,7 and 9).

yielded the mono-amine as the major products even after prolonged reaction time and in the presence of excess amine. Buchwald observed complete bis-amination of 2,6-dibromopyridine using $Pd_2(dba)_3$-dppp catalyst in the presence of excess amine. Our conditions, however, yielded mono-amine as the major products even after prolonged reaction times and in the presence of excess amine. This selectivity offers an advantage for further reaction with the other halogen substituents.

In the bicyclic systems, both quinoline and isoquinoline systems were employed for this studies. As shown in the Table (1) the 4-bromoisoquinoline (Entry **10** and **11**, Table **1**) underwent amination with morpholine and pyrolidine to yield the corresponding aminated products in excellent yields. In this study the chelating ligands such as BINAP and dppf worked with almost equal efficiency. However, the combination of $Pd_2(dba)_3$ and BINAP, offered better efficiency as compared to others. This was however, demonstrated by Buchwald *et al.* as well. The 3-bromoquinoline also underwent similar cross-coupling reactions with morpholine and cyclohexylamine (Entry **12** and **13**, Table **1**) to produce the corresponding aminated products in 68-78% yields.

With reference to the coupling partner the amine, both primary and secondary amines were employed for this study. A great deal of experimentation on the cross coupling of bromopyridines with primary and secondary amines was carried out in order to optimize the reaction conditions. Palladium sources, ligand, solvent and the support ($KF\text{-}Al_2O_3$) were optimized and several details are worthy of comment. Firstly, different palladium sources like $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(acac)_2$ and $Pd[PPh_3]_4$ complexing with either mono-phosphine [(*o*-tolyl)$_3$P] or *bis*-phosphines (BINAP and DPPE) were employed as the catalytic systems. The $Pd[(o\text{-tolyl})_3P]_2Cl_2$ and $Pd_2(dba)_3$/BINAP complexes were found to be most effective in this amination process. The formation of bis-(pyridyl) complexes using monophosphine ligands, as proposed by Buchwald, might possibly be avoided under these conditions. The reactions were carried out with or without a solvent. Clean reactions and better yields of the aminopyridines were obtained when the reactions were carried out on $KF\text{-}Al_2O_3$ surface with slight excess of amine and without solvent. Toluene and xyline have been used as solvents with almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination. 2-bromopyridine also yields 10-15% of

2,2′-bipyridyls by intermolecular coupling and such coupling is further increased in the presence of a solvent. The major limitations of this protocol are those 3-bromopyridine fails to cross couple with primary amines and partial dehalogenation (<5%) was observed in the case of 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline. In conclusion, we have shown that Pd(0) catalyzed amination of bromopyridines can be performed smoothly on the surface of basic alumina admixed with KF. The simplicity of the experimental conditions, good to excellent yields and favourable safety aspects represent a significant improvement and useful extension relative to Buchwald's procedure using the strong base, sodium *tert*-butoxide. Future work will include studies with more base-sensitive functionalities on the heterocyclic nucleus as well as with chiral amines

I.3: Experimental.

General remarks

All melting points and boiling points are uncorrected. M.P.s were determined in open capillary in silicone oil bath. Thin layer chromatoghraphy (TLC) was performed on silica gel 60 F_{254} coated alumium sheets (Merck, Germany) and spots were detected by UV-fluorescence and /or using iodine vapour. Silica gel G 60 (6o-120 mesh) was used for column chromatography. All evaporations were conducted under reduced pressure with bath temperature below 50 °C. IR spectra were recorded on Shimadzu FTIR 8300 spectrophotometer. For recording UV spectra, a Shimadzu UV-240 spectrophotometer was used. ^{1}H-and ^{13}C-NMR spectra were recorded on a Bruker spectrophotometer (operating at 300 or 400 MHz and 75 or 100 MHz respectively) using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as internal standard and chemical shifts are expressed in ppm (δ units). The peaks are characterized by s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet). Solvents and commercial reagents were purified and dried by conventional methods before use. Petroleum ether refers to the fraction of b.p. 60-80 °C. Ether refers to diethyl ether.

General procedure

Tris(dibenzylidineacetone)dipalladium(0) [$Pd_2(dba)_3$], tri-*o*-tolylphosphine [P(*o*-tolyl)$_3$], tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], *rac*-2,2'-*bis*(diphenyl-phosphino)-1,1'-binaphthyl [(±)-BINAP], palladium(II) acetate [$Pd(OAc)_2$], palladium(II) acetylacetone [$Pd(acac)_2$] were purchased from Aldrich Chemical Co.

Preparation of activated Al_2O_3

Basic alumina (Brockmann, Activity 1), (10 g) was purchased from SRL, India, and was heated at 210 °C under vacuam (0.5 mm of Hg) for 4h, cooled under N_2 and used for reaction

Preparation of activated KF-Alumina:

A mixture of basic alumina (Activity I according to Brockmann) and KF(4:1) (5 g) was taken in THF (5 ml) and after stirring for 30 minutes at room temperature it was evaporated to dryness. The solid residue was heated at 250 °C under vacuum (0.5 mm of Hg) for 4 hours, cooled under N_2 and used for reaction.

Preparation of Catalysts

Bis(tri-*o*-tolylphosphine)palladium(II) chloride, $Pd[(o\text{-tolyl})_3P]_2Cl_2$.

To an aqueous solution of NaCl (117 mg, 2 mmol) in water, solid $PdCl_2$ (177 mg, 1 mmol) was added and heated on a water bath until a clear solution appeared. Filtrate the solution and it was evaporated to dryness to get solid Na_2PdCl_4. An ethanolic (dehydrated) solution of Na_2PdCl_4 (160 mg, 0.54 mmol), was mixed with ethanolic solution of $P(o\text{-tolyl})_3$ (330 mg, 1.08 mmol) and shaking continuously until a yellow solid precipitate settled down. Filter the precipitate and washed with water to get 360 mg (yield; 84%) of $Pd[(o\text{-tolyl})_3P]_2Cl_2$. Melting point of $Pd[(o\text{-tolyl})_3P]_2Cl_2$ was found high.

1,1'-Bis(diphenylphosphino) [DPPF]

A mixture of N,N,N',N'-tetramethylethylenediamine (1.064 g, 9.152 mmol) and a 15% solution of *n*-butyllithium in hexane (6.3 ml, 10.26 mmol) was added with stirring over 30 min to a solution of ferrocene (0.93 g, 5 mmol) in dry hexane (30 ml) under nitrogen in a 3-lit., three-necked flask equipped with a stirrer, nitrogen inlet and reflux condenser. The solution was stirred for 4h at room temperature under nitrogen and then a solution of chlorodiphenylphosphine (1.885 g, 10.2 mmol) in hexane (2 ml) was added dropwise over a 20 min period with constant stirring. During this procedure the temperature of the solution rose to 48 °C. The reaction mixture was further stirred under nitrogen for 2h and then carefully quenched with distilled water (5 ml). The supernatant hexane layer was decanted from the brownish-orange solid and the solid was washed three times with distilled water and finally dissolved in hot dioxane (8 ml). Cooling this dioxane solution gave orange crystal (1.05 g, 38%), m.p.^{obs} 179-182 °C (lit.[105] 183-184 °C).

Representative procedure for amination: 4-(6-Bromopyridin-2-yl)morpholine (75) (Entry 1)

To a mixture of 2,6-dibromopyridine (473 mg, 2 mmol), morpholine (348 mg, 4 mmol), $Pd[(o\text{-tolyl})_3P]_2Cl_2$, (31 mg, 0.04 mmol) in 10 cc toluene was added activated Al_2O_3 /KF (4 : 1), (2 g). The reaction mixture was stirred by magnetic stirrer for 5 h at 90-100°C under nitrogen atmosphere. After cooling to room temperature, the mixture was washed repeatedly with ether (4x15 ml). After removal of ether, toluene was

removed by vacuum pump. Then the residue was purified by silica gel (60-120 mesh) column chromatoghraphy (petroleum ether : ethyl acetate = 20 :1) to give 380 mg 4-(6-Bromopyridin-2-yl)morpholine. Yield: 78%, m. p. 55-56 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (dd, 1H, *J*=8.1; 7.5 Hz), 6.78 (d, 1H, *J*=7.5 Hz), 6.50 (d, 1H, *J*=8.1 Hz), 3.79 (t, 4H, *J*=4.9 Hz), 3.49 (t, 4H, *J*= 4.9 Hz).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.8, 140.6, 139.9, 116.9, 105.1, 66.9, 45.6.

Spectral data for the compounds listed in Table 1

4-pyridin-2-yl-morpholine (76) [106] **(entry 2)**

Yield: 70%, liquid.
IR (neat): ν_{max} 2966, 1603, 1486, 1440, 1378, 1312, 1240 cm^{-1}
^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.20 (d, 1H, *J*=4.5 Hz), 7.49 (m, 1H), 6.64 (m, 2H), 3.82 (t, 4H, *J*=4.8 Hz), 3.48 (t, 4H, *J*=4.8 Hz).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ 159.4, 147.7, 137.3, 113.6, 106.7, 66.5, 45.4.

8-Pyridin-2-yl-1,4-dioxa-8-aza-spiro[4,5]decane (77) (entry 3)

Yield: 58%, liquid.
IR (neat): ν_{max} 2960, 1598, 1562, 1486, 1440, 1363, 1235 cm^{-1}
^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, 1H, *J*=4.4 Hz), 7.48 (m, 1H), 6.66 (d, 1H, *J*= 8.5 Hz), 6.56 (m, 1H), 3.96 (s, 4H), 3.68 (t, 4H, *J*= 5.4 Hz), 1.75 (t, 4H, *J*=5.4 Hz).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.7, 147.7, 137.3, 112.5, 106.9, 64.1, 43.2, 34.1.
Anal. Calcd. for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32.
Found C, 65.12; H, 7.44.

2-Benzylamino-6-bromopyridine (78) (entry 4)

Yield: 90%, m.p.85 °C
IR (Nujol): ν_{max} 3293, 1603, 1562, 1536, 1434, 1367 cm^{-1}
^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.27-7.36 (m, 5H), 7.20 (dd, 1H, *J*= 8.2; 7.5 Hz), 6.73 (d, 1H, *J*=7.5 Hz), 6.24 (d, 1H, *J*=8.2 Hz), 5.18 (br.s, 1H), 4.46 (d, 2H, *J*=5.9 Hz).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.7, 140.2, 139.5, 138.3, 128.7, 127.4, 127.3, 116.1, 104.5, 46.3.

8-(6-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane (79) (entry 5)

Yield: 62%, m.p. 99-100 °C

.IR (Nujol): ν_{max} 2966, 1588, 1552, 1491, 1440, 1342, 1245 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.24 (dd, 1H, *J*=8.4, 7.4 Hz), 6.68 (d, 1H, *J*=7.4 Hz), 6.53 (d, 1H, *J*=8.3 Hz), 3.97 (s, 4H), 3.65 (t, 4H, *J*=5.5 Hz), 1.73 (t, 4H, *J*=5.5 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.39, 139.9, 139.3, 115.2, 104.6, 64.1, 42.9, 34.1.

Anal. Calcd. for $C_{12}H_{15}BrN_2O_2$(299.17): C, 48.18; H, 5.05.

Found: C, 48.02; H, 5.38

2-Bromo-6-pyrrolidin-1yl-pyridine (80) (entry 6)

Yield: 91%, m.p. 88-89 °C.

IR (Nujol): ν_{max}2976, 1603, 1537, 1496, 1388 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.19 (dd, 1H, *J*=8.1; 7.5 Hz), 6.61 (d, 1H, *J*= 7.5 Hz), 6.20 (d, 1H, *J*=8.1 Hz), 3.40 (t, 4H, *J*=6.6 Hz), 1.99 (t, 4H, *J*=6.6 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 157.1, 140.3, 138.7, 113.7, 104.4, 46.7, 25.3.

4-Pyridin-3-yl-morpholine (81) [106] **(entry 7)**

Yield: 48%, liquid

IR (neat): ν_{max} 2966, 1665, 1583, 1446, 1455, 1434, 1352, 1255 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.22 (s, 1H), 8.04 (m, 1H), 7.19 (m, 2H), 3.80 (t, 4H, *J*=4.5 Hz), 3.11 (t, 4H, *J*=4.5 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.7, 140.8, 138, 123.4, 122, 66.6, 51.8.

4-(5-Bromopyridin-2-yl)morpholine (82) (entry 8)

Yield: 92%, m.p. 84-85 °C.

IR (Nujol): ν_{max} 2966, 1588, 1547, 1475, 1388, 1312, 1235 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.20 (s, 1H), 7.55 (dd, 1H, *J*=6.3 Hz), 6.52 (d, 1H, *J*=8 Hz), 3.81 (t, 4H, *J*= 6 Hz), 3.46 (t, 4H, *J*= 6 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 157.4, 148.5, 139.8, 108.2, 66.5, 45.5.

Anal. Calcd. for $C_9H_{11}BrN_2O$(243.10); C, 44.47; H, 4.56.

Found; C, 44.42; H, 4.72

8-(5-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane (83) (entry 9)

Yield: 73%, m.p.83-84 °C.

IR (Nujol): ν_{max} 2960, 1588, 1486, 1404, 1363, 1245 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, 1H, *J*=2.4 Hz), 7.50 (dd, 1H, *J*=8.9; 2.4 Hz), 6.57 (d, 1H, *J*=8.9 Hz), 3.99 (s, 4H), 3.65 (t, 4H, *J*=5.5 Hz), 1.75 (t, 4H, *J*= 5.5 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 157, 148.4, 139.6, 108.4, 107.3, 64.3, 43.5, 34.2.

4-Morphilin-4-yl-isoquinoline (84) (entry 10)

Yield: 86%, m.p. 134-136 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.98 (s, 1H), 8.19 (s, 1H), 8.11 (d, 1H, *J*=8.3 Hz), 7.95 (d, 1H, J=8.1 Hz), 7.59 (m, 1H), 3.97 (t, 4H, *J*=4.4 Hz), 3.16 (t, 4H, *J*=4.4 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 148.1, 143.1, 132.6, 131.3, 129.8, 129.2, 128.0, 127.2, 122.4, 67.2, 53.1.

4-Pyrrolidin-1-yl-isoquinoline (85) (entry 11)

Yield: 90%. Liquid.

IR (neat): ν_{max} 2960, 1629, 1578, 1501, 1409, 1342, 1255 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.76 (s, 1H), 8.14 (d, 1H, *J*=8.7 Hz), 8.02 (s, 1H), 7.86 (d, 1H, *J*=7.6 Hz), 7.60-7.49 (m, 2H), 3.45 (t, 4H, *J*=6.5 Hz), 1.99 (t, 4H, *J*=6.5 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.1, 141.3, 129.5, 129.2, 128.4, 128.0 127.5, 126.5, 123.8, 52.0, 25.1.

3-Morphilin-4-yl-quinoline (86) (entry 12)

Yield:78%, m.p. 91-92 °C.

IR (Nujol): ν_{max}2960, 1603, 1496, 1455, 1388, 1271, 1224 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.79 (d, 1H, *J*=2.5 Hz), 8.00 (d, 1H, *J*=8 Hz), 7.69 (d, 1H, *J*=8Hz), 7.53 (m, 2H), 7.34 (d, 1H, *J*=2.5 Hz), 3.93 (t, 4H, *J*=4.8 Hz), 3.28 (t, 4H, *J*=4.8 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.4, 144.2, 142.8, 128.7, 128.5, 127.1, 126.4, 126.3, 116.2,66.4, 48.9.

Cyclohexyl-quinolin-3-yl-amine (87) (entry 13)

Yield: 68%, m.p. 118-119 °C.

IR (Nujol): ν_{max} 3232, 3053, 2930, 1609, 1542, 1486, 1393, 1363, 1240 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.37(d, 1H, *J*=2.7 Hz), 7.93 -7.90(m, 1H), 7.60 -7.55 (m, 1H), 7.44 -7.30(m, 2H), 6.96 (d, 1H, *J*=2.7 Hz), 3.97 (br.s, 1H), 3.33 (m, 1H), 2.11 - 2.06 (m, 2H), 1.81 -1.64 (m, 2H), 1.43 -1.18 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 143.5, 141.7, 140.6, 129.5, 128.8, 126.7, 125.6, 124.4, 109.9, 51.4,32.8, 25.7, 24.8.

I.4: References

1. (a) Vara, J.; Perez-gonzalez, J.; Jimenez, A. *Biochemistry* **1985**, *24*, 8074; (b) Lacalle, R. A.; Pulido, D.; Vara, J. *Gene* **1989**, *79*, 375; c) De La Luna, S.; Ortin, J. *Methods In Enzymology* **1992**, *216*, 376.
2. Montgomary, J. A.; Secrist, J. A. In *Comprehensive Heterocyclic Chemistry;* Katrizky, A. R.; Ress, C. W.; Potts, K. T., Eds.; Pergamon: Oxford, **1984**; Vol. 1, p. 145.
3. Katrizky, A. R; Ress, C. W. In *Comprehensive Heterocyclic Chemistry.* Pergamon: Oxford, **1984**; Vol. 1, p.161.
4. Lechat, P.; Tesleff, S.; Bownan, W. C. *Aminopyridines and Similarly Acting Drugs; Pergamon Press*: Oxford, NY, **1982**.
5. See website for: Clonidine: http://www.fragilex.org/html/clonidine.htm
6. See website for: Prometryn:http://pmep.ccc.cornell.edu/profiles/extoxnet/ metirampropoxur /prometryn- ext.html.
7. See website for: Leucopterin:http://www.jbc.org/cgi/content/abstract/242/4/565
8. See website for: Mauveine: http://en.wikipedia.org/wiki/Mauveine.
9. (a) Sathyamoorthi,G.; Soong, M. L.; Ross, T. W.; Boyer, J. H. *Heteroatom. Chem.* **1993**, *4*, 603; (b) Araki, K.; Mutai, T.; Shigemitsu, Y.; Yamada, M.; Nakajima, T.; Kuroda, S.; Shimao, I. *J. Chem. Soc., Perkin Trans 2*, **1996**, 613-617.
10. MacDiarmid, A. G.; Chiang, J.-C.; Halpern, M.; Huang, W.-S.; Mu, S.-L.; Somasiri, N. L. D.; Wu, W.; Yaniger, S. I. *Mol. Cryst. Liq. Cryst.* **1985**, *121*, 173.
11. (a) MacDiarmid, A. G.; Mu, S.-L.; Somasiri, *M.* L. D.; Wu, W.; . *Mol. Cryst. Liq. Cryst.* **1985**, *121,*187; (b) Kitani, A.; Kaya, M.; Sasaki, K. *J. Electrochem. Soc.* **1986**, *133*, 1069.
12. (a) Gustafsson, G.; Cao, Y.; Treacy, G. M.; Klavetter, F.; Colanery, N.; Heeger, A. *J. Nature* **1992**, *357*, 477; (b) Yang, Y.; Westerweele, E.; Zhang, C.; Smith, P.; Heeger, A. J. *J. Appl. Phys.* **1995**, *77*, 694.
13. (a) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497; (b) Kempe, R.; Arndt, P. *Inorg. Chem.* **1996**, *35*, 2624-2649; (c) Nagao, N.; Mukaida, M.; Tachiyashiki, S.; Mizumachi, K. *Bull. Chem. Soc. Jpn.* **1994**,

67, 1802; (d) Maekawa, M.; Munakata, M.; Sow, T. K.; Hachiya, K. *Inorg. Chim. Acta* **1994**, *227*, 137; (e) Ranninger, M. C. N. *Acta. Crystallogr.* **1985**, *C41*, 21; (f) Alvila, L.; Pakkanen, T. A. *J. Mol. Catal.* **1993**, *84*, 145.

14. Katrizky, A. R.; Qiu, G.; Long, Q.-H.; He, H.-Y.; Steel, P. J. *J. Org. Chem.* **2000**, *65*, 9201.
15. Abignente, E.; Caprariis, P. D.; Fattorusso, E.; Mayol, L. *J. Heterocycl. Chem.* **1989**, *26*, 1875.
16. Vega, J. A.; Vaquero, J. J.; Alvarez-Builla, J.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317.
17. Dubinsky, B.; Shriver, D.A.; sanfilippo, P.J.; Press, J. B.; Tobia, A. J.; Rosenthale, M. E. *Drug dev. Res.* **19990**, *21*, 277.
18. (a) Katsura, Y.; Nishino, S.; Inoue, Y.; Tomoi, M.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*, 371; (b) Starrett, J. E.; Montzka, T. A.; Crosswell, A. R.; Cavanagh, R. L.; *J. Med. Chem.* **1989**, *32*, 2204.
19. Fisher, M. H.; Lusi, A. *J. Med. Chem.* **1972**, *15*, 982.
20. (a) Gullu, M.; Uzan, S.; Yalcun, S. *Tetrahedron Lett.* **2003**, *44*, 1939; (b) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993; (c) McGuigan, C.; Yarnold, C. J.; Jones, G.; Velazquez, S.; Barucki, H.; Brancale, H.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479; (d) Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2000**, *43*, 3125-3133; (e) Gangjee, A.; Devraj, R.; McGuire, J. J.; Kisliuk, R. L.; Queener, S.F.; Barrows, L. R. . *J. Med. Chem.* **1994**, *37*, 1169-1176.
21. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, 2001; pp.850-893.
22. Seeboth, H. *Angew. Chem. Int. Ed. Engl.* 1967, *6*, 307-317.
23. Gilbert, E.E. Sulfonation and Related Reactions; Willey: New York, **1965**, p.166
24. Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1972**, *37*, 3570.
25. Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681.
26. (a) Huisgen, R.; Rist, H. *Naturwissenschaften* **1954**, *41*, 358; (b) Roberts, J. D.; Simmons, H. E.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290; (c) Scott, F. L.; Oesterling, R. E. *J. am. Chem. Soc.* **1960**, *82*, 5284.

27. Levine, R.; Leak, W. W. *Science* **1995**, *121*, 780.

28. (a) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904; (b) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1958**, *3*, 197; (c) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

29. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

30. (a) Semmelhack, M. F.; Clark, G. R.; Farina, R.; Saeman, M. *J. Am. Chem. Soc.* **1979**, *101*, 217; (b) Semmelhack, M. F.; Yamishita, A. *Ibid*, **1980**, *102*, 592; (c) Davies, S. G.; Green, M. L. H.; Mingos, D. M. P. *Tetrahedron Report No.* 57. *Tetrahedron* **1978**, *34*, 3047; (d) Houghton, R. P.; Voyl, M.; Price, R. *J. Chem. Soc. Chem. Commun.* **1980**, 884.

31. Birch, A. I.; Kelley, L. F.; Narula, A. S. *Tetrahedron* **1982**, *38*, 1813.

32. Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

33. Eberson, L.; Jonsonn, L.; Wistrand, L. G. *Tetrahedron* **1982,** *38*, 1087.

34. Tiecco, M.; *Acc. Chem. Res.* **1980**, *13*, 51.; *Pure Appl. Chem.* **1981**, *53*, 239.

35. Kochi, J. K. *Organometallics Mechanisms andCtalysis*, Academic Press, New York **1978**, pp.168-180.

36. (a) Bacon, R. G. R.; Hill, H. A. O. *Quart. Rev. Chem. Soc.* **1964**, 95; (b) Chaltykyan, O. A. *Copper Catalytic reactions*, Consultants Bureau, New York **1966**.

37. *Encyclopedia of Chemical Technology*, Willey, New York **1963**, *2*(2^{nd} Edn.), 332-373.

38. Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463.

39. Krock, F. W.; Neett, R. *Euro. Pat.* **1982**, *31*, 783.

40. Vorozhtsov, N. N.; Kobelev, V. A. *Zh. Obshch. Khim.* **1977**, *13*, 1221.

41. Acheson, R. M. Acridines 1956, pp.122- 161, Interscience, New York.

42. (a) Matsuoka, M.; Makino, Y.;Yoshida, K.; Kitao, T. *Chem. Lett.* **1979**, 219; (b) Yoshida, K.; Matsuoka, M.; Yamashita, Y.; Kitao, T. *Ibid.* **1978**, 1317.

43. Takei, T.; Matsuoka, M.; Kitao, T. *Bull. Chem. Soc. Japan* **1981**, *54*, 2735.

44. Hager, F. D. *Org. Synthesis* **1948**, col. Vol.1 (2^{nd} Edn.), 544.

45. (a) Tuong, T. D.; Hida, M. *Bull. Chem. Soc. Japan* **1970**, *43*, 1763; (b) Tuong, T. D.; Hida, M. *J. Chem. Soc., Perkin Trans. II* **1974**, 674; (c) *Idem, Bull. Chem. Soc., Japan* **1971**, *44*, 765.

46. Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.

47. (a) Gujadhur, R.; Venkataraman, D.; Kintig, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791; (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315; (c) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 139.
48. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2637.
49. Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
50. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.
51. Gujadhur, R.; Venkataraman, D.; Kintig, J.T. *Tetrahedron Lett.* **2001**, *42*, 4791.
52. Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143.
53. Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.
54. (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927; (b) Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Nippon Kagaku Kaishi* **1985**, *3*, 547.
55. (a) Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* 1984, 25, 3175; (b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Am. Chem. Soc* **1985**, *50*, 5790; (c) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.
56. Paul, F.; Pat, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
57. Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
58. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* 1996, 118, 7215.
59. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* 1996, 118, 72117.
60. Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.
61. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
62. Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics*, **1996**, *15*, 2794.
63. Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568.
64. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.
65. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.
66. Beller, M.; Riermeier. T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073.
67. Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.
68. Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

69. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

70. Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.

71. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem.* **1995**, *107*, 1456-1459; *Angew. Chem. Int. Ed. Engl.***1995**, *34*, 1348.

72. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron.* **1996**, 52, 7525.

73. Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028.

74. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

75. (a) Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**,1135-1136; (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11695.

76. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 2287.

77. Frost, C. G.; Mendonca, P. *Chem. Lett.* **1997**, 1159.

78. Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181.

79. Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993.

80. Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

81. Ma, D.; Yao, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3075.

82. Hong, Y.; Tanoury, G. J.; Scott Wilkinson, H.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607.

83. (a) Salas, M.; Alvarez, M.; Joule, J. A. *Heterocycles* **1991**, *32*, 759; *Heterocycles* **1991**, *32*, 1391; b) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996,** *118*, 1028; c) Stierle, D. B.; Faulkner, D. J. *J. Nat. Prot.* **1991**, *54*, 1131.

84. (a) Gupton, J. T.; Tarrant, J. G.; Yu, R. H.; Solarz, T. L. *Synth. Commun.* **1992**, *22*, 3205; (b) Grundfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277; (c) LaMontagne, M. P.; Blumbergs, P.; Smith, D. C. *J. Med. Chem.* **1989**, *32*, 1728; (d) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311; (e) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1990**, *112*, 8195; (f) Queener, S. F.; Bartlett, M. S.; Nasar, M.; Smith, J. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 2166 ;(g) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.

85. Hofle, G.; Steglich, W. *Synthesis* **1972**, 619.

86. (a) Kempe, R.; Arndt, P. *Inorg. Chem.* **1996**, *35*, 2644; (b) Alvila, L.; Pakkanen, T. A. *J. Mol. Catal.* **1993**, *84*, 145.

87. (a) Sathyamoorthi,, G.; Soong, M. L.; Ross, T. W.; Boyer, J. H. *Heteroatom Chem.* **1993**, *4*, 603; (b) Araki, K.; Mutai, T.;Shingemitsu, Y.; Yamade, M.; Nakajima, T.; Kurada, S.; Shimao, I. *J. Chem. Soc.; Perkin Trans II* **1996**, 613.

88. Lechet, P.; Tesheff, S.; Bownan, W. C.; *Aminopyridines and Similarly Acting Drugs,* Pergamon Press: Oxford, New York, **1982.**

89. (a)D□Aproano, G.; Schiavon, G.; Zotti, G.; Leclerc, M. *Chem. Mater.* **1995**, *7*, 33; b)Negwer, M. Organic-Chemical Drugs and Their Synonyms: An Internationa Survey, 7th Ed.; Akademic: Berlin, 1994; c) MacDiarmid, A. G.; Epstein, A. J. In Science and Applications of Conducting Polymers; Salaneck, W. R.; Clark, D. T.; Samuelsen, E. J., Eds; Hilger: New York, **1991**.

90. (a) Contretas, J. M.; Parrot, I.; Sippl, W.; Rival, Y.; Wenmuth, C. G. *J. Med. Chem.* **2001**, *44*, 2707; (b) Wermuth, C. G. *J. Heterocycl. Chem.* **1998**, *35*, 1091.

91. (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. Acc. *Chem. Res.* **1998**, *31*, 805; (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1114; (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

92. (a) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.***1998**, *37*, 2046; (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S.I.; Shaughnessy, K. H.; Aleazar-Roman, I. M. *J. Org. Chem.* **1999**, *64*, 5575.

93. Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

94. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

95. Basu, B; Fred, T. *Acta Chem. Scand.* **1996**, *66*, 3820.

96. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th edn.; Blackwell Science: Oxford, 2000, 71; (b) Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599; (c) Walters, M. A.; Shay, J. J. *Synth. Commun.* **1997**, *27*, 3537.

97. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

98. Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731

99. Wattanabe, M.; Yamamoto, T.; Nishiyama, M. *J. Chem. Soc., Chem. Commun.* **2000**, *133*, 134.

100. Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

101. (a) Ando, T.; Yamawaki, J.; Hanafusa, T. *Chemistry Letters* **1981**, pp. 1143; b) Anto, T.; Yamawaki, J.; Kawate, T.; Hanafusa, T. *Bull. Chem. Soc. Jpn.* **1983,** *56,* 1885; c) Anto, T.; Yamawaki, J. *Chem. Lett.* **1979**, 45.

102. (a) Villemin, D. J. Chem. Soc., *Chem. Commun.* 1983, p. 1092; b) Blass, B. E.; Harris, C. L.; Portlock, D. E. *Tetrahedron Lett.* 2001, 42, 1611-1613; c) Kabashima, H.; Tsuji, H.; Nakata, S.; Tanaka, Y.; Hattori, H. *Appl. Cat. A* 2000, *194-195*, 227-240.

103. (a) Muzart, J.; Genet, J. P.; Denis, A. *J. Organomet. Chem.* **1987**,*326*, 623; (b) Roy, O.; Riahi, A.; Henin, F.; Muzart, J. *Tetrahedron* **2000**, *56*, 8133.

104. Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639.

105. Bishop, J. J.; Davison, A.; Katcher, D. W.; Lichtenbero, D.W.; Merril, R. E.; Smart, J. C. *J. Organomet. Chem.* **1997**, *27*, 241.

106. (a) Grasa, G. A.; Viciu, M. S.; Huang, J; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729; (b) Wagaw, S.; Buchwald, S. L.; *J. Org. Chem.* **1996**, *61*, 7240.