ORGANIC REACTIONS METHODOLOGY: STUDIES ON CARBON - NITROGEN HETERO BOND FORMING REACTIONS

Thesis submitted for the Degree of Doctor of Philosophy in Science of the University of North Bengal

By

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2004

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To Whomsoever It May Concern

This is to certify that Mr. Satadru Jha has carried out his work under my supervision. His thesis entitled "ORGANIC REACTIONS METHODOLOGY: STUDIES ON CARBON-NITROGEN HETERO BOND FORMING REACTIONS" is based on his original work and is being submitted for the award of Doctor of Philosophy (Science) Degree in Chemistry in accordance with rules and regulations of the University of North Bengal.

04.05.2004.

(Dr. B. Basu)

DECLARATION

The research work embodied in this thesis has been carried out at Department of Chemistry, North Bengal University, Darjeeling, under the supervision of Dr. B. Basu, Reader, Department of Chemistry. I solemnly declare that this work is original, and to my belief, the work has not been submitted in part or full, for any other degree or diploma.

Date: 04/05/04

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Any accomplishment requires the effort of many people and this work is not different. I am grateful to acknowledge to my fellow colleagues Mr. Pralay Das and Mr. M.M.H. Bhuiyan.

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Annexures: List of Publications

1. Basu, B.; **Jha, S.**; Mridha, N. K.; Bhuiyan, M. M. H. "Palladium-catalyzed amination of halopyridines on a KF-alumina surface", *Tetrahedron Lett.* **2002**, *43*(44), 7967-7969.

2. Basu, B.; Das, P.; Bhuiyan, M. M. H.; **Jha, S.** "Microwave-assisted Suzuki coupling on a KF-alumina Surface: Synthesis of Polyaryls", *Tetrahedron Lett.* **2003**, *44*, 3817-3820.

3. Basu, B.; **Jha, S.**; Bhuiyan, M. M. H.; Das, P. "A Simple Protocol for direct reductive amination of aldehydes and ketones usage potassium formate and catalytic palladium acetate", *Synlett.* **2003**, 555-557.

4. Basu, B.; Bhjuiyan, M. M. H.; **Jha, S.** "Palladium mediated chemoselective reduction of α,β-unsaturated cyano esters with potassium formate", *Synth. Commun.* **2003**, *33*(2), 291-296.

Poster Presentation in National Symposium.

Jha, S.; Basu, B. "Palladium-catalyzed amination of Halopyridines on KF-alumina surface", 5th National Symposium in Chemistry, Chennai, 2003, Abstract No. P 302 p. 340.

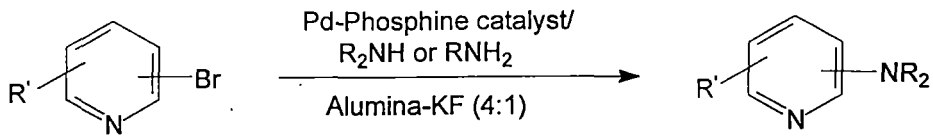
S U M M A R Y

The thesis entitled "ORGANIC REACTIONS METHODOLOGY: STUDIES ON CARBON – NITROGEN HETERO BOND FORMING REACTIONS" is principally concerned with investigations relating to developments of new organic reactions methodology, reagents and conditions with major interest to carbon–nitrogen bond forming reactions and its applications. The total work of this thesis has been divided into two parts: **Part–I** and **Part–II**. Each part comprises two sections: **Section–A**, and **Section–B**.

Part–I, Section–A describes studies on palladium-catalyzed amination reaction of halopyridines mediated on a surface of KF-alumina. As a prelude to this study, a brief introduction on the importance and various classical methods available for the syntheses arylamines and hetero-aryl amines has been depicted. The copper-catalyzed Ullmann reaction and relatively new palladium-catalyzed amination reaction, developed independently by Buchwald and Hartwig, have been reviewed. Recent advancements on the role of palladium sources, nature of ligands (i.e. the catalytic system), bases and solvents have been discussed.

In the present work, some of the lacunae of this useful palladium-catalyzed hetero cross-coupling amination have been addressed, with special emphasis on: (i) the use of strong base such as sodium *tert*-butoxide and (ii) the specific uses of bis-phosphine ligands. The literature revealed that the potassium fluoride impregnated on alumina (KF-alumina) has been successfully employed as the basic surface in many organic reactions to exploit its basicity on the surface. This section (**Part–I, Section–A**) has described our studies on palladium-catalyzed amination of halopyridines with primary and secondary amines on a surface of KF-alumina (Scheme1).

Scheme 1



Phosphine: P(*o*-tolyl)$_3$, DPPF, BINAP; Pd sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

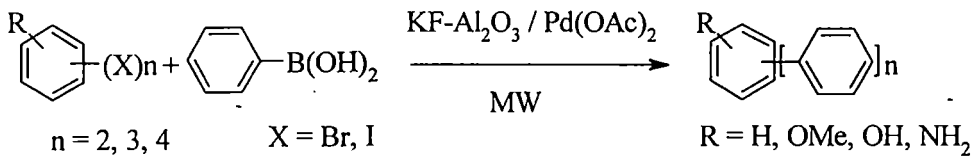
The reaction conditions have been optimized with reference to use of palladium sources, the ligands, solvent and the surface. The present study shows that Pd (0) catalyzed amination of bromopyridines can be performed smoothly on the surface of basic alumina admixed with potassium fluoride. The simplicity of the experimental conditions, good to excellent yields and favourable safety aspects represent significant improvement and useful extension relative to Buchwald's procedure using the strong base, sodium *tert*-butoxide. Although the bis-phosphine ligand [(±)-BINAP] was found to work as a better ligand, the monodentate tri-*o*-tolyl phosphine [(*o*-tolyl)$_3$P] also worked effectively in some cases. Further work may be undertaken with more base-sensitive functionalities on the coupling partners as well as with aryl halides.

[A preliminary account of this work has been published in *Tetrahedron Letter* 2002, *43*, 7967–7969].

Section–B deals with application of this KF-alumina surface in palladium-catalyzed C–C bond forming reaction. Kabalka et al. and Villemin et al. recently reported palladium-catalyzed C–C bond forming reactions such as Heck, Stille, Suzuki reactions using KF-alumina as the basic surface. However, although the Suzuki coupling reaction is one of the most useful methods yet developed for preparing both symmetrical and unsymmetrical biaryls, there are still improvements and further applications that could be made to render it more effective. This section (**Part–I Section–B**) describes our studies on palladium-catalyzed multi-Suzuki coupling of di-, tri- or tetra-haloaromatics with arylboronic acids mediated on KF-alumina surface leading to synthesis of terphenyls and higher homologues in one-pot reaction

(Scheme 2). The present study has thus established a fast, operationally simple procedure for rapid access to a variety of polyaromatic hydrocarbons.

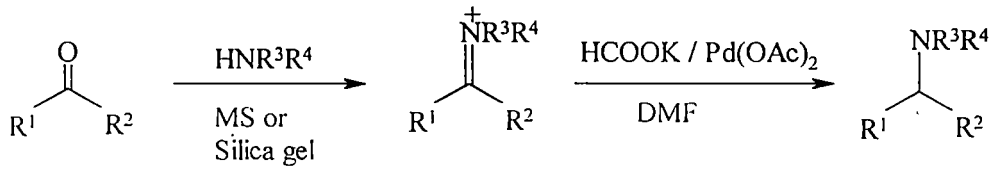
Scheme 2



[An account of this work has been published in *Tetrahedron Letter* 2003, *44*, 3817–3820].

Part–II of this dissertation comprises studies on the reduction of functionalized C–N and C–C double bonds using potassium formate as reductant and catalytic palladium acetate. **Section–A (Part–II)** delineates development of a simple protocol for direct reductive amination of aldehydes and ketones, including α,β–unsaturated carbonyl compounds, with the aid of HCOOK/$Pd(OAc)_2$ (Scheme 3). The term 'direct reductive amination' is used to describe a reaction in which a mixture of carbonyl compound and amine is treated with suitable reducing agent in a one-pot operation. In this connection, a brief review on direct reductive amination processes yet developed has been presented. The method described here can be useful for preparing all classes of amines from suitable carbonyl compounds via their imines.

Scheme 3



R^1 = Alkyl or Aryl
R^2 = H, Alkyl

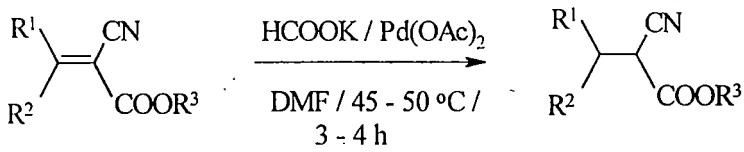
R^3 = H, Alkyl
R^4 = Alkyl

Since Pd-catalyzed "hydride addition" is probably the cause of the reduction of C–N double bond of the imines derived *in situ*, the possibility for asymmetric reductive amination using chiral ligands might be explored.

[The procedure has been published in *Synlett* 2003, (4), 555-557].

Part–II, Section–B represents an application of this reductant system [HCOOK/$Pd(OAc)_2$] in reducing highly functionalized conjugated alkenes (Scheme 4). The alkenes bearing other potentially reducible groups have been studied thus showing the efficiency of this reductant system. The present study constitutes a useful condition for chemoselective reduction of C–C double bonds of α,β–unsaturated cyanoesters.

Scheme 4



R^3 = Et, Sn(*n*-Bu)$_3$

[A preliminary account of this work has been published in *Synth. Commun.* 2003, *33*, 291–296].

The ability of this reductant to perform conjugate reduction of functionalized alkylidenecyanoacetate under homogeneous catalytic conditions offer further use of chiral ligands to promote asymmetric induction.

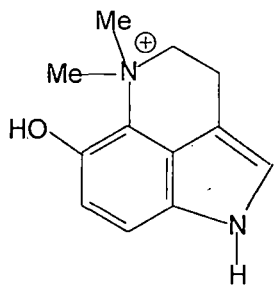
Part - I: Section - A

I-A: Palladium-Catalyzed Amination of Halopyridines on a KF-Alumina Surface

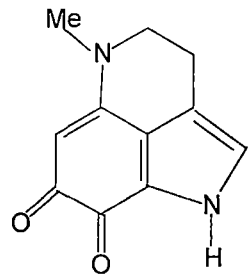
I-A.1: Heteroaromatic Amines and Their Synthesis

I-A.1.1: Introduction

Aromatic amines play a central role in many areas of modern day organic chemistry, including such diverse areas as polymers[1], photography[2] and medicine.[3] Enantiomerically enriched aniline derivatives are common structural units in agricultural and pharmaceutical chemistry.[4-10] The arylamine moiety is a structural component in a variety of synthetic and naturally occurring biologically active compounds such as in indole-based alkaloids. Several marine alkaloids posses the aryl amine as the subunits.[11a] These include dehydrobufotenine,[11b] the damirones,[12] as well as makaluvamines,[13] and discorhabdines,[14] batzellines,[15a] isobatzellines,[16] and prianosine.[17] These compounds have received considerable attention due to the fact that several exhibit potent *in vitro* cytotoxicity against human tumor cell lines, presumably acting as DNA topoisomerase II inhibitors.[15]

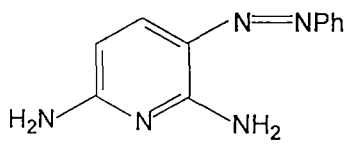


Dehydrobufotenine

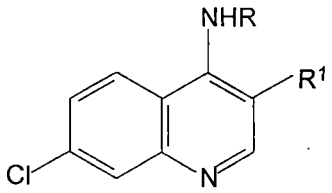


Damirone B

Heteroaryl amines are also common in pharmaceutical chemistry. Among the early examples, phenazopyridine was introduced in 1926 for treatment of infections of the urinary tract.[18] similarly, sontochin, chloroquine, amodiquine were introduced[18]



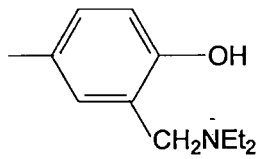
Phenazopyridine



Sontochin; $R^1 = Me$, $R = CHMe(CH_2)_3NEt_2$

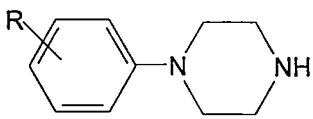
Chloroquine; $R^1 = H$, $R = CHMe(CH_2)_3NEt_2$

Amodiquine; $R^1 = H$, R =



during world war II, chloroquine was the drug of choice for treating overt attack of malaria. Unfortunately chloroquine – resistant stains of the parasite have now emerged. An alternative side chain is found in amodiaquine.[18]

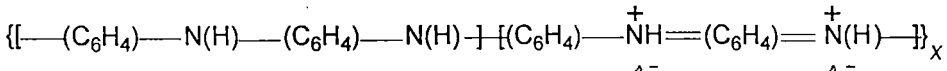
Arylpiperazines form key pharmacophoric elements in a wide range of drugs, which act within the mammalian central nervous system. In particular many *N*-substituted arylpiperazines are ligands for the various classes of serotonin (5-HT) receptors.[19]



Arylpiperazine

Polyaniline (PANI) has attracted much attention in the field of organic conducting polymers due to its robust nature in the doped emeraldine state.[20] Among the many industrial applications are its use as components in rechargeable batteries,[21] electromagnetic interference shielding,[22] and anticorrosion coatings for steel.[23]

The emeraldine salt form of polyaniline is believed to have the composition **(1)**

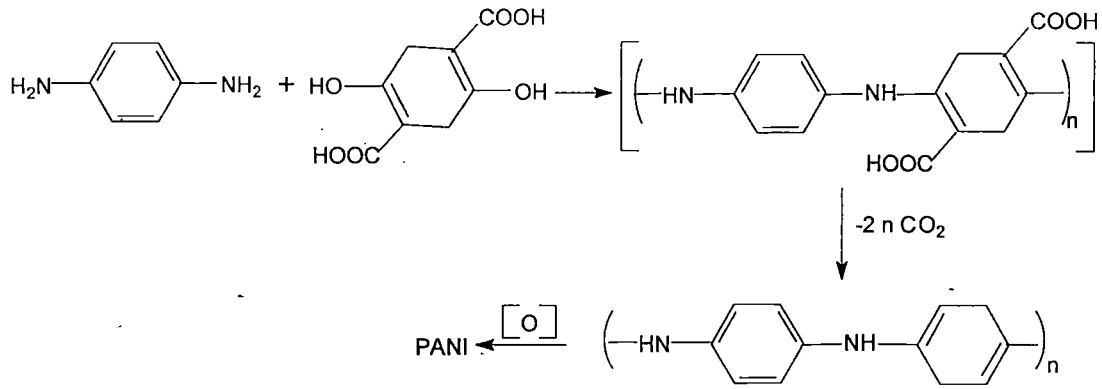


(1)

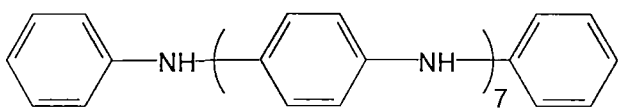
where A^- is an anion.

Wudl et al reported synthesis of PANI, using the modified Honzl route (Scheme 1).[24b]

Scheme 1



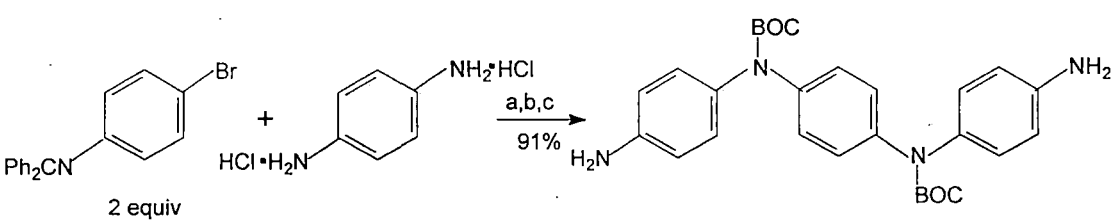
This group also reported synthesis of phenyl-capped octaaniline (COA) (**2**) using the same procedure. The COA has been shown, by several criteria, to have same properties of PANI (comparable UV-VIS, IR, CV, and Conductivity).[24]



C O A **(2)**

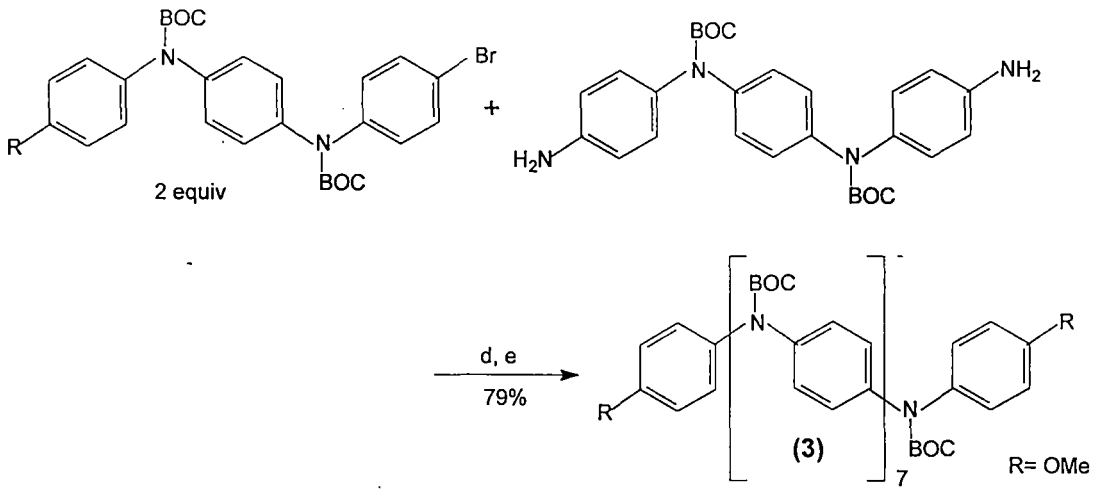
Buchwald et al expanded the repertoire of techniques available for constructing oligoanilines and their analogues to include a strategy based on Pd-catalyzed amination methodology. The *N*-BOC oligoaniline (**3**) has been synthesized as outlined in Scheme 2 & 3.[25]

Scheme 2



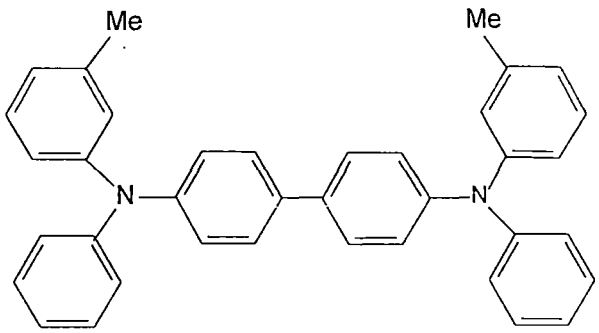
(a) $Pd(OAc)_2$ (1 mol %), (+)-BINAP (1.5 mol %); $NaOBu^t$ (4.5 equiv), toluene, 80 °C; (b) $(BOC)_2O$ (3 equiv), 4-DMAP (0.1 equiv), THF/toluene, reflux; (c) (i) $HONH_2$·HCl (2.5 equiv), pyridine, $CHCl_3$/THF/EtOH, rt, (ii) Et_3N.

Scheme 3



(d) $Pd_2(dba)_3$ (2 mol %), (+)-BINAP (5 mol %), $NaOBu^t$ (2.5 equiv), toluene, 80 °C; (e) $(BOC)_2O$ (3 equiv), 4-DMAP (0.1 equiv), THF, reflux.

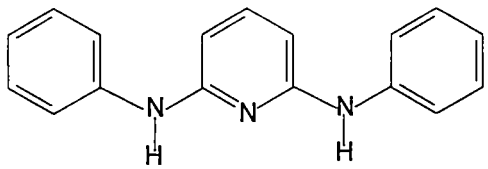
Triarylamines are an important class of compounds because they form stable aminium radical cations. Thus, triarylamines can be building blocks for high-spin polyradicals that have shown ferromagnetic coupling,[26,27] as well as for conductive polymers.[28] Perhaps most commonly, triarylamines have been used as the hole-transport layer in electroluminescent devices.[29-32] Stable radical cations can also initiate pericyclic reactions,[33] act as electrocatalysts,[34,35] or act as mild and selective oxidizing agents.[36] High purity triarylamines find applications in xerographic photoreceptors, as constituents of non-linear optical chromophores useful in the design of integrated electroptic switches and modulators.[37] One such example of triarylamine macromolecules is TPD.



N,N'-Diphenyl-*N,N'*-bis(3-methylphenyl)-1,1'-biphenyl-4,4'-diamine

TPD

Heteroaromatic amines such as aminopyridines are used as acyl transfer reagents in organic chemistry[38,39] and as ligands in inorganic and organometallic chemistry.[40-44] Additionally, aminopyridine derivatives have been used as fluorescent dyes[45,46] and also are biologically important as central nervous system stimulants.[47]



N,N'-Diphenyl-pyridine-2,6-diamine

I-A.1.2: Arylamines: Preparative Methods

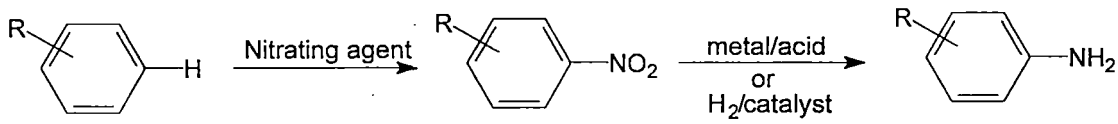
Despite the structural simplicity of arylamines, synthesis of these compounds is often difficult. A large number of synthetic methods for the preparation of aniline derivatives have been reported.[48] The major classical preparative methods are: (i) electrophilic nitration and subsequent reduction, (ii) electrophilic substitution, (iii) nucleophilic substitution by S_NAr, (iv) benzyne and (v) $S_{RN}1$ reaction. On the other hand, transition-metal-catalyzed hetero cross-coupling (C-N) reactions to prepare arylamines are of major interests in the recent years. Copper-mediated (The Ullmann reaction) couplings (page 12) generally occur at high temperatures, often give products from diarylation, and are typically substrate specific. However, copper-mediated Ullmann coupling is still the reaction of choice for large- and industrial-scale production of arylamines. Over the last decade, an important development has been made independently by Buchwald and Hartwig and others. The Pd-catalyzed C-N coupling reaction of aryl halides (or triflates) with amines has recently become the most important method for laboratory scale synthesis of a variety of arylamines.

A brief review on the various preparative methods of arylamines, including merits, demerits and plausible mechanisms, is dicussed below:

I-A.1.2a: Electrophilic Nitration & Reduction:

Most aromatic compounds, whether of high or low reactivity, can be nitrated; because a wide variety of nitrating agents is available (Scheme 4).[49] For benzene, the simple alkylbenzenes, and less active compounds, the most common reagent is a mixture of

Scheme 4



concentrated nitric acid and sulfuric acids, but for active substrates such as amines, phenols, and pyrroles, the reaction can be carried out with nitric acid alone, or in water, acetic acid, or acetic anhydride. Others nitrating agents include $NaNO_2$ and trifluoroacetic acid,[50] N_2O_4 (which gives good yields with polycyclic hydrocarbons[51]), N_2O_5 in CCl_4 in the presence of P_2O_5 (if anhydrous conditions are required)[52], $EtONO_2$, and nitronium salts[53] such as NO_2^+ BF_4^-, NO_2^+ PF_6^-,and NO_2^+ $CF_3SO_3^-$. Aromatic hydrocarbons and halobenzenes are nitrated in high yields with clay-supported cupric nitrate (claycop).[54]

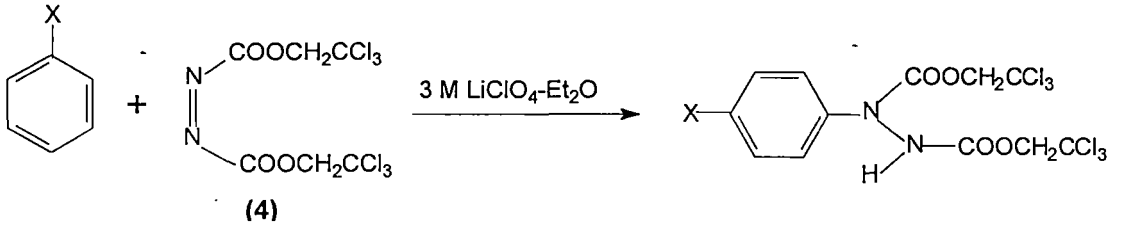
Aromatic nitro compounds can be easily reduced to amines using most common reducing agents such as metal (Zn, Sn, or Fe, or sometimes other metals) and acid, or by catalytic hydrogenation (Scheme 4).[55] Among other reducing reagents used[56] have been AlH_3-$AlCl_3$, hydrazine and a catalyst[57], $TiCl_3$,[58] Al-$NiCl_3$-THF,[59] formic acid and Pd-C,[60] and sulfides such as NaHS, $(NH_4)_2S$, or polysulfides. Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, though aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$.[61] Amines are also the products when nitro compounds (aryl) are reduced with $HCOONH_4$-Pd-C.[62] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (though ketones are reduced). With optically active alkyl substrates this method gives retention of configuration.[63]

I-A.1.2b: Electrophilic Substitution:

The concept of making use of azodicarboxylates (4) as an electrophilic source of nitrogen NH_2^+ has been well established over the last few years.[64-68] Leblanc et al[69] reported the amination of electron-rich arenes by an electron-deficient

azodicarboxylate, namely bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD). The amination reactions were conducted in 3 M lithium perchlorate-diethyl ether or acetone solution according to Scheme 5.[70]

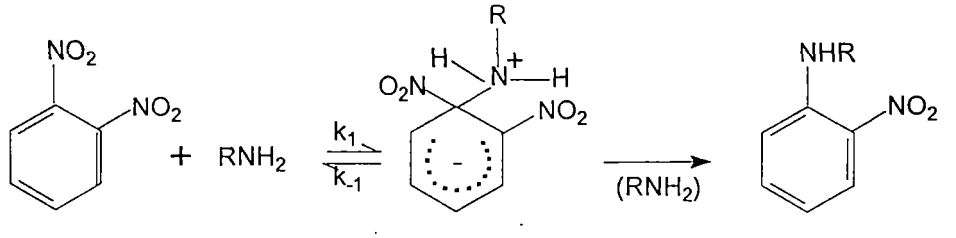
Scheme 5



I-A.1.2c: Aromatic Nucleophilic Substitution : The S_NAr Mechanism

It is well known that a nitro group *ortho* to electron-withdrawing groups (in general nitro groups) in an aromatic compound can be readily replaced by nucleophilic reagents[71-80] Most of the studies of this reaction have been performed with anionic nucleophiles, in protic or aprotic solvents. The use of aliphatic amines as nucleophiles in non-polar solvents is less common.[72,76,77,80] In this case typical aromatic nucleophilic substitutions (S_NAr) have been reported for the denitration reaction; mechanisms involving either base catalysis[76] or spontaneous decomposition of the anionic intermediate have been proposed.[72] The typical S_NAr mechanism[81] when aliphatic amines are the nucleophiles and 1,2-dinitrobenzene (1,2–DNB) is the aromatic substrate, can be represented according to Scheme 6. Silber et al reported that the substitution of 1,2-DNB by piperidine in *n*-hexane is believed to follow a wholly base-catalyzed S_NAr mechanism.[82]

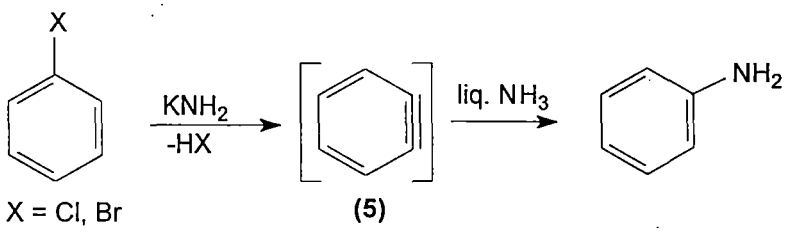
Scheme 6



I-A.1.2d: Aromatic Nucleophilic Substitution: The Benzyne Mechanism

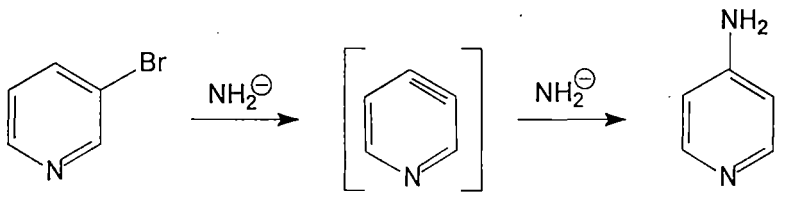
The rearrangements of nonactivated aryl halides which are initiated by strong nucleophiles were not studied extensively until it was found[83] that aryl halides gave, with excess sodium or potassium amide in liquid ammonia or with lithium piperidide in diethyl ether, fair to good yields of the corresponding amines (Scheme 7). These results have been interpreted in terms of a logical mechanism which involves benzyne type intermediates (**5**).[84,85]

Scheme 7



In the case of heteromatic halides, heteroaryne intermediates have been postulated. The existence of a γ-pyridyne intermediate has been postulated to account for the product obtained when 3-bromopyridine reacts with sodamide in liquid ammonia as outlined in Scheme 8.[86]

Scheme 8



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

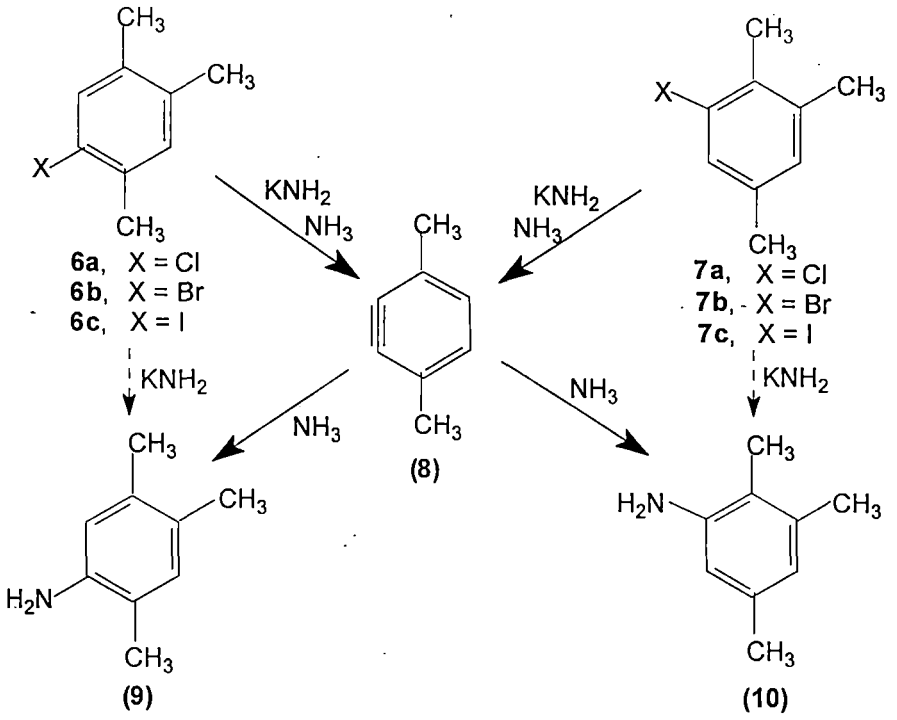
triphenylmethide, anilide, fluorenyl and thiophenate have been widely used in lieu of alkali metal amides, the functional group tolerence along with formation of other products are the major drawbacks for this method.[87,88,89]

I-A.1.e: Aromatic Nucleophilic Substitution by $S_{RN}1$ Mechanism:

The radical chain $S_{RN}1$ mechanism of aromatic nucleophilic substitution was first recognized in 1970.[90] The reactions of 5- and 6-iodopseudocumene with KNH_2 in liq. NH_3 occur in part by the aryne mechamism and in part by a nonrearranging electron-transfer, radical mechanism ($S_{RN}1$). According to the aryne mechanism,[91] the reactions of 5- and 6- halopseudocumenes (**6** and **7**, respectively) with KNH_2 in liquid ammonia should proceed via the same aryne intermediate (**8**) and form 5- and 6-pseudocumidine (**9** and **10**, respectively) in identical proportions. Neither the identity of the halogen nor its location (5 or 6 position) should affect the product ratio. These expectations are fulfilled insofar as reactions of bromo compounds **6b** and **7b** and chloro compounds **6a** and **7a** are concerned. With KNH2 in NH_3, these afford **9** and **10** in high yield and with a **10** : **9** product ratio varying from 1.45 to 1.55. However, from iodo compounds **6c** and **7c**, the **10 : 9** product ratios were 0.63 and 5.85, respectively (with 0.29 M KNH_2) The fact that each of the iodo substrates forms some cine-substitution product indicates that each reacts in part via aryne mechanism. However, the wide divergences of the pseudocumidine **10 : 9** ratio from the "aryne ratio" of about 1.5 demonstrate that some other mechanism also plays a major role (Scheme 9).

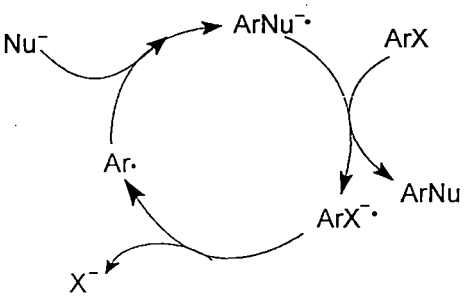
To explain the iodo results, it has been proposed,[90,92] that beside the benzyne mechanism, the free radical mechanism is also operating (Scheme 10). Aryl iodides generally are somewhat less reactive in S_NAr reactions that their chloro or bromo analogs, whereas they are generally more reactive than the corresponding chlorides in aryne formation and only slightly less reactive than the corresponding bromides.[93]

Scheme 9



The initiation devices devised so far were essentially of three types: injection of solvated electrons into the solution by addition of alkali metals in liquid ammonia,[94] injection of electrons by means of an electrode set at a suitable potential,[95] and photochemical stimulation.[94,96] In the first two cases the initiation steps involve the formation of the anion radical of the substrate, $ArX^{\cdot-}$, which then enters the propagation cycle. The exact nature of the photoinitiation process giving rise to one of the three species $ArX^{\cdot-}$, $Ar^{\cdot}$, $ArNu^{\cdot-}$ functioning in the propagation cycle still remains open to question. The initiation mechanism of $S_{RN}1$ reactions occurring in the dark without purposely added electron-donating initiators[97] is even more obscure.

Scheme 10

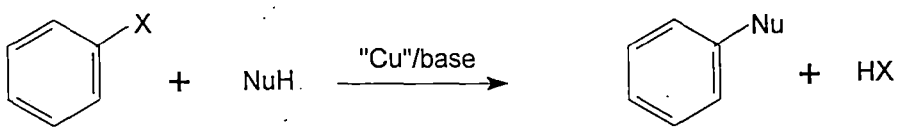


I-A.1.2f: Transition-Metal Promoted Amination of Arylhalides

Copper-Mediated Ullmann Reaction:

Displacement of the halogen from aromatic halides by amines under the catalytic action of copper salts has been used widely as a synthetic tool since its discovery by Ullmann.[98] The Ullmann condensation of aryl halides with amines is traditionally carried by heating with copper powder in the presence of bases such as sodium carbonate or hydroxide according to Scheme 11.[99] This reaction has been proved to be a powerful method of synthesizing diarylamines of research and industrial interest.[100]

Scheme 11

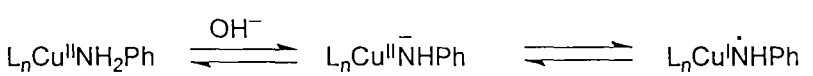


NuH = $ArNH_2$, Ar_2NH, X = Cl,. Br, I. "Cu" = Cu metal, oxides, salts, alloys, complexes, etc

base = Na_2CO_3, KOH, NaH etc.

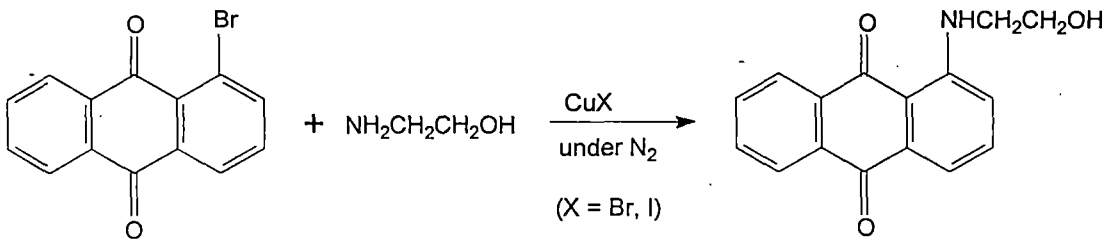
Important information on the kinetics of amines Ullmann condensations is available. The reaction is zero order in amine with the rate-determining step being the loss of halide from the substrate with the reactivity order being I > Br > Cl >> F.[101,102] The use of copper(I) oxide and copper(I) bromide in the condensation of diphenylamine and *o*-bromonitrobenzene in DMA is reported to be less effective than the traditional method.[103] The condensation of 1-bromoanthraquinones (**11**) with aniline in aqueous solution is catalyzed by copper(II) salts, however, kinetic and ESR studies indicate that the effective catalyst is a copper(I) species.[104-106] Further evidence in support of this comes from the marked accelerating effect produced by reducing agents such as Sn^{2+}, Fe^{2+} and Ti^{3+} and the inhibition caused by molecular oxygen. This condensation is also favoured by an increase in the hydroxide ion concentration. The hydroxide ion is thought to deprotonate the amine and thereby facilitate the reduction of copper(II) (Scheme 12).

Scheme 12



During the condensation of 1-bromoanthraquinone (**11**) with 2-aminoethanol in aprotic solvents an induction period is observed when copper(I) bromide or iodide was used as catalyst (Scheme 13). This induction period was found to be associated with

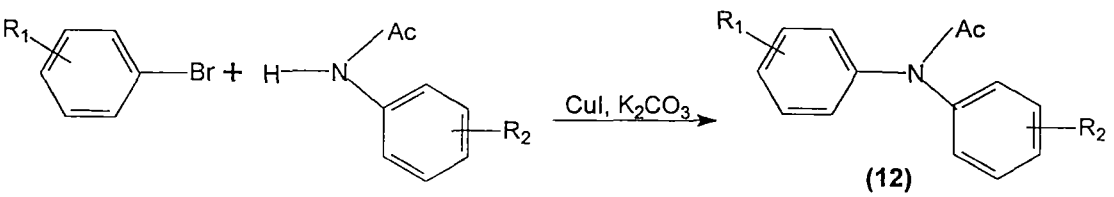
Scheme 13



the formation of a copper(II) species, since the induction period vanishes when copper(II) bromide is added.[107,108] The ESR spectrum of the 1-bromoanthraquinone (**11**), aminoethanol, copper(I) bromide system showed the presence of both a copper(II) species and the 1-bromoanthraquinone radical anion.[109,110] Although the copper(II) species alone was found to have little catalytic activity, it led to an increase in the activity of copper(I). The Ullmann coupling often requires high temperatures (~ 200 °C) and the use of copper salts in greater than stoichiometric amounts. The reaction is also very sensitive to the substitution on the aryl halide.

Goldberg found[111] that the condensation of an aryl bromide and acetanilide in the presence of potassium carbonate and copper iodide yields an *N*-acetyldiarylamine (**12**) Scheme 14. The Goldberg reaction usually gives high yields of stable, easily handled *N*- acetyldiarylamines (**12**) from readily available substances. It was also found that

Scheme 14

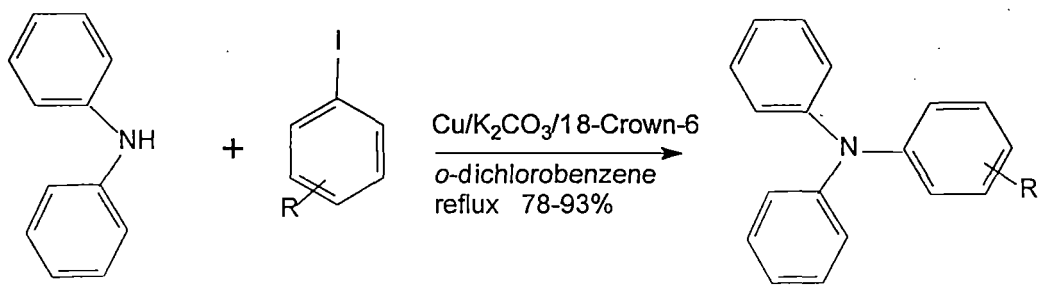


aryl chlorides may react under the Goldberg conditions. Aryl bromides containing two *ortho* substitutents, however, give only low yields of *N*-acetyldiarylamines. The necessity to use high temperatures (>200 °C),[112] highly polar solvents, and often large amounts of copper reagents, as well as the modest yields in many cases often realized, have undoubtedly prevented these reactions from being employed to their full potential. However, there has been a resurgence of more economical copper-mediated systems that circumvent some of the limitations of classical Ullmann-Goldberg-type CcN couplings. Some of the recent developments on the Ullmann reaction are delineated below.

Recent Developments on the Ullmann Reaction Using Catalysts:

Copper-mediated CcN coupling has remained the reaction of choice for large- and industrial-scale production of substituted arylamines.[113,114] Conventionally, triarylamines are produced by Ullmann condensation of aryl iodides and diarylamines with copper (stoichiometric or catalytic quantities in the form of a metal, alloy. or Cu(I)/Cu(II) salt.[115-117] Gauthier et al[116] reported preparation of a variety of substituted triphenylamine derivatives in nearly quantitative yields by the use of 18-crown-6 as a phase transfer catalyst under the Ullmann reaction conditions, as described in Scheme 15. The presence of a phase-transfer catalyst induces rate acce-

Scheme 15



0.66 equiv

R = *o*-CH_3, *m*-CH_3, *p*-CH_3
m-OCH_3, *p*-OCH_3
o-Cl, *m*-Cl, *p*-Cl

Cu powder (2 equiv)
K_2CO_3 (3 equiv)
18-Crown-6 (3equiv)
o-dichlorobenzene (1.7 mL)

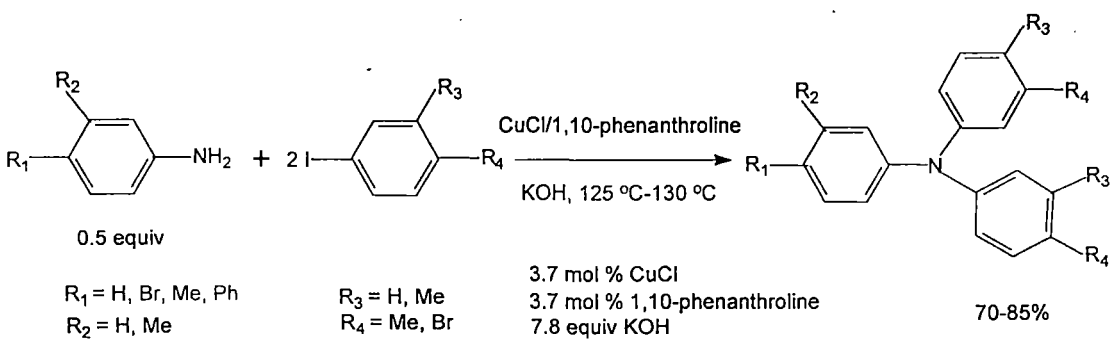
leration and increases considerably the yields of triphenylamine derivatives. This phase-transfer-catalytic process may not be applicable when base sensitive substituents are present in the molecules. The procedure, however, does not obviate

the requirement for high temperature, and the long reaction times make it unattractive for large scale industrial applications. Catalyst effects still persist, as is common when potassium carbonate is used as base, and the high cost of the crown ether would necessitate its recovery and reuse.

Milder Ullmann-type methodologies for the *N*-arylation of anilines,[117-119] amides,[120] and nitrogen heterocycles[121] have been reported in the literature. Gujadhur et.al[118] reported a synthetic protocol for the synthesis of functionalized diaryl- and triarylamines under mild conditions, using a soluble, air-stale copper(I) complex, $Cu(PPh_3)_3Br$, as the catalyst and cesium carbonate as the base at 120 °C. This catalyst is selective for aryl iodides and the synthetic protocol tole- rates various functional groups. However, the reactions were incomplete in 24 h (by TLC) if NMP was used as the solvent or if the aryl halide was bromobenzene. The reactions were also failed if *N,N*-dimethylaminopyridine (DMAP), potassium carbonate or sodium methoxide was used as the base instead of Cs_2CO_3. However, CuI and CuBr with or without PPh_3 as a ligand were not active for this reaction.

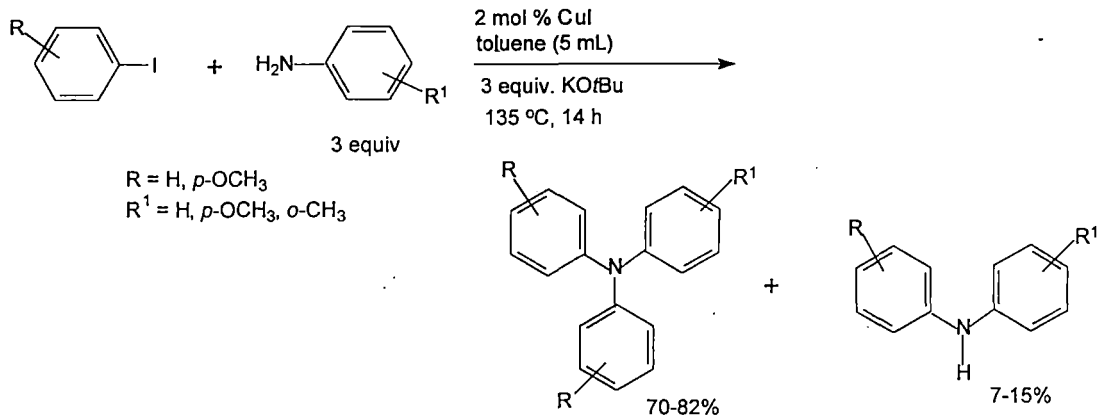
Goodbrand and Hu[113] have reported ligand–accelerated single-step catalytic synthesis of triarylamines with high selectivity using CuCl/1,10–phenanthroline catalyst system and KOH as a base at 125 °C according to Scheme 16. In this case also, CuCl alone (in the absence of 1,10-phenanthroline as a ligand) produced very low yields of triarylamines.

Scheme 16



Chaudhari et al[37] have demonstrated a simple and efficient methodology for thesynthesis of triarylamines in a single-step using CuI and potassium tertiary butoxide as the base (Scheme 17).

Scheme 17

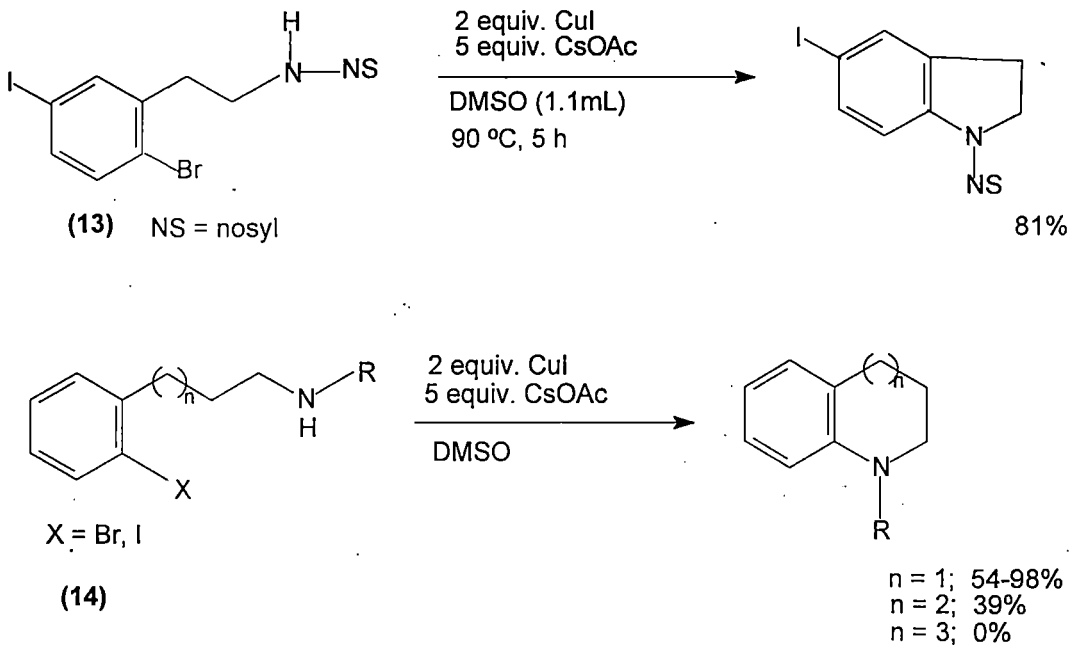


This is the first report on the catalytic synthesis of triarylamines with a Cu catalyst in the absence of promoting ligands under relatively lower temperature conditions (135 °C). A few substituted amines were also tested and the catalyst was found to be tolerate of substituents present on the ring except for a nitro group. A variety of N- or P-containing ligands were examined using iodobenzene and aniline as model substrates and CuI as a catalyst: with chilating bidentate ligands, higher activity was observed. Use of chelating ligands (1 equiv. to Cu) gave triarylamines with high activity and selectivity.

Fukuyama et al[122] developed a new protocol for copper-mediated intramolecular amination, which tolerates a variety of *N*-protecting groups and proceeds under mild conditions with inexpensive reagents (Scheme 18). A unique combination of copper iodide and cesium acetate was found to mediate intramolecular amination of aryl halides under mild conditions. During the optimization process, it was revealed that the coincidental use of cesium acetate as the base was in fact crucial for the reaction.[123] No amination occurred when non-carboxylate bases such as cesium carbonate or sodium *tert*-butoxide was used, while the reaction proceeded sluggishly when potassium acetate was used. On the other hand, absence of air in the solvent dramatically improved the yield and the reproducibility. However, addition of

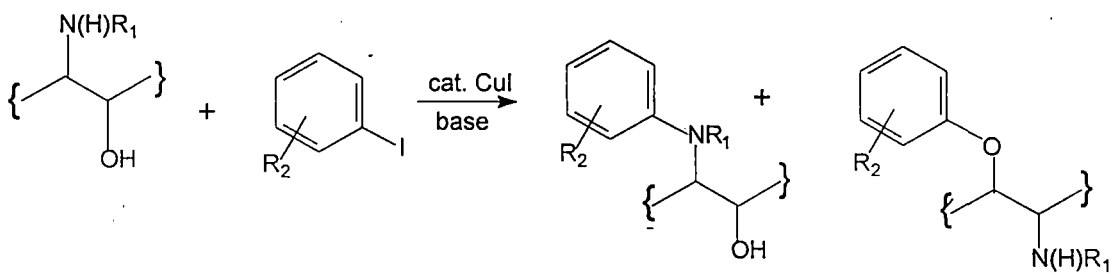
phosphine or amine ligands did not provide any improvements. The cyclisation-amination of (**13**) and (**14**) were carried out under this conditions, as outlined in Scheme 18.

Scheme 18



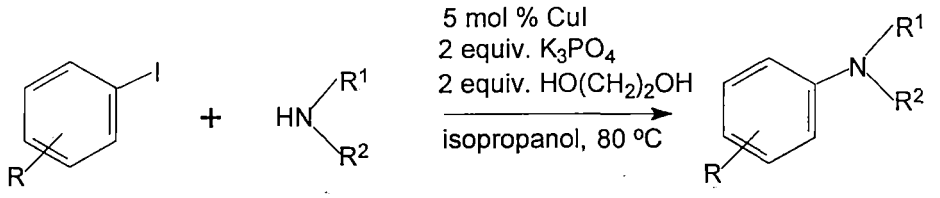
Buchwald and Coworker[124] demonstrated copper-catalyzed arylation of α-amino alcohol using base (Scheme 19).

Scheme 19



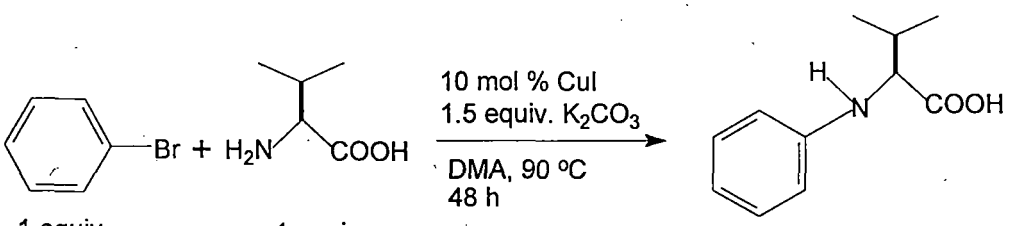
Buchwald et al[125] have developed an efficient copper-catalyzed coupling reaction of alkylamines with functionalized aryl iodide using CuI as catalyst and ethylene glycol as ligands described in Scheme 20. This reaction can be performed in air.

Scheme 20

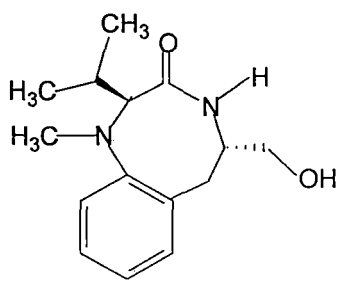


There are only a few reports on improved, direct copper-mediated amination of aryl halides with limited substrates, such as α– and β–amino acids,[126] imidazoles,[127] amide-containing heterocycles.[128] Dewai et al[126] disclosed the coupling of optically pure α–amino acids (**15**) with aryl halides producing enantiopure *N*-aryl-α–amino acids (**16**) with retention of configuration using ligand-free CuI catalyst and potassium carbonate as a base (Scheme 21). This reaction can be completed at much lower temperature than typical Ullmann condensation including even for electron-rich aryl halides, which indicates that an accelerating effect induced by the structure of the α-amino acid exists in this reaction. α-Amino acids with larger hydrophobic groups give higher coupling yields, while those with smaller hydrophobic groups only deliver lower yields and no coupling products were detected for those with hydrophilic groups. No racemization was observed in most cases of this coupling reaction. In

Scheme 21



addition, by using this reaction, a facile and stereoselective synthesis of benzolectam-V8, a new protein kinase C activator, was developed.



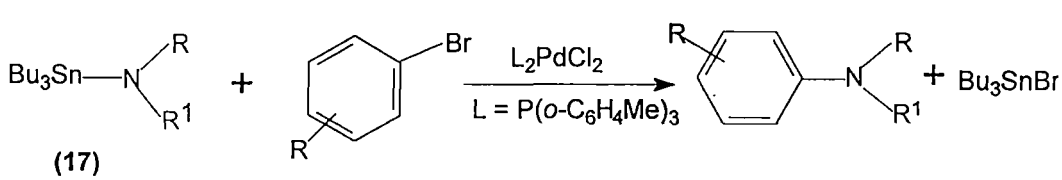
benzolactam-V8

Palladium-Catalyzed Amination (Buchwald - Hartwig Type):

Transition-metal-assisted amination of aryl halides has developed in the past few years as a most viable and direct method leading to the synthesis of a large variety of substituted amines.[129-139] The most exciting developments in catalysis is undoubtedly the advent of a practical, mild and efficient protocol for catalytic carbon-nitrogen cross-coupling reaction. Early development of *N*-aryl synthesis proved to be quite difficult and limited in generality.[48,140] The transition-metal-mediated coupling of amines with aryl halides is regioselective, does not require activating groups. Palladium-catalyzed synthesis of *N*-substituted anilines using aryl halides or halide equivalent has proven to be a very useful and versatile method in organic synthesis.[141-145] Recent developments of palladium-catalyzed in amination of aryl halides seems to have overwhelmed copper-mediated systems in terms of mildness, practicality and versatility.[141,143,145,146] Most of the palladium-catalyzed amination methods employ electron-rich phosphine ligands,[147,148] possessing either a ferrocene[133,149] or a biphenyl backbone,[150,151] or bulky nucleophilic *N*-heterocyclic carbenes (sometimes referred to as "phophine mimics").[152-154] Chelating phosphines such as 1,1′-bis(diphenylphosphino)ferrocene (DPPF)[155] and 2,2′-bis (diphenylphosphino)-1,1′-binaphthyl (BINAP)[156,157] have been demonstrated to exhibit improved catalytic activity in this type of transformation. Commonly used base in palladium-catalysed aminations are sodium-*t*-butoxide ($NaOBu^t$),[141] Cs_2CO_3,[158] K_3PO_4,[142,143] MeONa and ^{i}PrONa.[159]

In 1983, Kosugi and Migita[160] described the coupling of tin amides (**17**) with aryl bromide using palladium catalyst containing tri-*o*-tolylphosphine as ligand as outlined in Scheme 22.

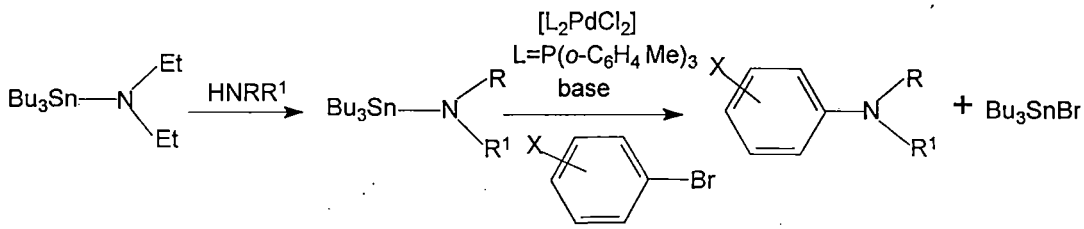
Scheme 22



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. Only unhindered dialkyltin amides gave substantial amounts of amination product. Guram and Buchwald[161] showed that the chemistry could be extended beyond electron-neutral aryl halides according to Scheme 23. With tin amides derived *in situ*, this chemistry was extended to aryl halides bearing alkoxycarbonyl, amino, and alkoxo groups.

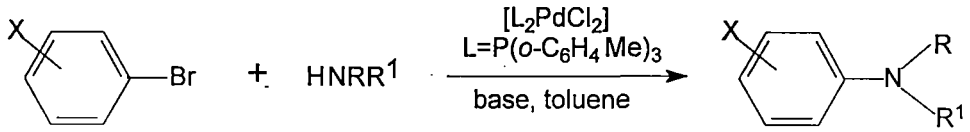
Scheme 23



X = alkylcarbonyl, amino, alkoxo group

As these reactions were limited in scope and possessed problems from the toxicity and environmental instability of tin amides, the research group of Hartwig[162] and Buchwald[163] concurrently published their results on tin-free amination of aryl halides (Scheme 24). They reported the palladium-catalyzed amination of aryl halides in the presence of alkoxide or silylamide bases that significantly improved upon amination procedures avoiding toxic and air sensitive aminostannanes.

Scheme 24

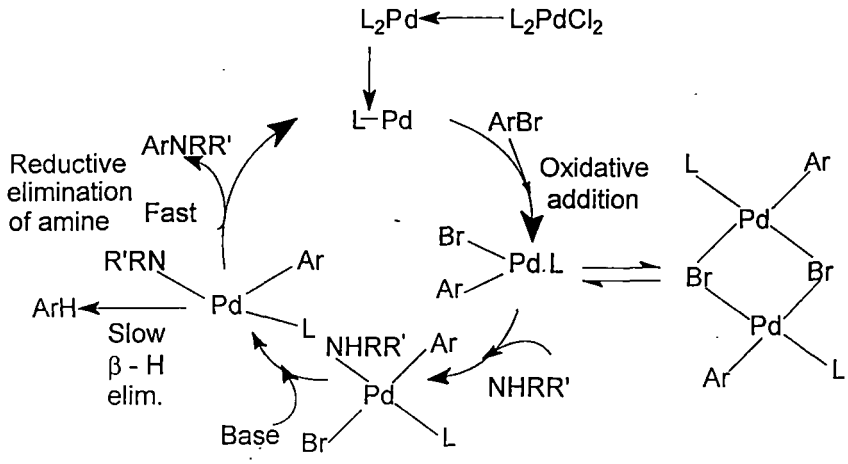


X = *o*-, *m*- or *p*-alkyl, phenacyl, amino, alkoxy
base = $NaOBu^t$ or $LiN(SiMe_3)_2$

Hartwig demonstrated through kinetics studies that oxidative addition, palladium-nitrogen bond formation and reductive elimination proceed through monophosphine palladium complexes when P(*o*-tolyl)$_3$ is used as the ligand (Scheme 25).[164-167]

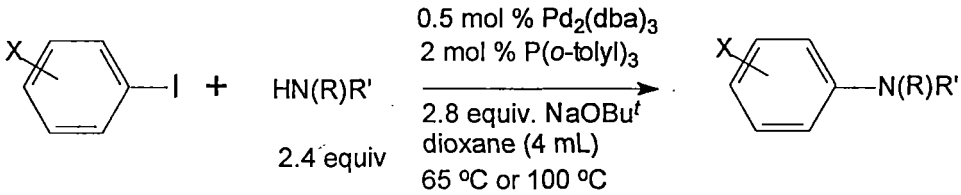
Scheme 25

Proposed Catalytic Cycle:



The original attempt of Hartwig and Buchwald to utilize aryl iodides as substrates were also largely unsuccessful. Buchwald et al[168] developed a reasonably efficient protocol with which to convert aryl iodides to anilines, significantly expanding their amination process as outlined in Scheme 26.

Scheme 26



X = *p*-, *o*-Me; *p*-, *m*-OMe, Cl, $CONEt_2$

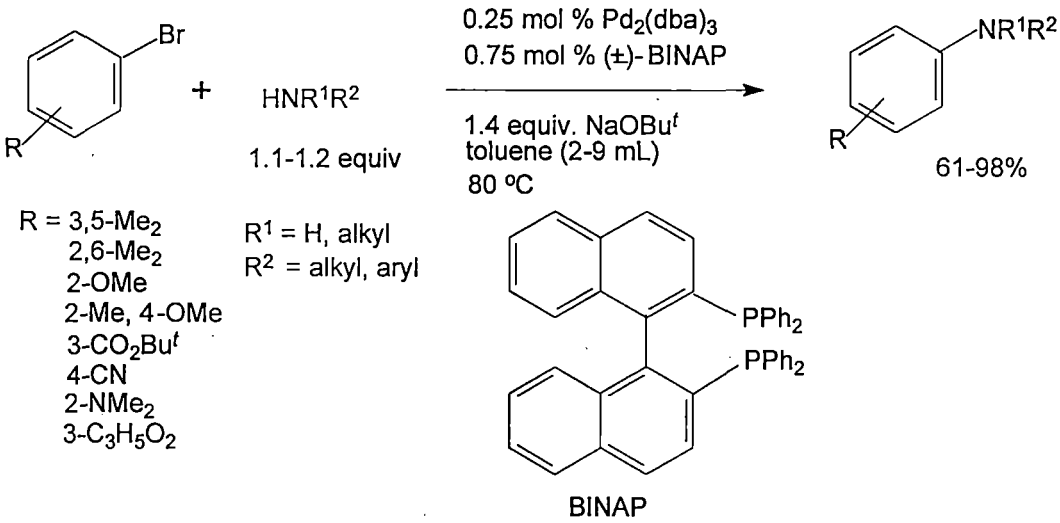
In their earlier studies, Buchwald and Hartwig had shown that primary amines could be coupled with a limited number of aromatic bromides using the Pd(0)/P(*o*-tolyl)$_3$ catalyst system. However, this was not a general reaction and in the absence of a *para*-electron-withdraing substituent or an *ortho*-substituent on the aryl bromide, only a low conversion of starting materials to products was observed.

Role of Ligands:

Several limitations were, however circumvented by employing bidentate phosphine ligands, such as DPPF or BINAP.[155,156] The palladium complexes derived from these bidentet ligands provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary alkyl amines as well as with anilines.

Buchwald et al [156] reported a palladium-catalyzed procedure for the cross-coupling of aryl bromides and primary amines that employed chelating bis-(phosphine) ligands (±)-BINAP according to Scheme 27.

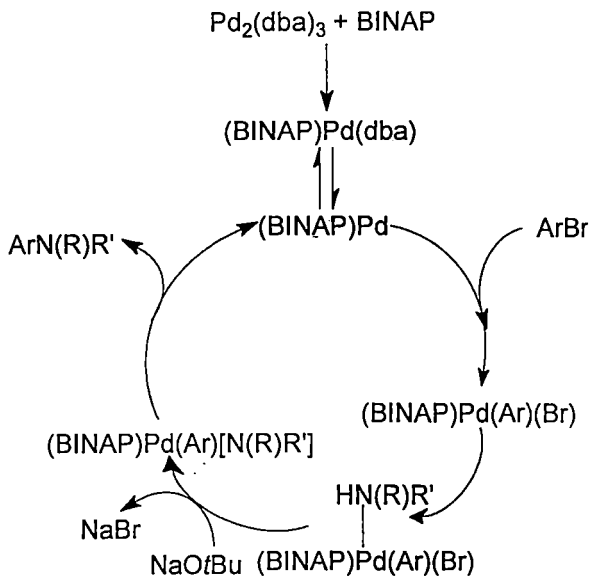
Scheme 27



The efficiency of this system is presumably due to the ability of the chelating bis-(phosphine) ligands to inhibit side reactions, such as β-hydride elimination from an amidopalladium intermediate and the formation of bis-(amine) complexes that lead to products of hydrodebromination (Scheme 28).

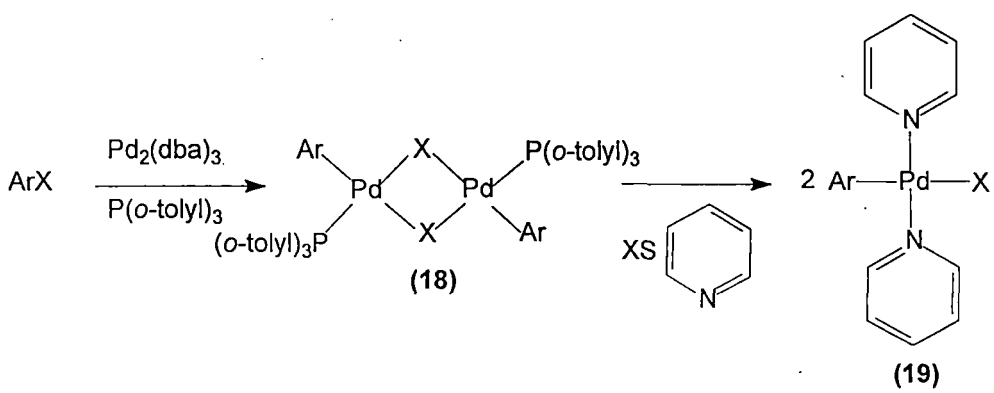
Scheme 28

Proposed Catalytic Cycle:



Amination of bromopyridine was also largely unsuccessful by using Pd(0)/P(*o*-tolyl)$_3$ complexes.[169] It has been shown that pyridine inhibits the Pd(0)/P(*o*-tolyl)$_3$ catalyzed amination of aryl bromides[169] and also displaces a P(*o*-tolyl)$_3$ ligand from key catalytic intermediates such as the oxidative addition product (**18**) to form complexes such as bis(pyridyl) derivative (**19**) (Scheme 29).[165,169]

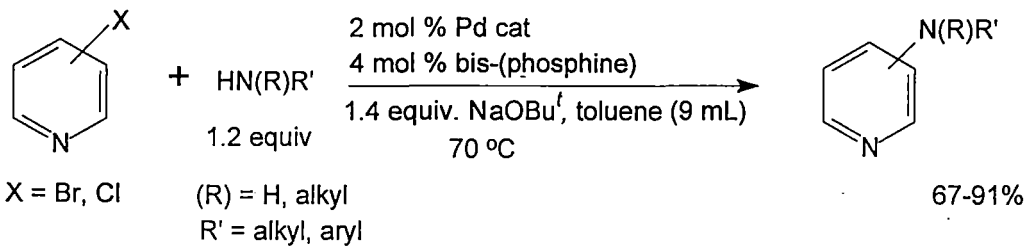
Scheme 29

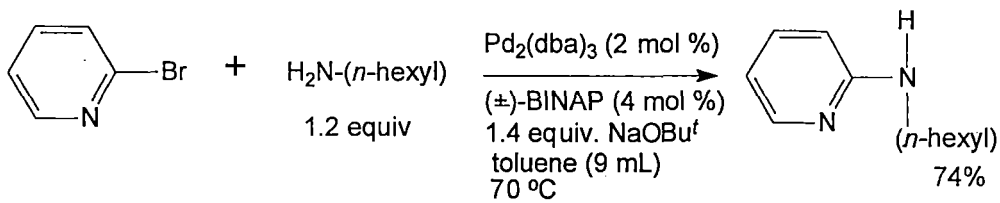


Buchwald, however, circumvented this ligand-exchange problem by replacing the monophophine with bis-(phosphine) ligand.[169] They showed that the amination of bromopyridine can be efficiently performed by using Pd(0)/(±)-BINAP as the catalytic system (Scheme 30). Activated substrates are not required and relatively

non-nucleophilic amines such as primary amines and anilines may be arylated. They postulated that chelating bis-(phosphine) ligand does not undergo ligand-exchange with excess pyridine, and

Scheme 30





consequently, the formation of bis-(pyridine) complexes (**19**), which terminate the catalytic cycle, is prevented.

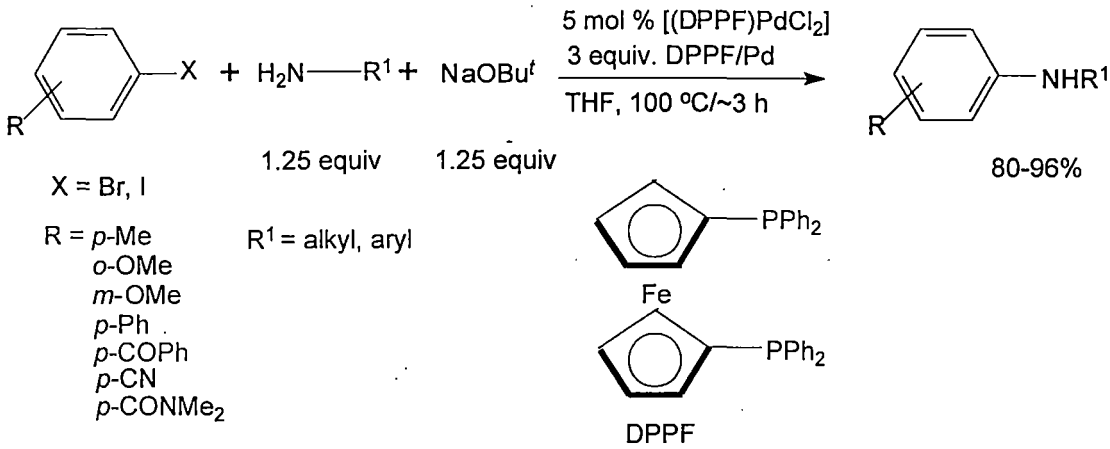
Hartwig group discovered[155] a second generation catalytic system for amination of aryl halide amination catalyst (DPPF)$PdCl_2$, which is based on chelating ligands. This catalyst provided high yields of mixed, secondary arylamines from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(*o*-tolyl)$_3$ catalyst system (Scheme 31).

In addition to the practical advantages of this system, these results reveal a number of important concepts:

- the catalytic cycle involves bis-(phoshphine) intermediates;
- sterically encumbered phosphines are not necessary for high-yielding, intermolecular amination of aryl halides;
- the favorable selectivity for reductive elimination over β-hydrogen elimination results from chelation and large bite angle, rather than from steric effects;

- a wide range of chelating ligands may lead to optmization of reaction rates and yields.

Scheme 31

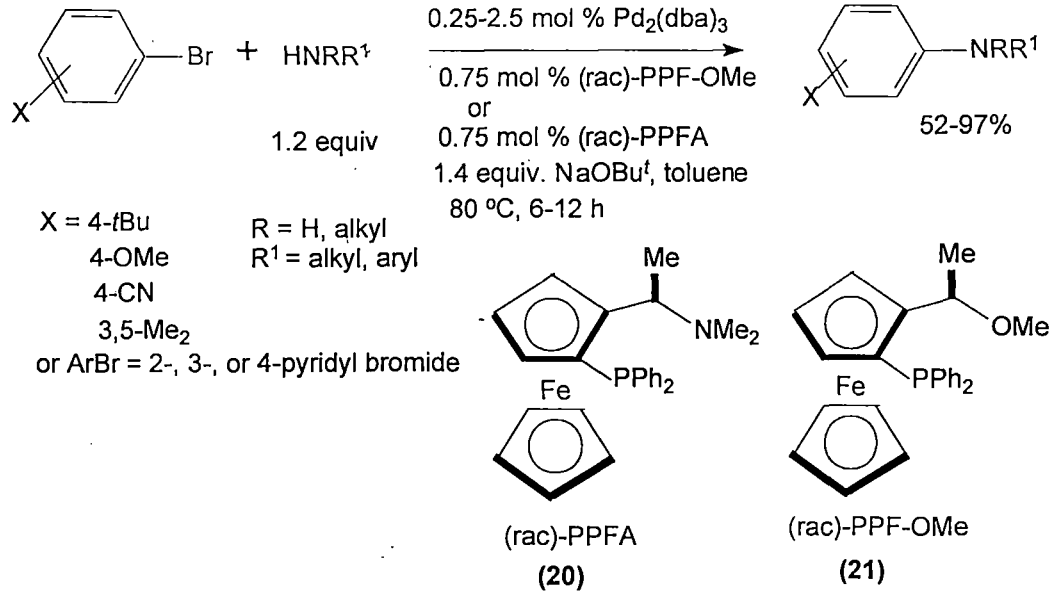


Palladium-catalyzed amination of aryl halides based on the use of the monophoshphine ligand, P(*o*-tolyl)$_3$ or bis-phosphine ligands, BINAP and DPPF, lead to efficient coupling of primary amines and secondary cyclic amines, the arylation of secondary acyclic amines remains problematic; the corresponding tertiary aromatic amines are generally formed in low yields. This was especially true when electron-rich arenes were used as coupling partners.

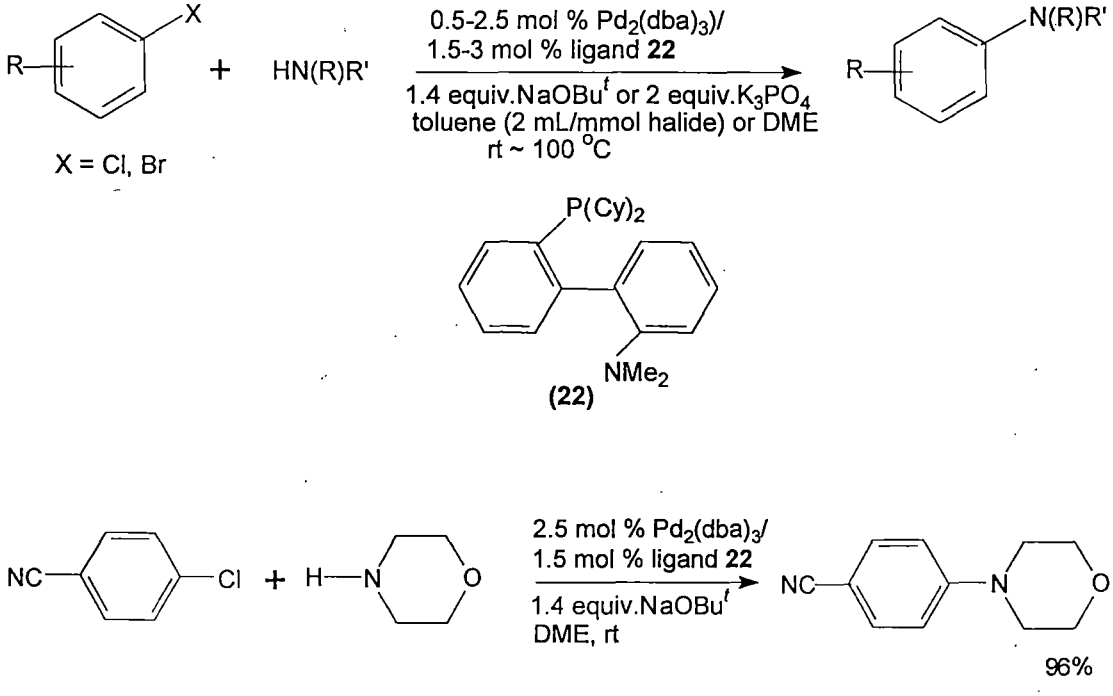
Buchwald and coworkers[149] reported that palladium complexes derived from ligand (rac)-PPFA (**20**)[170] and (rac)-PPF-OMe (**21**)[170,171] are highly effective for the aryl amination reaction of acyclic secondary amines (Scheme 32). This procedure is extremely effective in coupling secondary anilines and acyclic secondary amines with both electron-poor and electron-rich aryl bormides.

The lack of a general palladium-based catalyst for aryl chloride substitution reactions[135,136-138,147,172]as well as the elevated temperatures often required prompted Buchwald and Coworkers to search for more active ligands. Buchwald et al[132] demonstrated that the ligand (**22**)/Pd(0)catalyst system is the first example of a room temperature amination of an aryl chloride (Scheme 33).

Scheme 32



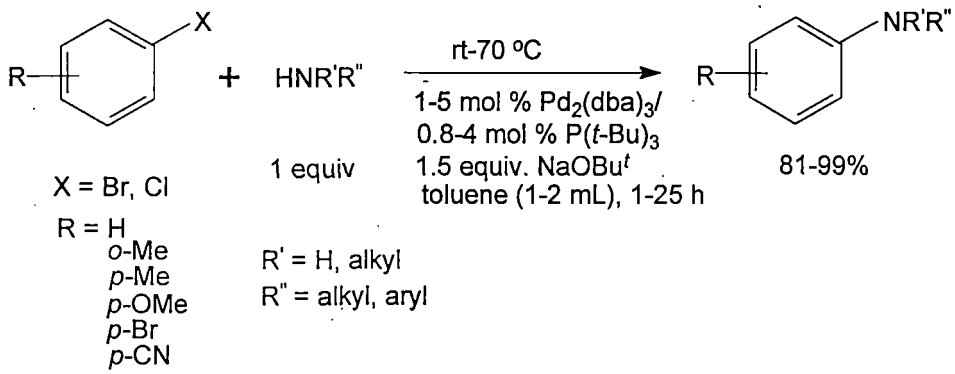
Scheme 33



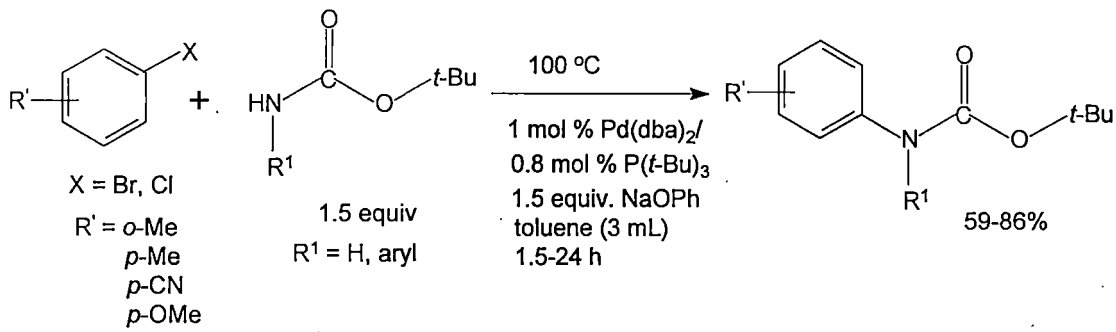
Third generation ligands such as P(*t*-Bu)$_3$,[148] (*o*-biphenyl)P(*t*-Bu)$_3$[150] and heterocyclic carben[153] create catalysts with increased activity and allow milder conditions to be used.

The group of Hartwig[148] described that the reaction of aryl bromides with amines occurs at room temperature when using Pd(0) and P(*t*-Bu)$_3$ in a 1:1 ratio, and the reaction of aryl chloride occurs at room temperature to 70 °C (Scheme 34). The arylation of carbamates also occur using P(*t*-Bu)$_3$ as ligand (Schemes 35).

Scheme 34



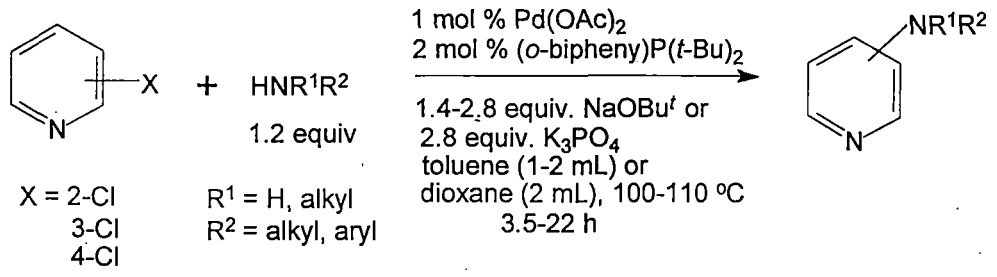
Scheme 35

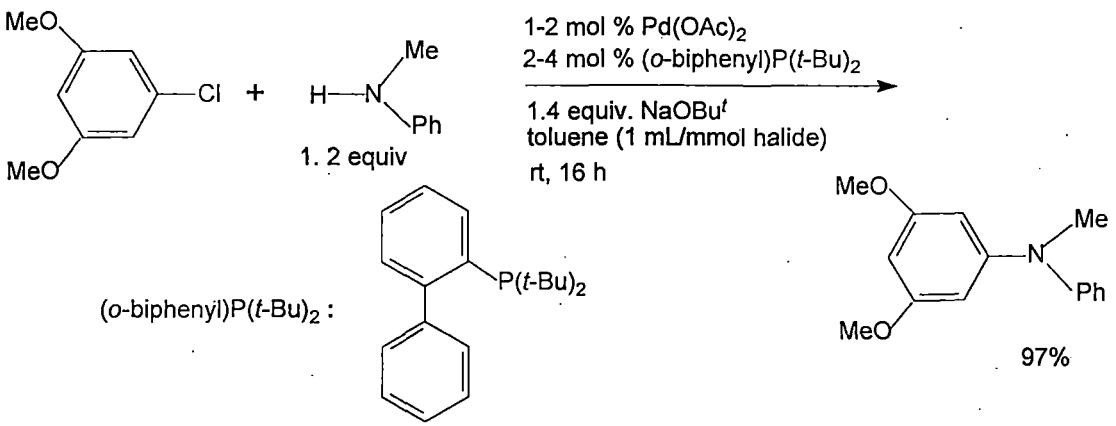


Recently Buchwald and co-workers[150] reported that palladium complexes supported by (*o*-biphenyl) P(*t*-Bu)$_2$ or (*o*-biphenyl)PCy$_2$ are efficient catalysts for the catalytic amination of a wide variety of aryl halides (Scheme 36 & 37). Use of ligand (*o*-biphenyl) P(*t*-Bu)$_2$ allows for the room-temperature catalytic amination of many aryl chloride, bromide substrates, while ligand (*o*-biphenyl)PCy$_2$ is effective for the amination of functionalized substrates or reactions of acyclic secondary amines. The catalysts perform well for a large number of different substrate combinations at 80-110 °C, including chloropyridines and functionalized aryl halides using 0.5-1.0 mol % Pd. Their effectiveness is believed to be due to a combination of steric and

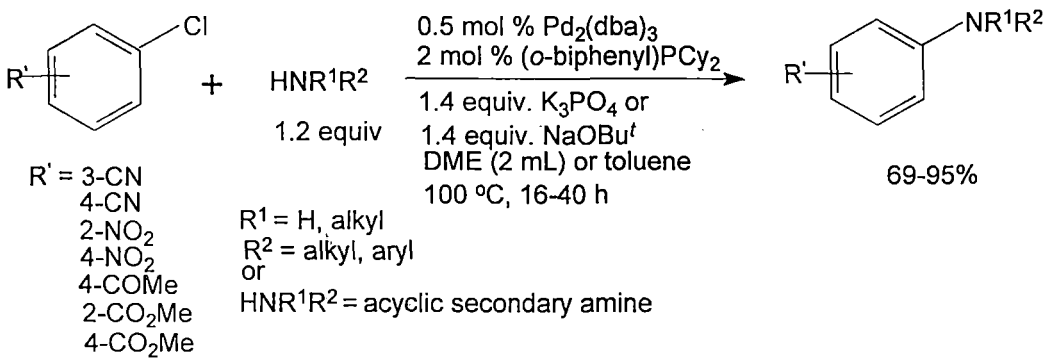
electronic properties that promote oxidative addition, Pd-N bond formation, and reductive elimination.

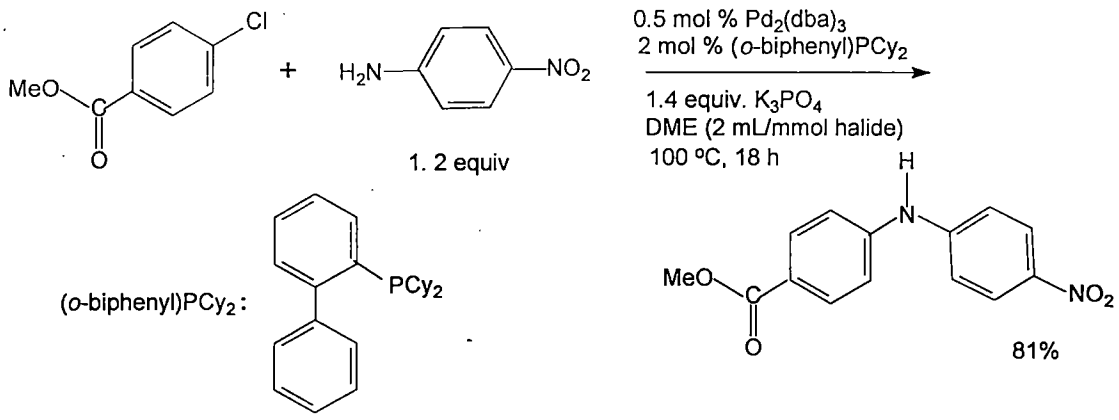
Scheme 36





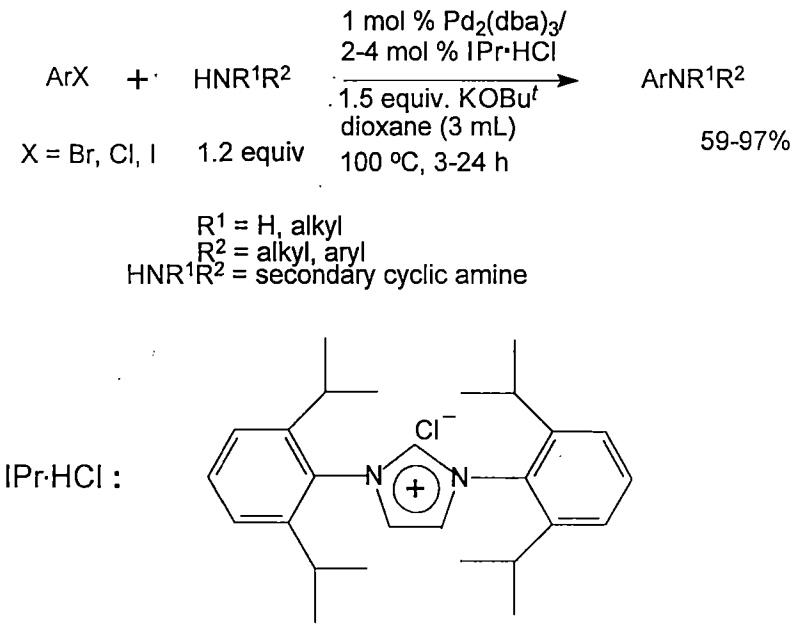
Scheme 37





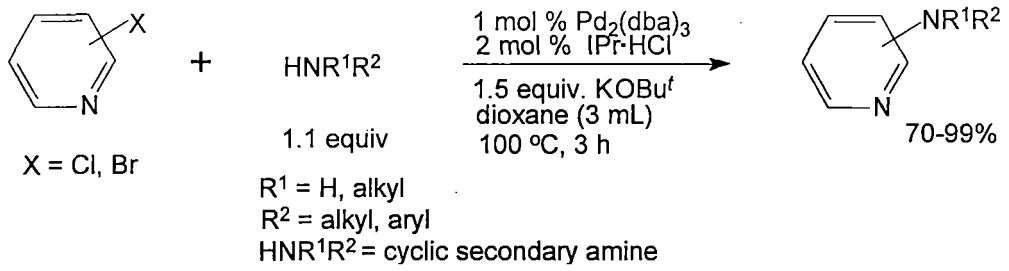
The research group of Nolan[153] discovered that Pd(0)/IprHCl/KOBu^t system was found to be highly effective for the amination of electron-neutral, electron-poor aryl chlorides as well as sterically hindered substrates with a variety of primary and secondary cyclic and acyclic amines (Scheme 38).

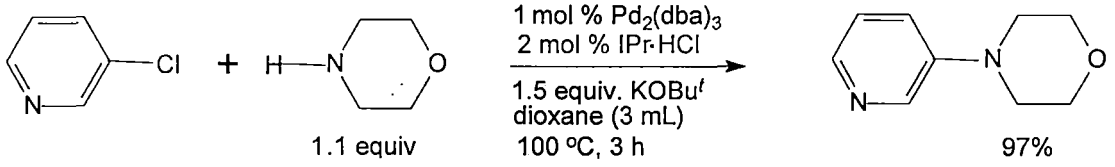
Scheme 38

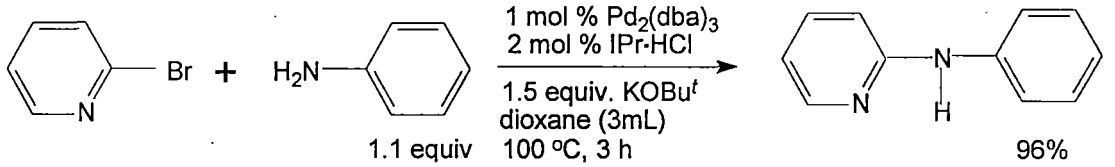


This catalytic system proved its effectiveness in the amination of various heteroaryl halides (Scheme 39).

Scheme 39

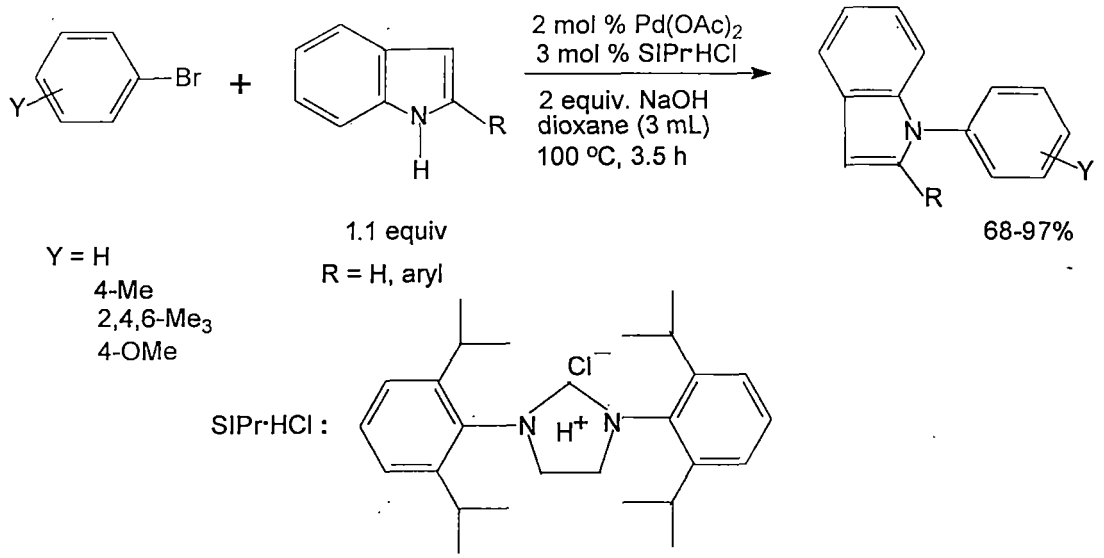






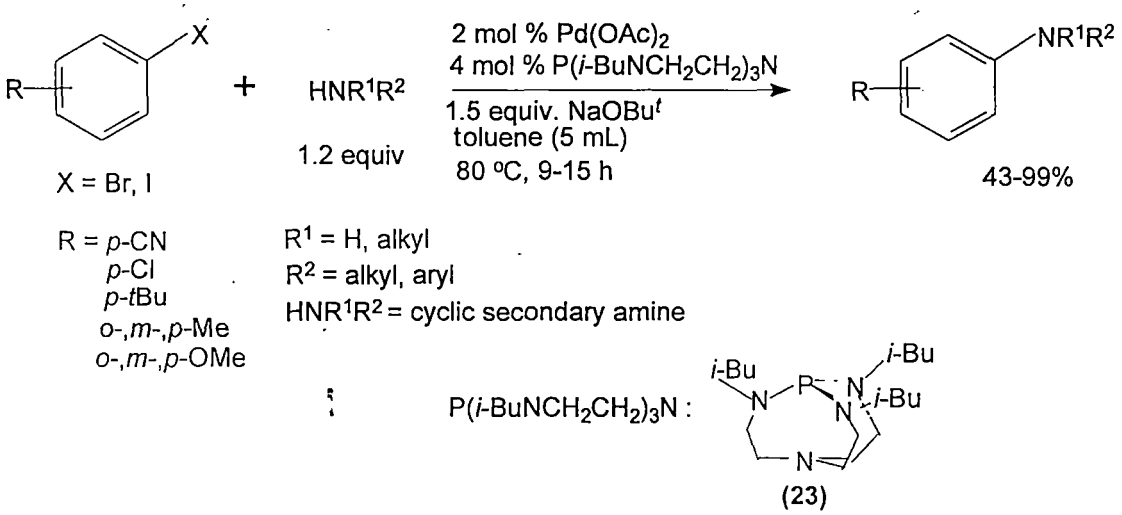
The ligand is also effective for the synthesis of benzophenone imines which can be easily converted to the corresponding primary amines by acid hydrolysis. Less reactive indoles were converted to *N*-aryl-substituted indoles using as supporting ligand the more donating SIPr·HCl (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene. The $Pd(OAc)_2$/SIPr·HCl/NaOH system is efficient for the *N*-arylation of diverse indoles with aryl bromides (Scheme 40). The general protocol developed has been applied successfully to the synthesis of a key intermediate in the synthesis of an important new antibiotic. Mechanistically, palladium-to-ligand ratio studies strongly support an active species bearing one nucleophilic carbene ligand.

Scheme 40

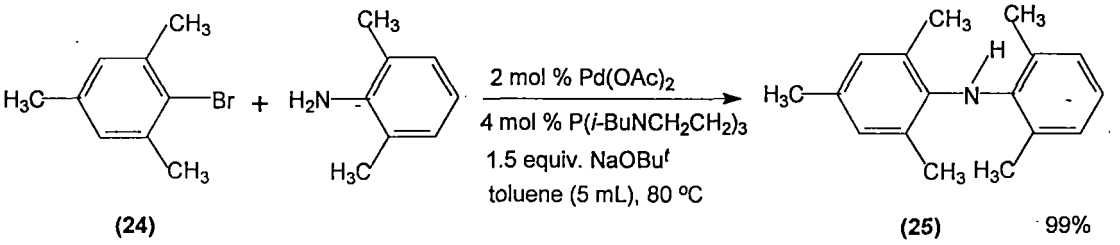


Verkade et al[173] demonstrated that commercially available bicyclic triaminophosphine P(*i*-BuNCH$_2$CH$_2$)$_3$N (**23**) functions uncommonly efficiently in amination reactions. Various aryl bromides and iodides are readily coupled with a range of amines, including primary and secondary anilines, cyclic secondary amines, primary amines branched at the α-position and (with limited success) acyclic secondary amines (Scheme 41).

Scheme 41



Steric hindrance on either coupling partner was well tolerated, often giving the desired product in almost quantative yield. For example, 2-bromomesitylene (**24**) reacted with 2,6-dimethylaniline to give tetra-*ortho*-substituted arylamine product (**25**) in 99% isolated yield.



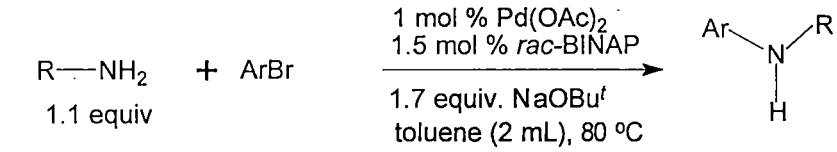
(**24**) (**25**) 99%

Several salient features of bicyclic triaminophosphine are (i) commercial availability, (ii) optimum steric effects provided by the *i*-butyl groups and (iii) electron- richness of the phosphorous arising from the donating capability of all three virtually planer nitrogens adjacent to the phosphorus, as well as the possibility for augmented basicity of the phosphorus arising from transannular bonding between the bridgehead nitrogen and the phosphorus atom.

The palladium-catalyzed amination of aromatic halides with hindered *N*-alkyl-substituted anilines was reported by Buchwal et al[174] using xantphos (**26**) or 2-(di-phenylphosphino)-2′-(*N*,*N*-dimethylamino) biphenyl (**27**) as ligands as outlined in Scheme 42.

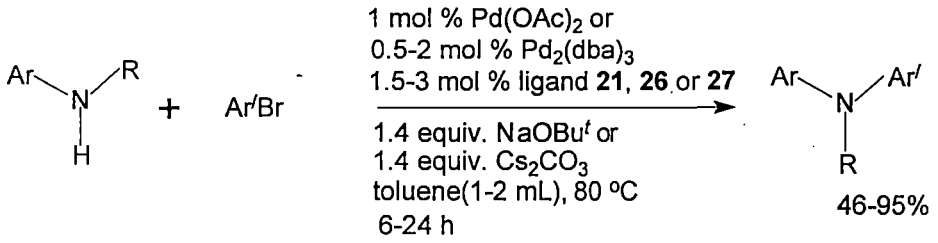
Prasad and coworkers[175] described an efficient synthesis of hindered *N*-alkyl-substituted diarylamines (**28**) by an amination of aromatic bromides either a combination of $Pd(OAc)_2$ and P(*t*-Bu)$_3$ or the new, commercially available air-stable and easily handled solid palladium (I) tri-*tert*-butylphosphine bromide dimer, [Pd(μ-Br)(*t*-Bu_3P)]$_2$ as the catalyst (Scheme 43).

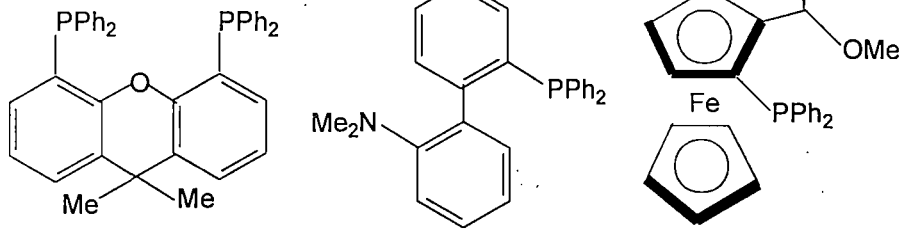
Scheme 42



rac-BINAP = (±)-BINAP

R = alkyl
Ar, Ar′ = aryl



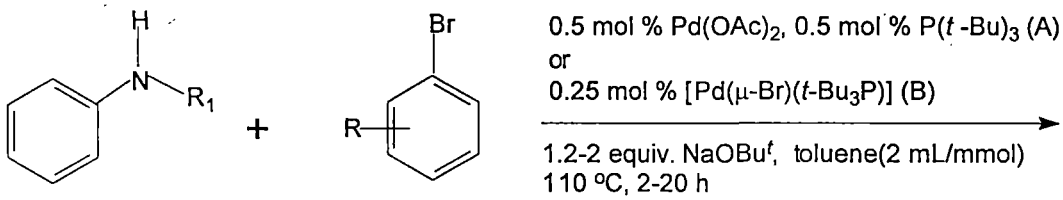


Xantphos
(26)

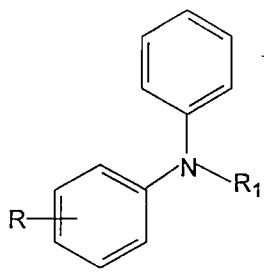
(27)

PPF-OMe
(21)

Scheme 43



0.82 equiv
R_1 = alkyl



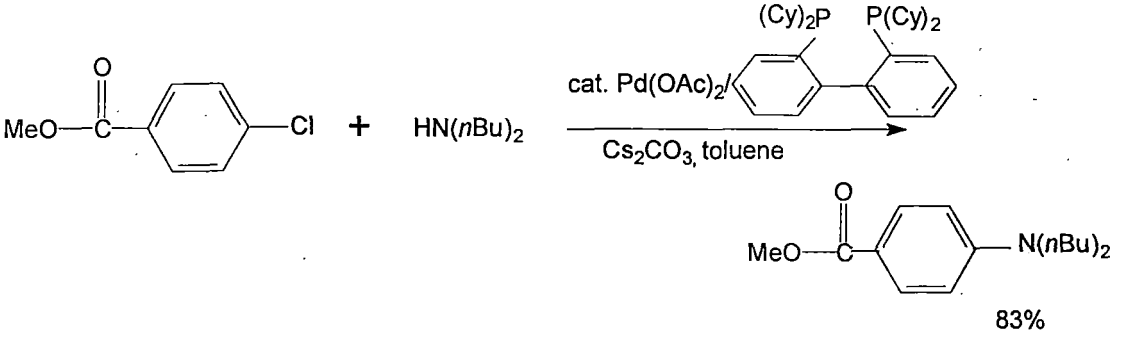
(28) 12-90% (A)
51-93% (B)

Use of Bases:

The palladium-catalyzed aromatic amination reaction is also very sensitive to the nature of base. Apart from using sodium *tert*-butoxide, with sodium methoxide, the *m*-bromotoluene slowly decomposes to *m*-xylene, while with potassium carbonate, no convertion to product is obtained. Bases weaker than sodium *tert*-butoxide such as K_2CO_3, Na_2CO_3, DABCO, DBU, Proton Sponge, Et_3N, Na_3PO_4, and NaOH failed to promote this hetero C-N coupling reaction.

One of the major problems associated with using NaO^{t}Bu is that substrates containing base-sensitive functional groups are difficult to aminate. For example, 4-bromoacetophenone did not undergo amination. However, when the weak base Cs_2CO_3 was employed, a much wider variety of functional groups are tolerated. Buchwald observed that using Cs_2CO_3, substrates containing methyl and ethyl esters or nitro groups are coupled with a variety of amines.[157]

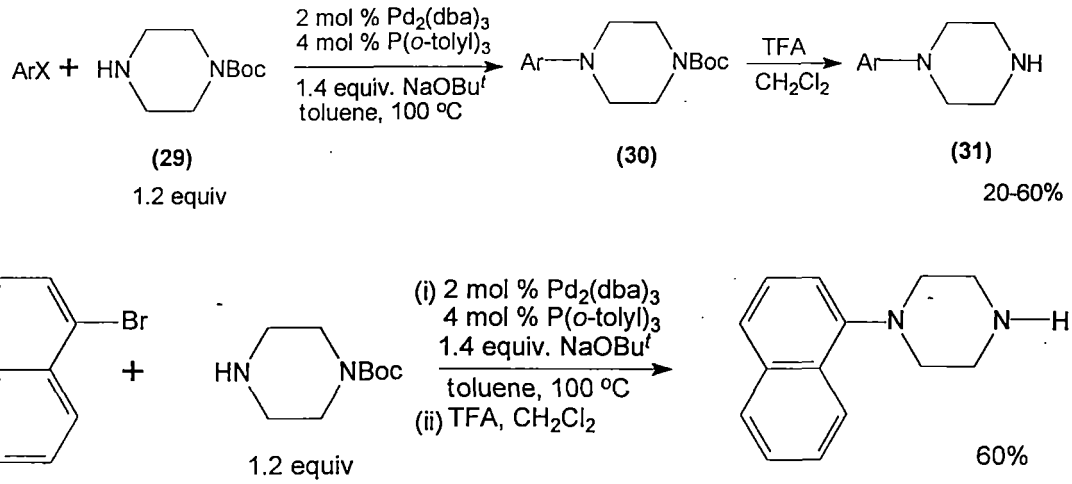
Aryl bromides containing functional groups sensitive to NaOBu^t could be converted to the corresponding aniline derivative by using also K_3PO_4 as the base. Aryl chloride containing functional groups sensitive to NaOBu^t could be converted to the corresponding aniline derivative by using Cs_2CO_3 as the base.



A Few Applications of Palladium-Catalyzed Amination Reaction:

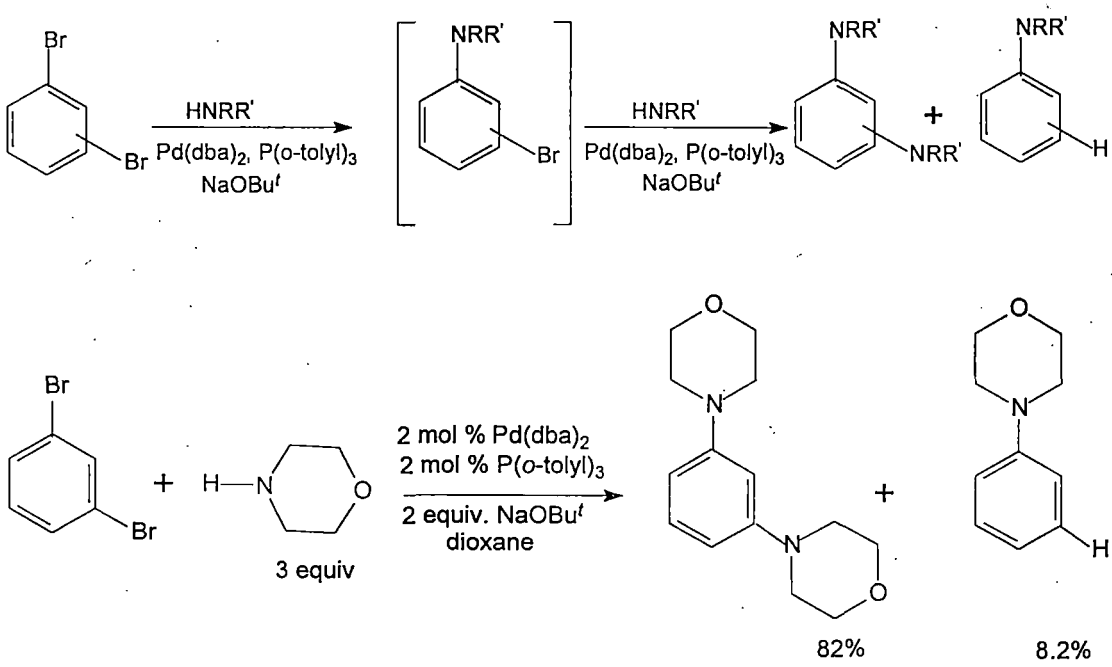
Thomas et al[176] reported that a series of bicyclic arylpiperazines (**31**) can be made efficiently by reaction of bromoarenes with *N*-Boc-piperazine (**29**) under palladium-catalyzed aromatic amination condition[170,172,178] followed by standard deprotection of the Boc-protected arylpiperazines (**30**) with trifluoroacetic acid as described in Scheme 44.

Scheme 44



Beletskaya et al[177] revealed that diaminobenzenes are obtained starting from *m*- and *p*-dibromobenzenes and secondary amines in the presence of $Pd(dba)_2/P(o\text{-tolyl})_3$ and sodium *tert*-butoxide in moderate to good yields (Scheme 45). Reductive dehalogenation of aryl dibromides is, however, a side reaction under these conditions.

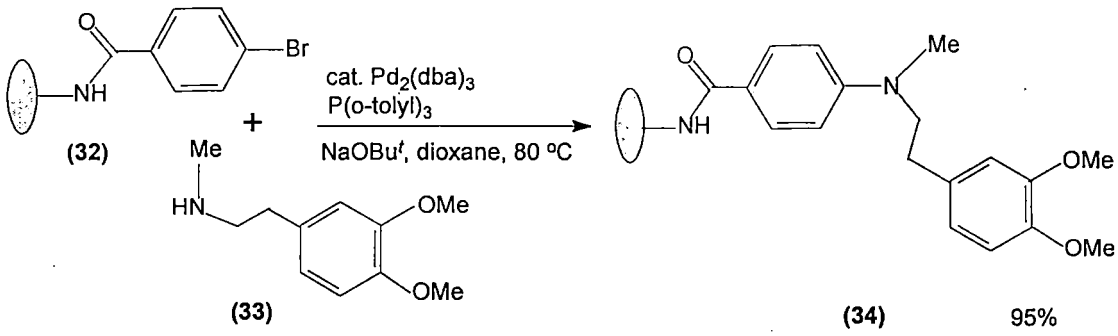
Scheme 45



Two groups reported methods for the solid phase synthesis of aryl amines employing the palladium-catalyzed amination protocol. The discovery that the Pd(0)/P(*o*-

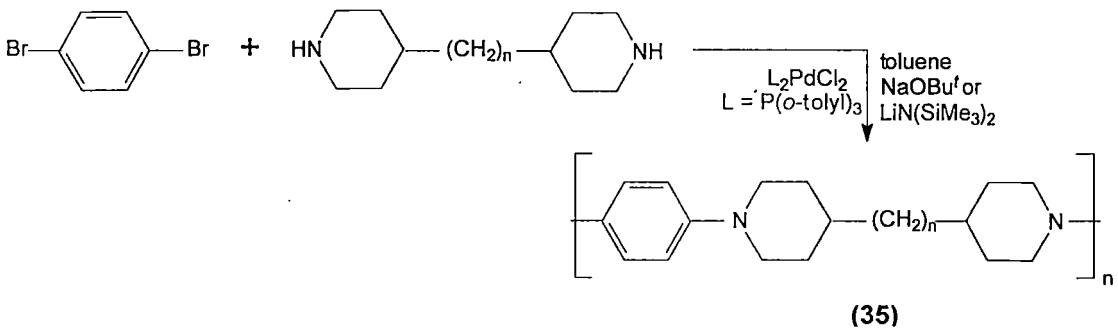
tolyl)$_3$, catalyst system is effective in the coupling of secondary amines such as (**28**) with polymer bound aryl bromide (**27**) to afford high yields of product (**29**) has been reported by Willoughby and Chapman (Scheme 46).[178] The use of BINAP as a ligand allowed the coupling of primary amines in high yields and with excellent purities. Ward and Farina independently reported similar findings.[179] This methodology will no doubt prove useful for constructing combinatorial libraries of aniline derivatives for biological screening.

Scheme 46



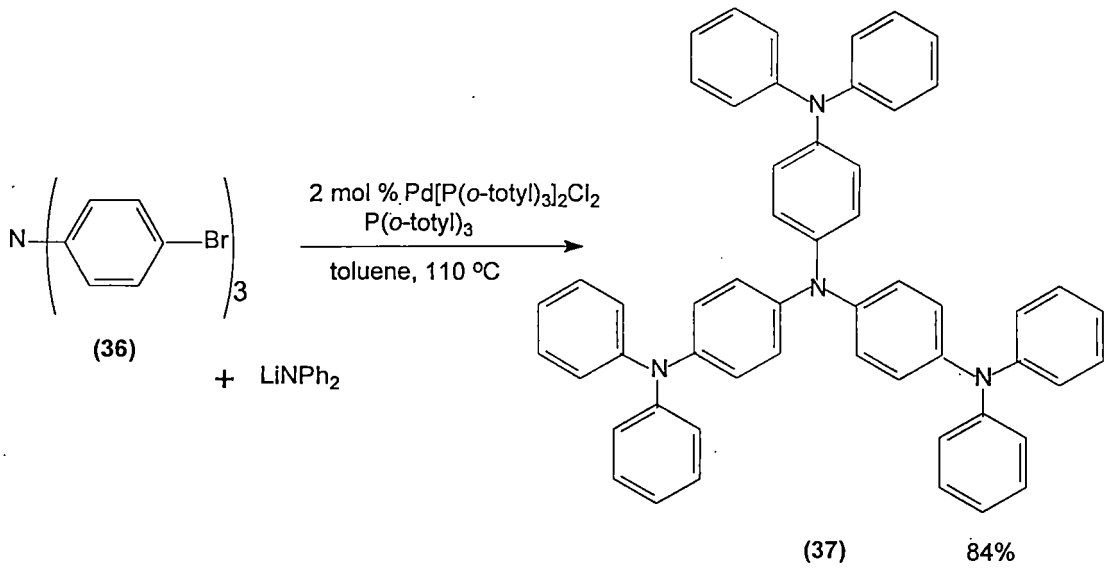
Two groups disclosed the synthesis of oligomers or polymeric arylamines using palladium-catalyzed chemistry.[180,181] One group used the initial amination of aryl halides with dialkylamines to prepare arylamine polymers (**35**).[180] This chemistry is a step-growth polymerization shown in Scheme 47.

Scheme 47



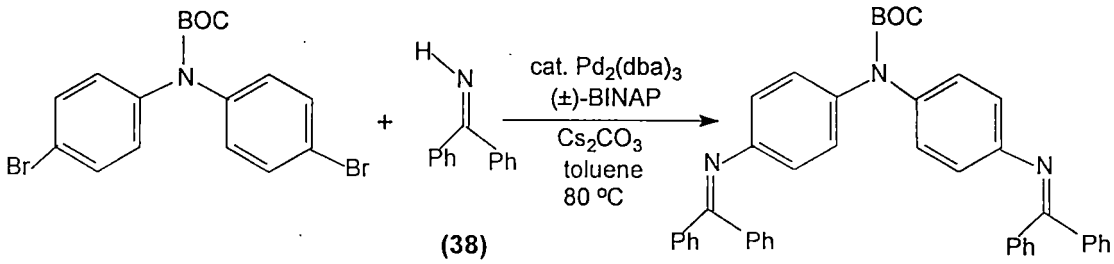
The other group[181] prepared high molecular weight triarylamine dendrimers. The first generation dendrimer (**37**) is prepared from tris-(4-bromophenyl)amine (**36**) and lithium diphenylamide (Scheme 48). The yield for the reaction is 84% which is far superior to the modest yields obtained by copper-mediated Ullmann chemistry.

Scheme 48



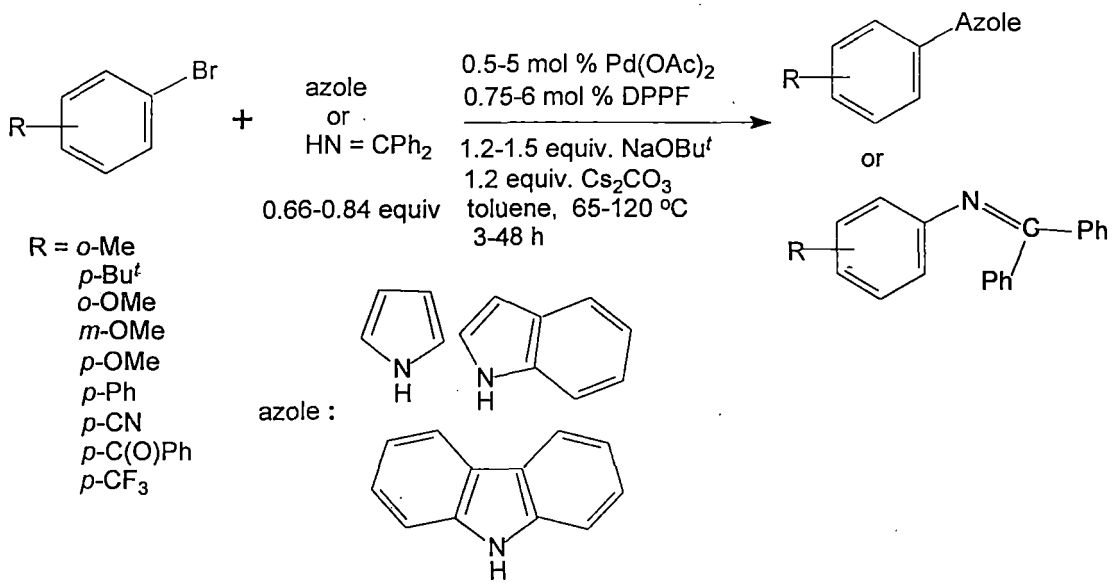
Buchwald showed that benzophenone imine (**38**) can undergo palladium-catalyzed C-N coupling reaction (Scheme 49).[182]

Scheme 49



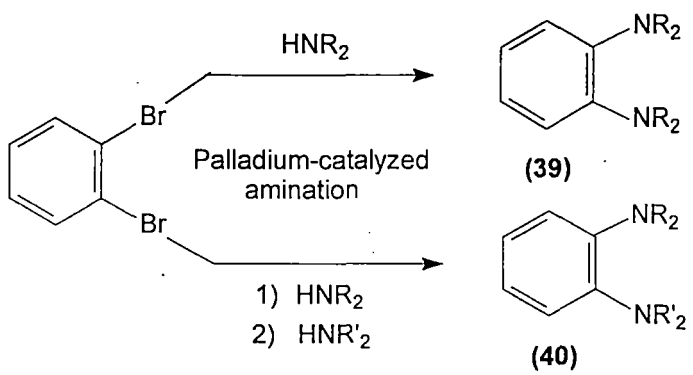
Hartwig et al[183] published a general palladium-catalyzed arylation of azoles and imines using DPPF-ligated palladium (Scheme 50).

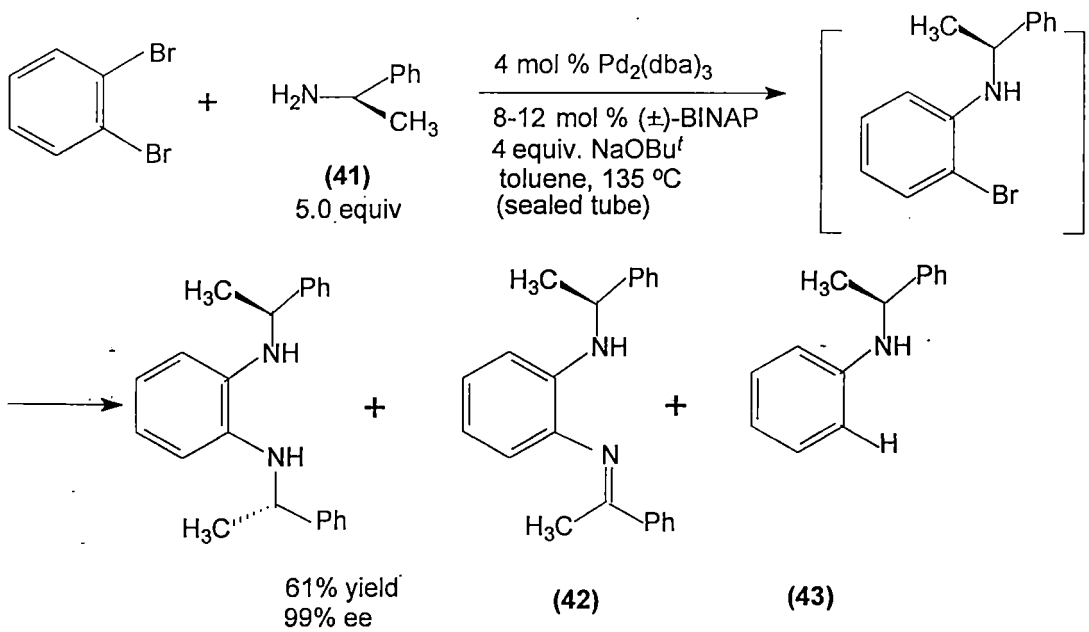
Scheme 50



The group of Driver[184] reported that direct palladium-catalyzed amination of *o*-dibromobenzene provide chiral *N,N'*-disubstituted 1,2-benzenediamines in good to excellent yields. The amination was executed stepwise and in one pot to give symmetrically and unsymmetrically substituted 1,2-benzenediamines [(**39**) & (**40**) respectively] (Scheme 51). Incorporation of chiral primary amines (**41**) was possible without recemization using catalytic $Pd_2(dba)_3$–BINAP along with other products (**42**) and (**43**).

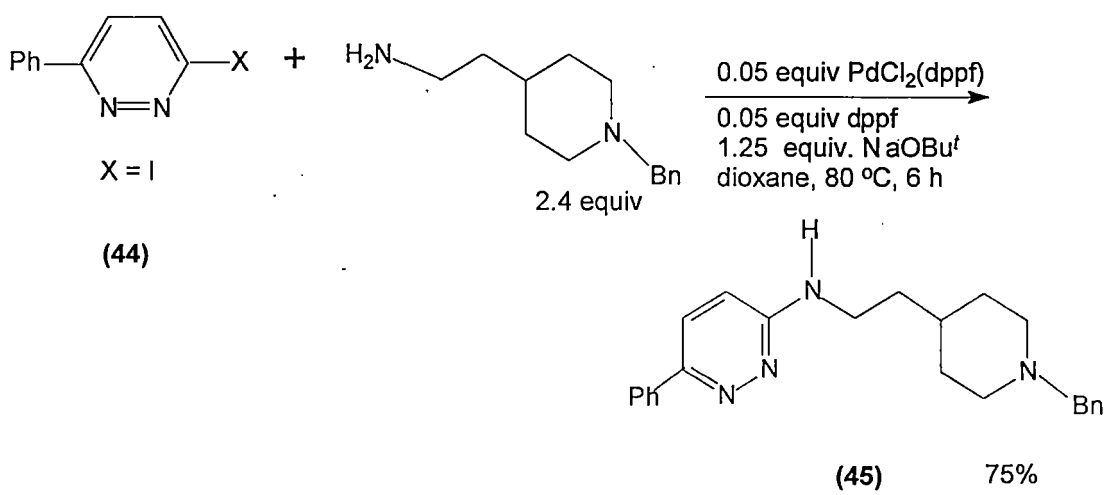
Scheme 51





Hilbert et al.[185] developed an operationally simple and efficient palladium-assisted amination of 3-iodo-6-aryl pyridazines (**44**) according to Scheme 52. This new route allows access to a wide-ranging series of pharmacologically useful pyridazine derivatives (**45**).

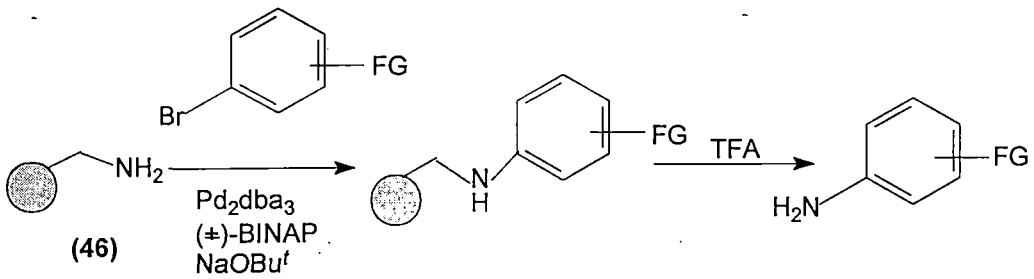
Scheme 52



Weigand et al[186] reported the first example of the Pd(0)-catalyzed amination of aryl halides using Rink-resins (**46**) as nitrogen source (Scheme 53). $Pd_2(dba)_3$/BINAP/

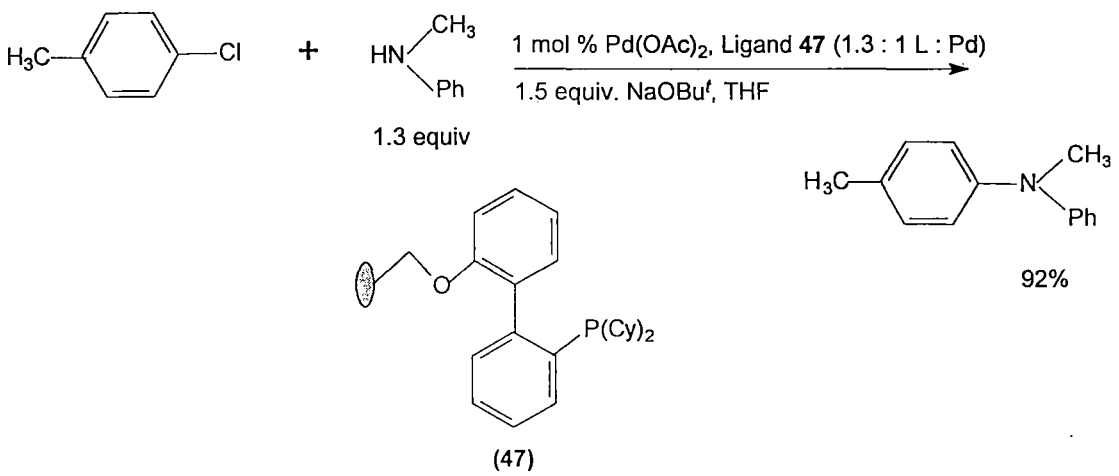
NaOBu^t was found to be the most efficient catalyst/base system, while a solvent mixture of dioxane and *tert*-butyl alcohol was shown to exhance the selectivity toward the desired monoarylation. Moderate to good yields and excellent purities of the amination products were found with electron-poor aryl halides, while electron-rich aryl halides failed to react under these conditions.

Scheme 53



Buchwald et al.[187] used a dialkylphophinobiphenyl ligand anchored to a polymer support and demonstrated its utility in palladium-catalyzed cross-coupling reactions. In combination with a palladium source, ligand (**47**) forms an active resin-bound catalyst for amination of unactivated aryl iodide, bromide or chloride (Scheme 54). Reactions using the electron-rich phosphine ligand (**47**) are the first successful examples of the use of aryl chloride substrates with a solid-supported catalyst for amination. The resin bound catalyst can be recycled without additional palladium in the amination reactions. Use of the solid-supported electron-rich phosphine ligand (**47**) led to an active catalyst system for the palladium-catalyzed amination reaction.

Scheme 54

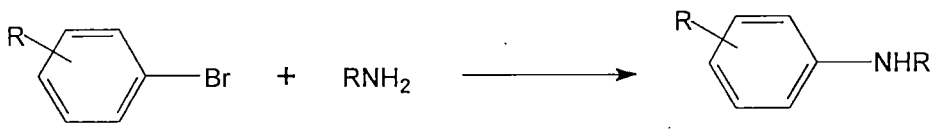


I-A.2.1:Present Work: Background, Objectives and Strategy

The *N*-aryl moiety represents an important motif in natural products,[11b] pharmaceutical and medicinal compounds,[3,18,188] as well as in polymer and materials.[1,25,180-181,189] Heteroaromatic amines are widespread in nature and are common in synthetic chemistry. Among the variety of heteroaromatic amines, aminopyridines are important in various fields of chemistry. They have been used as acyl transfer reagents in organic chemistry[38,39] and are biologically known to act as central nervous system stimulants.[47] Besides, their derivatives are often used as ligands in coordination and organometallic chemistry,[40-44] they have found industrial applications as fluorescent dyes.[45,46] The aminopyridazine nucleus can be found in dopaminergic, serotoninergic, cholinergic and GABA-ergic ligands as well as in monoamine oxidase and acetylcholine esterase inhibitors.[190]

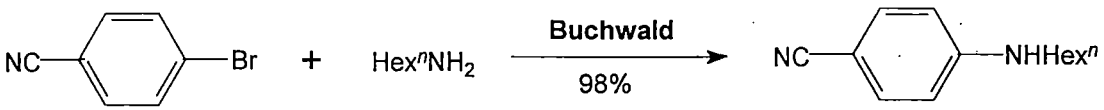
Because of the importance of heteroaromatic amines in various fields of chemistry and applications, the development of new and more general methods for their preparations is of significant interest. Since the present work is concerned with the preparation of aminopyridines and *N*-heteroarylamines, we confine our discussion on the preparative methods of aminopyridines and derivatives. As discussed in the introduction, most of the early preparative methods for aminopyridine involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions. 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. New reaction procedures involving palladium-ligand-catalayzed amination of aryl halides, developed independently by Buchwald and Hartwig, offer a convenient method for the preparation of a wide variety of aryl/heteroarylamines.[155,156] A few reactions are given below.

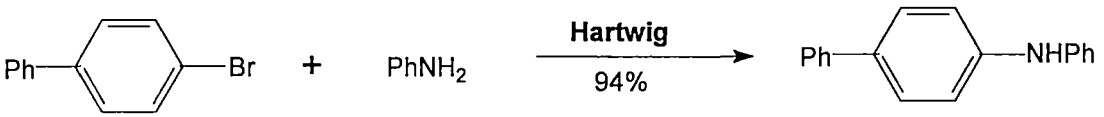
The catalytic system involving Pd(0)/P(*o*-tolyl)$_3$ complexes is effective catalyst for the cross-coupling of arylbromides and aminostannanes and for the cross-coupling of aryl halides and amines in the presence of sodium *tert*-butoxide. However, applying



Buchwald
Cat. $Pd_2(dba)_3$
$P(o\text{-tolyl})_3$
$NaOBu^t$
Toluene, 80 °C

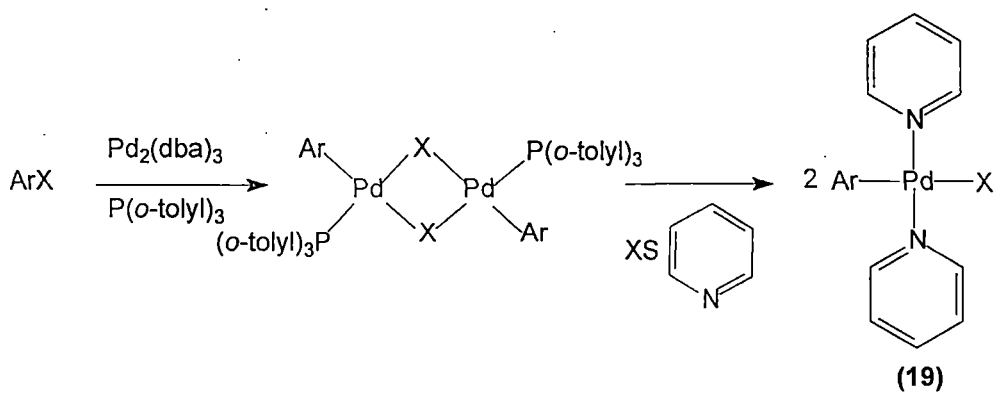
Hartwig
Cat. $PdCl_2$
DPPF
$NaOBu^t$
THF, 100 °C





this protocol to the amination of bromopyridine was initially unsuccessful. Buchwald and his coworkers reasoned that the catalytic cycle (p. 22) is probably inhibited with the displacement of $P(o\text{-tolyl})_3$ ligand by pyridine nucleus.[169] They showed that such complexes (**19**) may be easily formed if pyridine is present in the reaction medium, as outlined in Scheme 29.

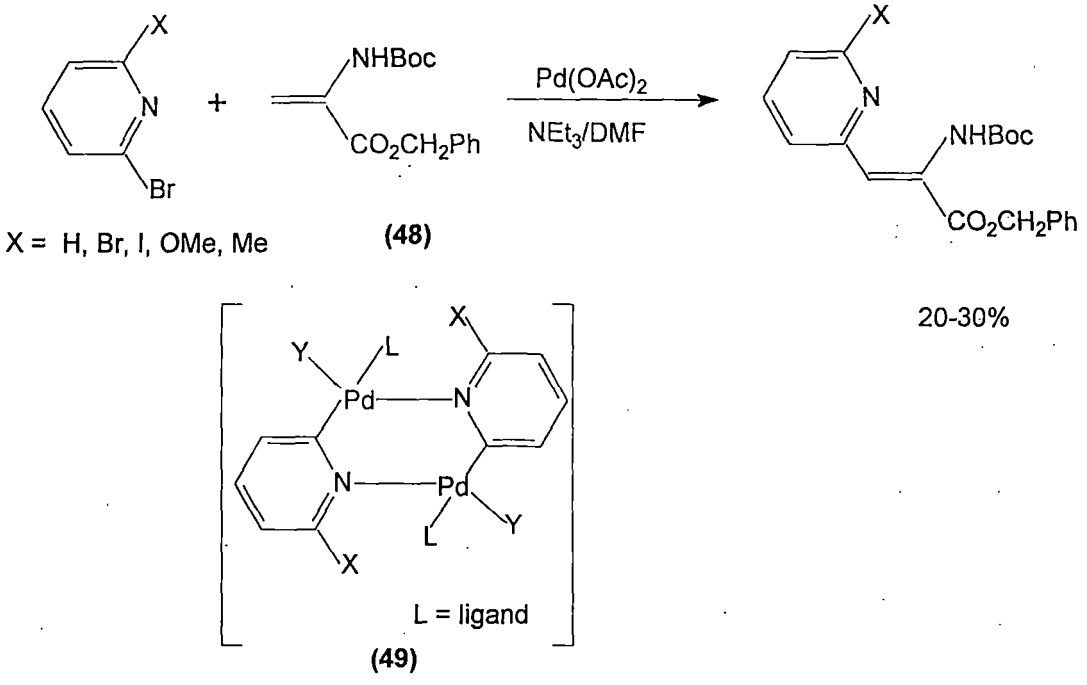
Scheme 29



(19)

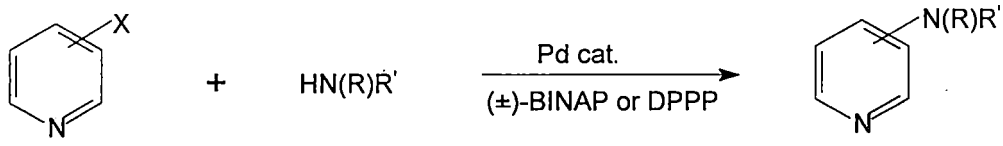
Such observations were also noticed by Basu and Frejd, while performing bis-Heck-couplings of 2,6-dibromopyridine with dehydroamino acid derivative (**48**) (Scheme 55).[191] The formation of the bis-complex (**49**), after the first oxidative addition of Pd(0), inhibited the catalytic cycle and only the mono-coupled products were isolated in <30% yield.

Scheme 55



The ease exchange of ligands was, however, circumvented by using chelating bis-(phosphine) as the ligand. Buchwald found that the chelating bis-(phosphine) does not undergo ligand exchange with excess pyridine, and consequently, the formation of bis-pyridine complexes (**19**), which terminate the catalytic cycle is prevented. In an NMR tube experiment pyridine (2.1 μL, 0.26 mmol) was added to a solution of [(R)-Tol-BINAP]Pd(4-benzonitrile)(Br) (10 mg, $1x10^{-3}$ mmol) in $CDCl_3$. The ^{1}H-NMR spectrum of the [(R)-Tol-BINAP]Pd(4-benzonitrile)(Br) complex remain unchanged. Accordingly, Buchwald employed either BINAP or DPPP as the bis-chelating ligand to achieve amination of bromopyridines in good to excellent yield (Scheme 56).

Scheme 56



1 equiv

X = Br, Cl

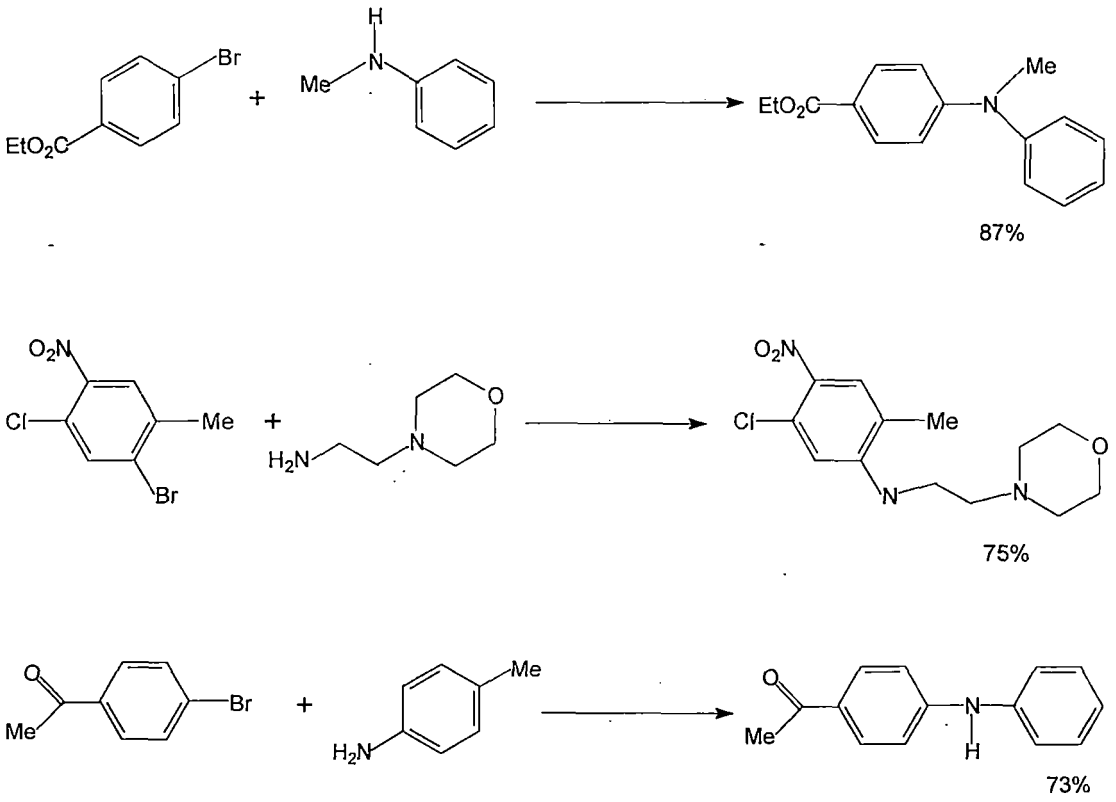
1.2 equiv

Conditions A : 2 mol % $Pd_2(dba)_3$ and 4 mol % DPPP; conditions B : 2 mol % $Pd_2(dba)_3$ and 4 mol % (±)-BINAP; conditions C : 4 mol % $Pd(OAc)_2$ and 4 mol % DPPP; conditions D : 4 mol % $Pd(OAc)_2$ and 4 mol % (±)-BINAP

As mentioned in the introduction part (p.18, 33) that the amination procedure is also very selective to the nature of base used. The most effective base has been found to be the sodium *tert*-butoxide in excess amount (> stoichiometric amounts). One of the major problems in using sodium *tert*-butoxide is its basicity, which greatly limits the functional group tolerance of the process. 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. The use of a weaker base Cs_2CO_3 has been found to be better where a much variety of functional groups are tolerated (Scheme 57).[157]

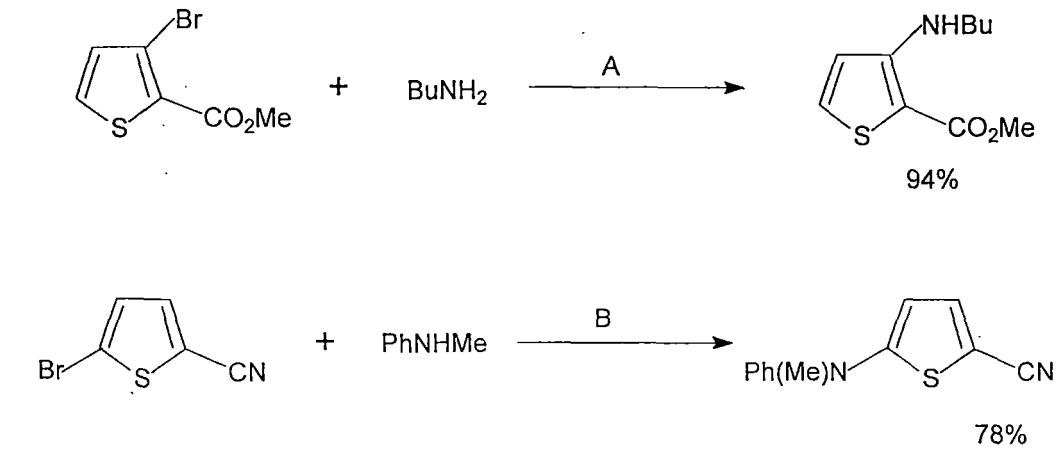
Although the weaker base CS_2CO_3 has been successfully employed for haloaromatics[157] and halothiophenes[192] (Scheme 58), the case of halopyridines was not studied. Furthermore, the use of cesium carbonate is limited due to its high solubility in organic solvent and hygroscopic nature. The present investigation has therefore been directed to address the following limitations in palladium-catalyzed cross-coupling of bromopyridines and amines.

Scheme 57



Conditions : 1 equiv of halide, 1.2 equiv of amine, 1.4 equiv of CS_2CO_3, cat. $Pd_2(dba)_3$ or $Pd(OAc)_2$, cat. BINAP (1.5 L/Pd) , toluene (0.25M), 100 °C.

Scheme 58

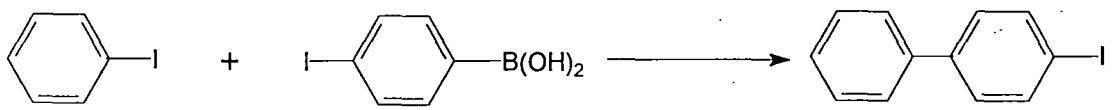


Condition A : 1.4 equiv Cs_2CO_3, 5 mol % $Pd_2(dba)_3$-10 mol % BINAP; condition B : 1.4 equiv Cs_2CO_3, 10 mol % $Pd(OAc)_2$-10 mol % BINAP

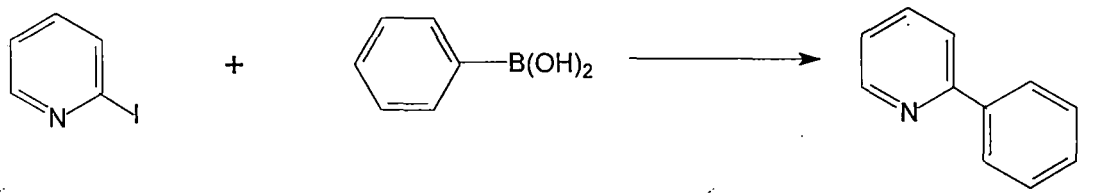
We reasoned that the use of a solvent-free basic surface might be suitable for amination reactions. As revealed in the literature, potassium fluoride (KF) impregnated on alumina (Al_2O_3) has been successfully employed as the basic surface in many organic reactions so as to exploit its basicity on the surface[193] and very recently palladium-catalyzed C-C couplings (Suzuki, Heck, Stille, Trost-Tsuji) have been reported using KF-alumina under mono-mode microwave irradiation (Scheme 59).[194] Muzart et al.[195] disclosed C-O hetero cross-coupling in Pd-catalyzed Baylish-Hilman reaction on KF-alumina surface (Scheme 60). A few applications of KF-alumina in various Pd-catalyzed organic reactions are outlined below (Schemes 60 & 61).

Scheme 59

Suzuki reaction :

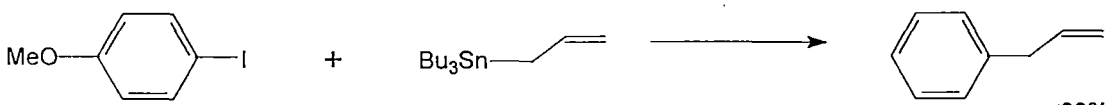


98%



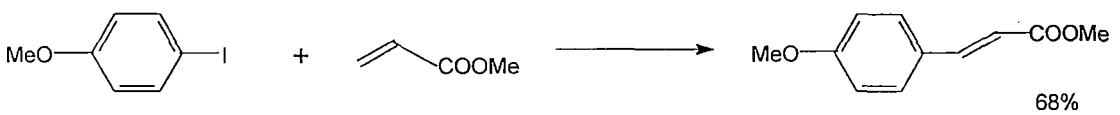
66%

Stille reaction :



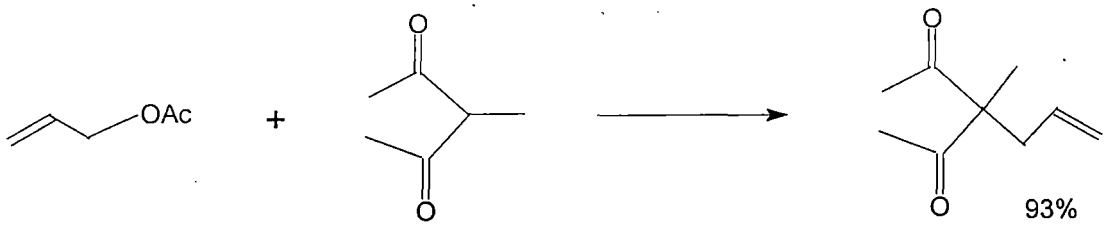
68%

Heck reaction :



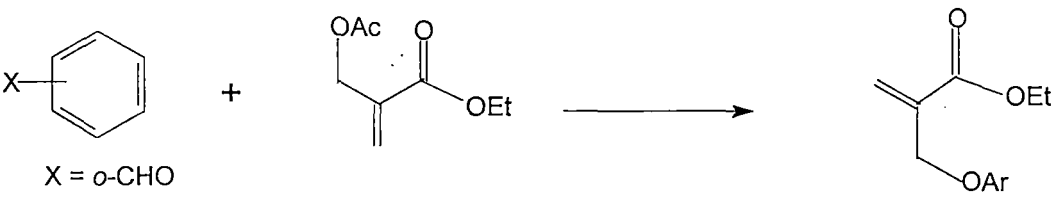
68%

Trost-Tsuji reaction:



Conditions : cat. $Pd(OAc)_2$ or $Pd_2(dba)_3$/KF-Al_2O_3 under MWI

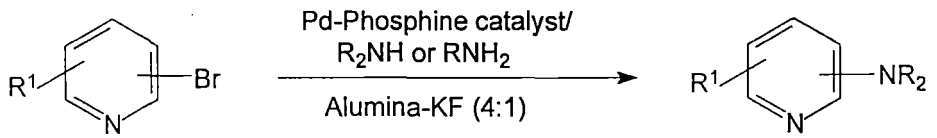
Scheme 60



Conditions : $Pd_2(dba)_3$·$CHCl_3$-PPh_3/KF-Al_2O_3 in THF at rt for 4.5 h

The role of mono- or bis-phosphine ligands in palladium-catalyzed hetero cross-coupling of halopyridines on a solid surface could be an interesting study. The present work describes our results, which eventually constitute a convenient and efficient heterogeneous method for C-N coupling by Pd-catalyzed amination of halopyridines on KF-alumina (basic) surface (Scheme 61).

Scheme 61



P(*o*-tolyl)$_3$, DPPF, BINAP; Pd sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

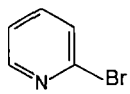
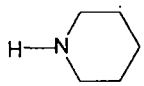
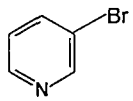
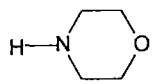
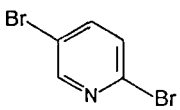
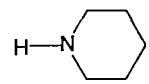
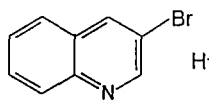
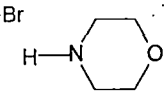
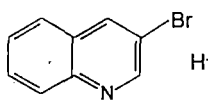
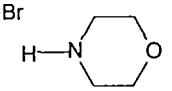
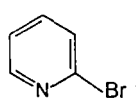
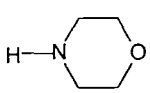
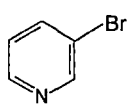
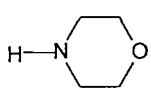
I-A.2.2: Present Work: Results and Discussion

Prior to studies on amination reaction on the surface of KF-alumina, we initially attempted the same reaction using only alumina (basic) as the surface. The results were , however, not encouraging, as may be seen from Table 1.

A mixture of 2-bromopyridine and piperidine (1 : 1.5) and $Pd[(o\text{-tolyl})_3P]_2Cl_2$ (2 mol %) was admixed on a surface of activated basic alumina (see experimental section) and the solid mixture was taken in toluene and heated with stirring under N_2 at 80-100 °C for 10 h. TLC showed a new spot, which was isolated by column chromatography on silica gel. A solid compound was obtained (25%), characterized as 2,2′-bipyridyl (m.p.^{obs} 68-71 °C and lit.[196] 70-73 °C) by ^{1}H-NMR. Similar reactions with 3-bromopyridine with morpholine (entry 2, Table 1), 2,5-dibromopyridine with piperidine (entry 3, Table 1) and 3-bromoquinoline with morpholine (entry 4, Table 1), however, gave neither any bis-coupled products nor the desired aminated products. Instead, the starting materials were recovered (40-65%) in most cases. Several variants did not change the course of the reaction in the desired direction.

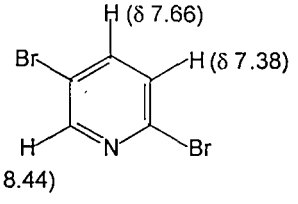
As mentioned in the preceding pages (p. 45, 46) that KF on alumina has been successfully employed in palladium-catalyzed C–C and C–O bond-forming reactions,[194,195] we became interested to turn our attention to using KF-alumina as the surface for the amination of halopyridines. KF-alumina was prepared according to the literature procedure,[193d, 197] where the ratios of KF : alumina were used in (2 : 3). Attempts to using such KF : alumina (2 : 3) showed improved results indeed, although the percentage of yields of the aminated products ranged between 20-50%. On the other hand, changing the proportions of KF-alumina to 1 : 4 gave a remarkable incremental change in terms of the yields of the desired products.

Table 1

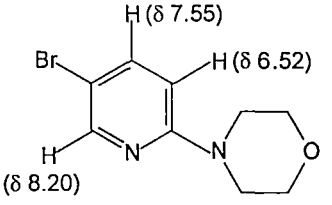
Entry	Substrate	Amine	Catalyst	Solvent/Temp/Time	Observation
1.			$Pd[(o\text{-tolyl})_3P]_2Cl_2$	Toluene/80-100 °C/10 h	2,2′-Dipyridyl (25%) and 2-Bromopyridine (50%)
2.			$Pd(acac)_2$/DPPF	Toluene/70 °C/12 h	3-Bromopyridine (40%)
3.			$Pd[(o\text{-tolyl})_3P]_2Cl_2$	Toluene/100 °C/8 h	2,5-Dibromopyridine (65%)
4.			$Pd_2(dba)_3$-$CHCl_3$	Toluene/70 °C/12 h	3-Bromoquinoline (50%) and Quinoline (10%)
5.			$Pd(o\text{-tolyl})_3P]_2Cl_2$/ CuI	Toluene/80 °C/10 h	3-Bromoquinoline (50%) and Quinoline (10%)
6.			$Pd(acac)_2$/DPPF	Toluene/80 °C/5 h	2-Bromopyridine (50%) and 2,2′-Dipyridyl (10%)
7.			$Pd_2(dba)_3$/DPPF	Toluene/100 °C/12 h	3-Bromopyridine (40%)

As can be seen from the results presented in Table 2, the amination on KF-alumina worked efficiently with different bromo-pyridines. While 2-bromopyridine reacts with different amines smoothly, 3-bromopyridine undergoes amination in relatively poor yield. In case of 2-bromopyridines (entries 1, 2; Table 2) the formation of homo-coupled 2,2′-bipyridyl could not be avoided (10-15%). While carrying out the reaction using solvent (toluene), such coupling is further increased. Using 1,4-dioxa-8-aza-spiro[4,5]decane as the amine, the labile ketal group remained unchanged during the reaction conditions as well as the work-up. The ketal methylene group in the aminated product exhibited a sharp singlet at δ 3.96 ppm corresponding to four hydrogens.

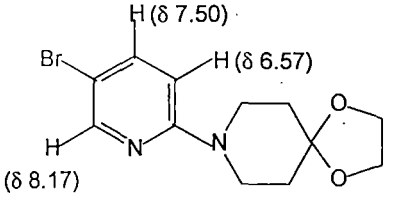
Dibromopyridines were reacted with a variety of amines (entries 3–6 and 8, 9; Table 2). Both primary and secondary amines were used for these reactions. In all the cases, however, mono-amine derivatives were obtained in good to excellent yields. In the case of 2,5-dibromopyridine, amination occurs selectively at the 2-position, which was settled unambiguously by comparison of NMR spectra. In 2,5-dibromopyridine, the proton at the 6-position appeared as the doublet at δ 8.44 ppm while the same proton (C_6) in 2-morpholino-5-bromopyridine displayed as a doublet at δ 8.20 ppm. similarly, the C-4 proton displayed as a doublet of doublet at δ 7.66 and 7.55 ppm respectively. The major shifting was observed in the case of C-3 proton, which appeared as a doublet at δ 7.38 and 6.52 ppm respectively. Similar trends were also noticed in the NMR spectrum of 8-(5-bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane.



2,5-Dibromopyridine



2-morpholino-5-bromopyridine

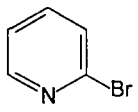
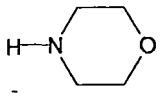
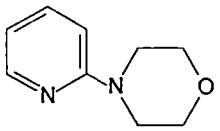
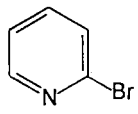
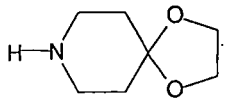
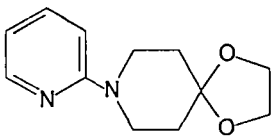
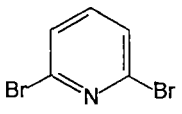
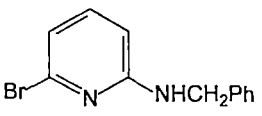
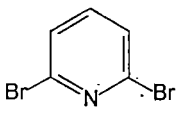
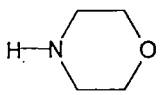
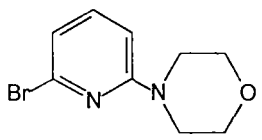
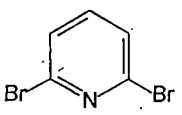
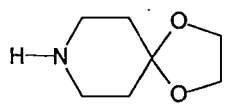
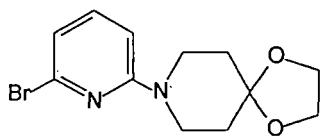
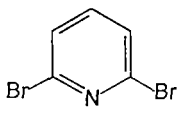
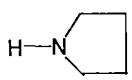
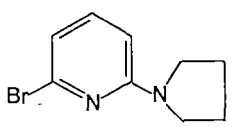
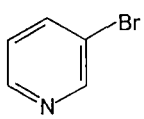
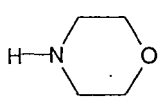
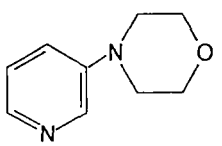


8-(5-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane

Buchwald observed complete bis-amination of 2,6-dibromopyridine using $Pd_2(dba)_3$–DPPP catalyst in presence of excess aniline. Our conditions, however, yielded mono-amine as the major products even after prolonged reaction time and in the presence of excess amine (entries 3–6; Table 2). This selectivity offers an advantage for further reaction with the other halogen substituents.

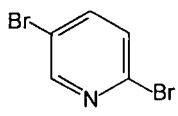
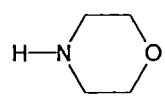
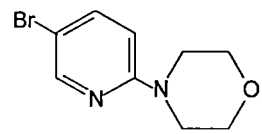
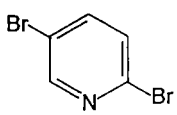
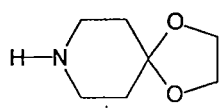
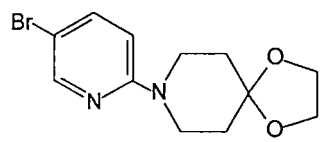
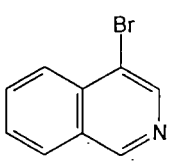
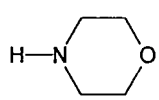
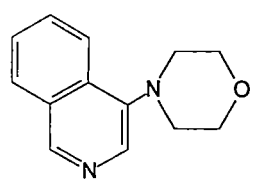
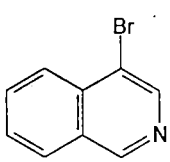
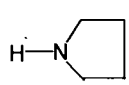
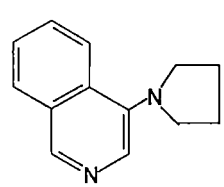
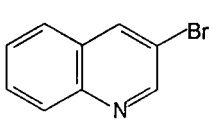
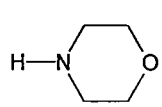
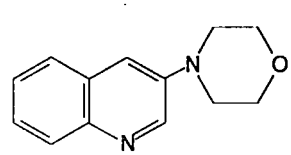
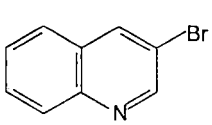
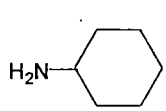
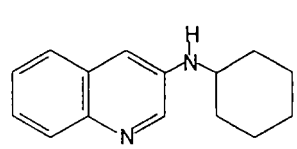
In the bicyclic systems, 4-bromoisoquinoline (entires 10 and 11; Table 2) and 3-bromoquinoline (entries 12 and 13; Table 2) underwent amination efficiently. Buchwald and co-workers reported a single example on bicyclic system, where 3-bromoquinoline coupled with *N*-methyl aniline in presence of $Pd_2(dba)_3$-(±)-BINAP catalytic system. According to them, the BINAP-catalytic system remains the most active and general catalyst, although DPPP has been used as the bis-chelating ligand complexing with $Pd_2(dba)_3$. With regard to the catalytic system, the generality is

Table 2. Palladium-catalyzed amination of halopyridines on KF-alumina surface

Entry	Bromoarene	Amine	Catalyst[a]	Conditions[b]/ time (h)	product	% yield[c]
1.			[A]	2 / 8	 **(50)**	70
2.			[A]	2 / 8	 **(51)**	58
3.		H_2NCH_2Ph	[H]	2 / 8	 **(52)**	90
4.			[A]	1,2 / 5	 **(53)**	78
5.			[A]	2 / 5	 **(54)**	62
6.			[A]	2 / 5	 **(55)**	91
7.			[F]	1,2 / 9	 **(56)**	48

continued.....

Continued..... **Table 2**

Entry	Bromoarene	Amine	Catalyst[a]	Conditions[b]/ time (h)	product	% yield[c]
8.			[A]	1,2 / 5	 **(57)**	92
9.			[A]	2 / 5	 **(58)**	73
10.			[E], [F]	1, 2 / 6	 **(59)**	86
11.			[F]	2 / 6	 **(60)**	90
12.			[F]	2 / 6	 **(61)**	78
13.			[F]	2 / 8	 **(62)**	68

[a] [A] Pd[(*o*-tolyl)$_3$]$_2$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] Yield 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**, **9**)

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somewhat limited. For example, Buchwald's attempt to couple 4-bromopyridine hydrochloride with amines (morpholine or *n*-hexylamine) employing mixtures of Pd$_2$(dba)$_3$ and either DPPP or (±)-BINAP were unsuccessful. However, these substrates were efficiently transformed when Pd(OAc)$_2$ was employed as the palladium sources. Thus, the source of palladium as well as the chelating bis-phosphine combination was primarily important for efficient and successful coupling .

In order to optimize our conditions on KF-alumina surface, we attempted hetero-coupling with various combinations of palladium sources as well as the ligands (both monophosphine [(*o*-tolyl)$_3$P] or bis-phosphine (BINAP and DPPF). As given in the Table 2, the Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$ and Pd$_2$(dba)$_3$/(±)-BINAP complexes were found to be most effective in this amination process. The mono-dentate ligand Pd[(*o*-tolyl)$_3$P]$_2$Cl$_2$ worked effectively to couple 2-bromopyridine with different amines. Thus, as anticipated, the formation of bis-(pyridyl) complexes (**19**) using mono-phosphine ligand may possibly be avoided under these conditions. In the case of bicyclic systems, however, the combination of Pd$_2$(dba)$_3$-(±)-BINAP, was found to be better active catalytic system. Several reactions were also studied with the other bis-phosphine ligand, DPPF. Any of the combinations, Pd$_2$(dba)$_3$-DPPF; Pd(OAc)$_2$-DPPF; Pd(acac)$_2$-DPPF, however, did not work better than the BINAP ligand. Surprisingly, our condition did not work efficiently with 3-bromopyridine. Among the various catalytic systems employed for 3-bromopyridine, the Pd$_2$(dba)$_3$-BINAP worked better, which led to the formation of the 3-morpholinopyridine in 48% yield.

We also optimized our reaction conditions with reference to using the solvents. Clean reactions and better yields of the aminopyridines were obtained when the reactions were carried out on KF-Al$_2$O$_3$ surface with a slight excess of amine and without the solvent. Use of toluene or xylene have almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination. Thus, when 4-bromo isoquinoline

coupled with morpholine in presence of $Pd(acac)_2$-DPPF in toluene (2 mL), addition of DMF resulted in formation of isoquinoline in major amount.

I-A.2.3: Conclusion

In conclusion, an expedient procedure for the Pd(0)-catalyzed amination of bromopyridines has been developed on the surface of basic alumina admixed with potassium fluoride. The basic surface offers advantages of avoiding the use of strong bases such as sodium *tert*-butoxide. The catalytic system appears to be more general in terms of mono- or bidentate phosphine ligands. 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. Further application of this procedure may be undertaken with more base-sensitive functionalities on the heterocyclic nucleus as well as with chiral amines. Secondly, the procedure may also be explored in the case of aryl bromides. Studies in this direction are under active pursuit in this laboratory. An account of this investigation has been published in *Tetrahedron Lett.* **2002**, *43*, 7967.

I-A.3: Experimental

I-A.3.1: General remarks

All melting points and boiling points are uncorrected. M.P.s were determined in open capillary in silicone oil bath. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} coated aluminium sheets (Merck, Germany) and spots were detected by UV-fluorescence and/or using iodine vapour. Silica gel G 60 (60-120 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 spectrometer. For recording UV spectra, a Shimadzu UV-240 spectrometer was used. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker spectrometer (operating at 300 or 400 MHz and 75 or 100 MHz respectively) using $CDCl_3$ as solvent. Tetramethysilane (TMS) was used as an 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(dibenzylideneacetone)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(diphenylphosphino)-1,1′-binaphthyl [(±)-BINAP], palladium (II) acetate [$Pd(OAc)_2$], palladium(II) acetylacetone [$Pd(acac)_2$] were purchased from Aldrich Chemical Co.

Preparation of catalysts:

Tris(triphenylphosphino)palladium(II) chloride $Pd[(o\text{-tolyl})_3]_2Cl_2$

To a solution of NaCl (117 mg , 2 mmol) in 5 mL water was added $PdCl_2$ (177 mg, 1 mmol). A complex of Na_2PdCl_4 was immediately formed which is soluble in water. The water was removed by evaporation. The solid complex (Na_2PdCl_4) (250 mg, 0.85 mmol) was taken in ethanol (20 mL) and P(*o*-tolyl)$_3$ (513 mg, 1.7 mmol) was added in

ethanol and then refluxed for a 30 min on a water bath. A yellow precipitate was appeared and was filtered off and washed with (3 x 10 mL) ethanol. The solid complex was dried under vacuo to afford the desired complex $Pd[(o\text{-tolyl})_3]_2Cl_2$ was (520 mg, 65%).

1,1′-Bis(diphenylphosphino)ferrocene [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-liter, three-necked flask equipped with a stirrer, nitrogen inlet and reflux condenser. The solution was stirred for 4 h at room temparature 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 2 h 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 crystals (1.05 g, 38%), m.p.^{obs} 179-182 °C (lit.[198] 183-184 °C).

Preparation of activated Al_2O_3

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

Preparation of activated Al_2O_3/KF

A mixture of basic alumina (Brockmann, Activity I) and KF (4 : 1) (5 g) was taken in distilled THF (5 mL) and after stirring for 30 min 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 h, cooled under N_2 and used for reaction.

Representative procedure for amination: 2-Benzylamino-6-bromopyridine (**52**)

To a mixture of 2,6-dibromopyridine (473 mg, 2 mmol), benzylamine (856 mg, 8 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol) and (±)-BINAP (50 mg, 0.08 mmol) was added activated Al_2O_3/KF (4 : 1) (2 g). The mixture was intimately stirred at 90-100 °C for 8 h under nitrogen. After cooling to room temperature the semi-sold mass was washed repeatedly with ether (4 x 15 mL), combined and concentrated. The residue was purified by silica gel column chromatography (petroleum-ether : EtOAc = 20 : 1) to give 2-benzylamino-6-bromopyridine (**52**) (475 mg, 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 7.36-7.27 (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.

Compounds (**50**)-(**62**) were prepared using similar procedures as mentioned in Table 2.

4-Pyridin-2-yl-morpholine (**50**)[153,169]

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): d 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 (**51**)

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 = 4.5 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, 137.2, 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.

4-(6-Bromopyridin-2-yl)morpholine (53)

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.

8-(6-Bromopyridin-2-yl)-1,4-dioxa-8-aza-spiro[4,5]decane (54)

Yield: 62%, m.p. 99-100 °C.

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

^{1}H-NMR ($CDCl_3$): 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 ($CDCl_3$): 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-1-yl-pyridine (55)

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, 138.6, 113.7, 104.4, 46.7, 25.3.

4-Pyridin-3-yl-morpholine (**56**)[169]

Yield: 48%, liquid

IR (neat): ν_{max} 2966, 1665, 1583, 1496, 1455, 1352, 1255 cm^{-1}

^{1}H-NMR ($CDCl_3$): 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 ($CDCl_3$): δ 146.7, 140.8, 138, 123.4, 122, 66.6, 51.8.

4-(5-Bromopyridin-2-yl)morpholine (**57**)

Yield: 92%, m.p. 84-85 °C.

IR (Nujol): V_{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, 139.7, 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 (**58**)

Yield: 73%, m.p. 83-84 °C.

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

^{1}H-NMR ($CDCl_3$): 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 ($CDCl_3$): δ 157, 148.4, 139.6, 108.4, 107.3, 64.3, 43.5, 34.2.

4-Morpholin-4-yl-isoquinoline (**59**)

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 (**60**)

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($CDCl_3$, 75MHz):δ 144.1, 141.3, 129.5, 129.2, 128.4, 128.0, 127.5, 126.5, 123.8, 52.1, 25.1.

3-Morpholin-4-yl-quinoline (**61**)

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 = 8 Hz), 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 (**62**)

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.

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Part – I: Section – B

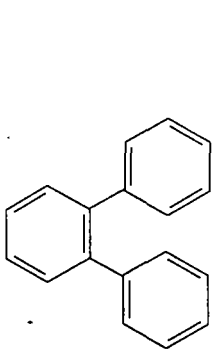
I-B: KF-Alumina Mediated Palladium-Catalyzed C-C Coupling Reaction: Synthesis of Polyaryls

I-B.1: Background, Objectives and Strategy

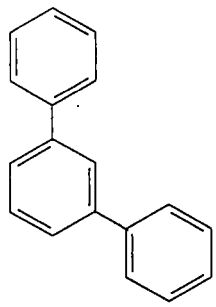
After the initial success of using KF supported on alumina in palladium-catalyzed C–N bond-forming reactions, we became interested to explore its efficacy in C–C bond forming reactions. Although our studies were primarily aimed at the construction of C–N bonds, we extended our studies to C–C forming reaction also as a further application of using KF supported alumina surface. As mentioned in this dissertation (Part–I Section-A) that KF-alumina has been reported to mediate several palladium-catalyzed C–C bond forming processes, such as Heck, Stille, Suzuki coupling reactions,[1] we wanted to extend the Suzuki coupling between polyhaloaromtics with arylboronic acid so as to develop a convenient technique for the synthesis of polyaromatic hydrocarbons (PAH).

I-B.1.1: A Brief Introduction on PAH

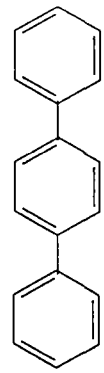
Polycyclic aromatic hydrocarbons (PAH) constitute an enormously large family of organic molecules of widely differing structures.[2] Biaryls and higher homologues are an important class of conjugated polyaromatic compounds, originating from benzene as unique building blocks. On one side, multinuclear aromatics develop the concept of aromaticity and supramolecular benzene chemistry. An excellent review on the supramolecular benzene chemistry has been recently published by Mullen et al.[3] On the other side, the PAH lead to wide applications in material and biological sciences.[4] Polyaryls find several applications as liquid crystals,[4a] laser-dyes[4b] and conducting polymers.[4c,d] For example, the terphenyls (*o*-, *m*-, *p*-isomers) are used industrially as heat storage and transfer agents and as textile dye carriers whilst the *p*-isomer has found application as a laser dye. 9,10-Diphenylanthracene (**1**) is used as a fluorescer in a peroxyoxalate chemiluminescence system.[5]



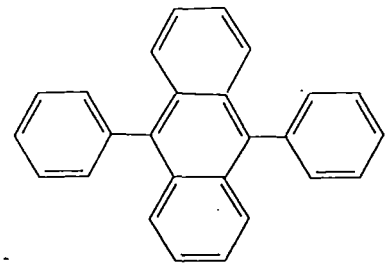
o-Terphenyl



m-Terphenyl



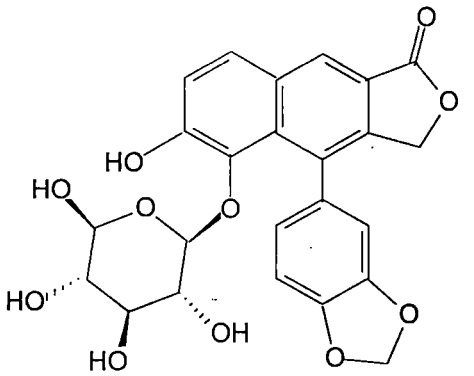
p-Terphenyl



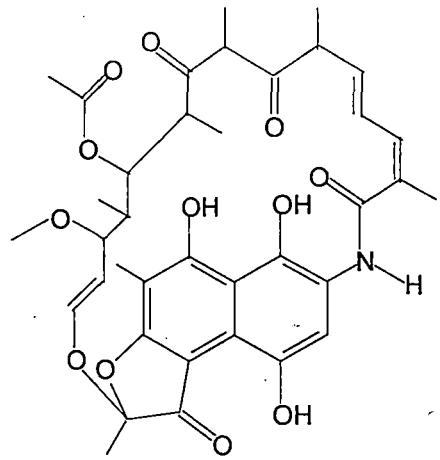
9,10-Diphenylanthracene **(1)**

Polycyclic aromatic hydrocarbons (PAH) are well known as potential carcinogenic compounds. However, it is also known that PAH are soluble in lipid, can be metabolized and can interact with cellular constituents such as proteins and nucleic acids. It is widely accepted that metabolic activation of PAH is responsible for their carcinogenic properties.[2,6] Since they require metabolic activation, they are considered indirect acting carcinogens. While PAH are considered potentially carcinogenic, substituted PAH derivatives, in contrast, may serve as anticancer agents and as chemotherapeutics. In a recent article, Banik and Becker have made clear that suitably substituted polycyclic aromatic compounds can inhibit cancer cell growth even though there was a concept that these are only potential carcinogens.[7] The polycyclic aromatic compounds provide the planar structure suitable to DNA intercalation. Phenanthro[*c*]thiophenes with appropriate substituents have been shown to intercalate with calf thymus DNA specifically at the sites of A–T sequence.[8]

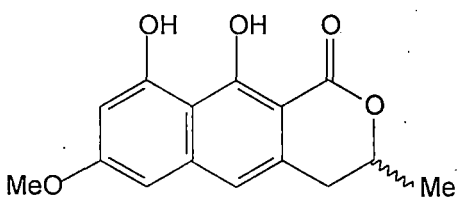
In addition, biaryls and higher homologues are often present as subunits in numerous biologically active natural products, pharmaceuticals and agrochemicals.[9] Polyaromatics also possess original physical properties which could lead to applications as organic conductors or semiconductors.[10] Last but not the least, di- or triaromatic rings are the backbone of some of the most efficient and selective ligands for asymmetric catalysis, especially when atropisometry is possible (such as BINAP or Binaphthylamine). A few structures of the natural products incorporating biaryls and higher homologues are mentioned below:



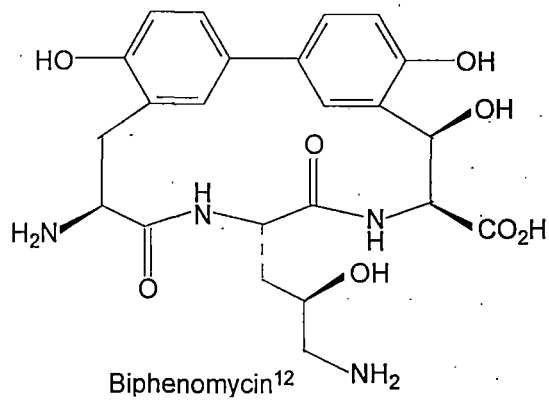
Biaryl system in lignans[9a]



Rifamycin[11]



Semivioxanthin[9d,e]

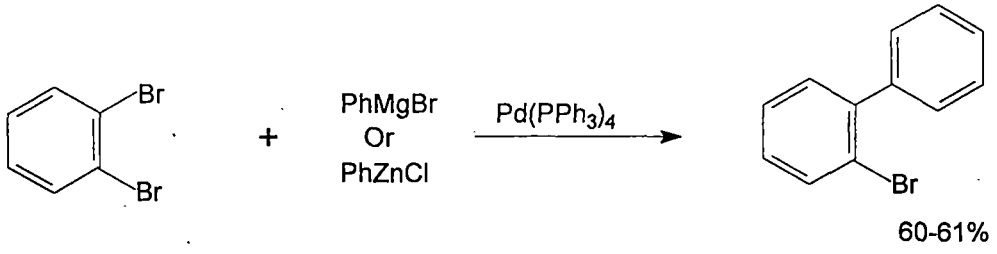


Biphenomycin[12]

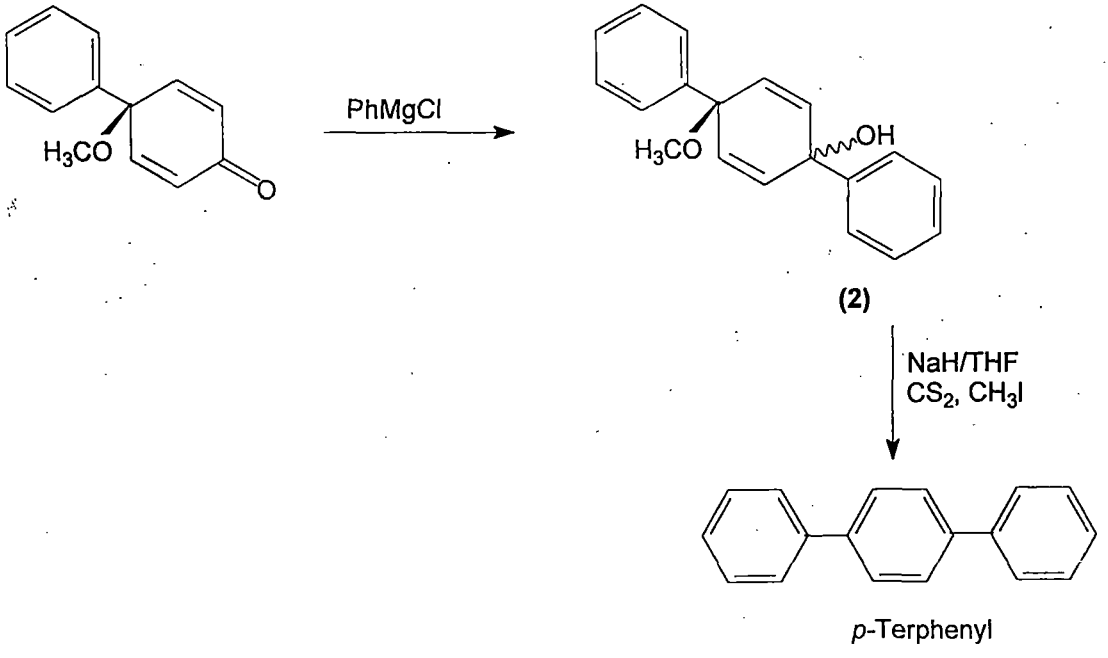
Research on PAH and their derivatives are still receiving attention from synthetic organic chemists, medicinal chemists and biologists. The development of new and convenient synthetic methods for aryl-aryl bond formation has been of considerable interests to organic chemists for many years. An excellent review has been published very recently.[13]

A variety of methods are available for the synthesis of biaryls via coupling of benzene rings promoted by different reagents.[13,14] Transition metal-catalyzed aryl-aryl bond formation is one of the most important tools for preparing biaryls and higher homolouges. The transition metal-catalyzed cross-coupling of Grignard reagents with dihalobenzenes[14b,c] and other methods[14d] produce the desired terphenyls in poor yields. Kumada and coworkers reported selective monoarylation

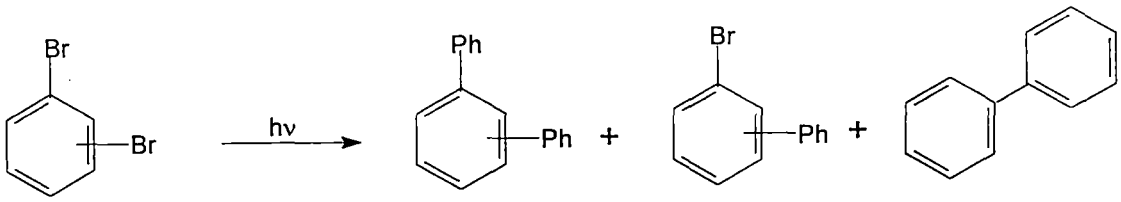
of aromatic dihalides with Grignard and organozinc reagents in palladium-catalyzed reactions.[14c]



Morrow et al.[15] reported an alternative reaction of aryl quinone derivatives with the Grignard reagents and subsequent reductive aromatization of the Grignard adduct (**2**) with triethylsilane could lead to the formation of *p*-terphenyls. Such two-step procedure requires suitable aryl quinone derivatives, which are not ease accessible compounds.

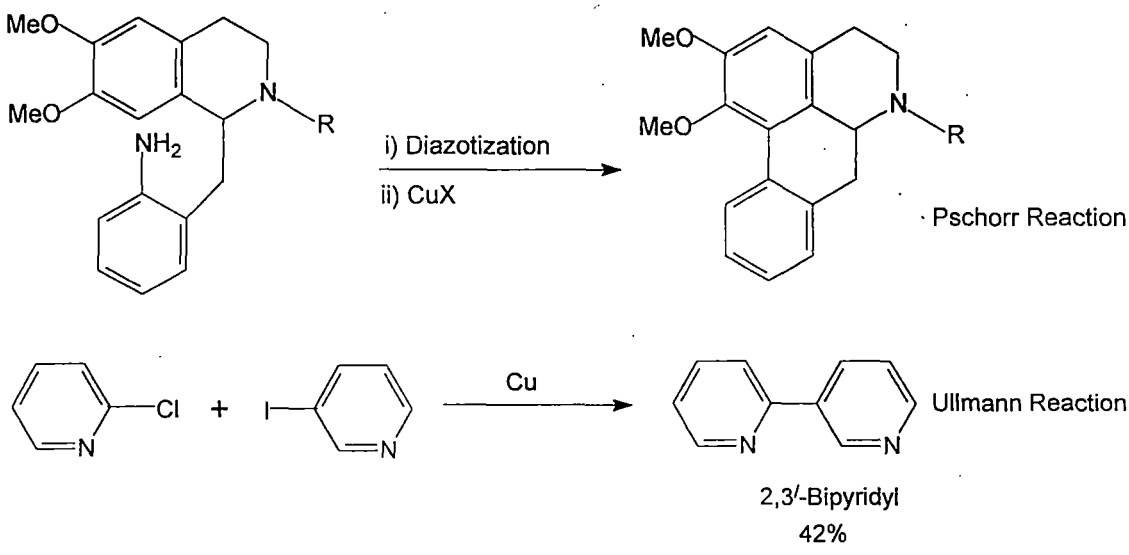


Nakada and coworkers reported that terphenyls can be prepared by photoreaction of polyhalobenzenes.[14d] Such formation of terphenyls is, however, accompanied by monohalobiphenyls and dehalogenated products.



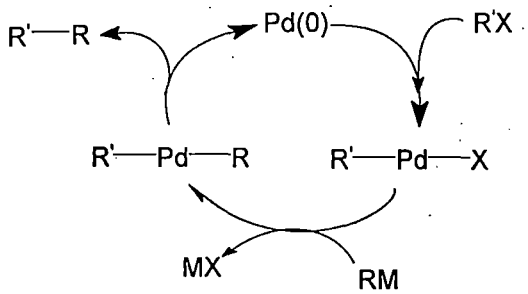
Conditions: 32 W low-pressure Hg are lamp under N_2 atm at 25 °C

The Pschorr reaction and the Ullmann reaction have long been employed by chemists to generate a C–C bond between two aromatic nuclei.[16] The Pschorr reaction involves the intramolecular substitution of arenas by aryl radicals that are generated by the reduction of arene diazonium salts with copper (I) ion. On the other hand, the Ullmann reaction involves coupling between two aryl halides in presence of finely divided copper metal. Generally, the reactions require high temperature (>200 °C) and are not effective for unsymmetrical coupling reactions. The preparation of unsymmetrical biaryls has been made possible via Ullmann reaction, which, however, requires an excess of the "activated" aryl. Several variants in terms of copper metal or copper salts either in stoichiometric amounts or as a catalyst, uses of ligands, lowering the temperature and other reaction conditions have been developed over the last two decades and a comprehensive review is available.[13,17] Since the review articles describe most of the recent advancements in this area, the details of aryl-aryl bond formation reactions need not be discussed here further.



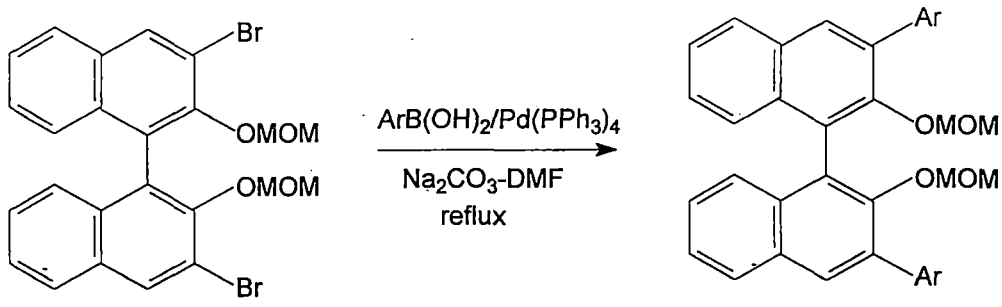
Most of the classical methods are often complicated by harsh reaction conditions, lack of selectivity and generality, or the requirement of expensive reagents. Moreover, many of the methods are not being recognized from the viewpoint of green chemistry. Recent literature reports confirm that palladium-catalyzed Suzuki coupling reactions of aryl halides with aryl boronic acids (or esters) have become convenient and widely used synthetic methods for regioselective aryl-aryl bond formation.[13,14,18] The reasons are manifold: ease of access of the organoboronic species, broad range of functional group tolerance, low toxicity of the inorganic residues, especially compared to tin-containing compounds etc. Several recent reviews described the use of Suzuki methodology, especially one by Suzuki himself – in 1995.[18b] The mechanism of the Suzuki reaction is commonly depicted as a general catalytic cycle involving oxidative addition–transmetallation–reductive elimination sequences (Scheme 1). In this case, oxidative addition is often the rate-limiting step.[18b]

Scheme 1

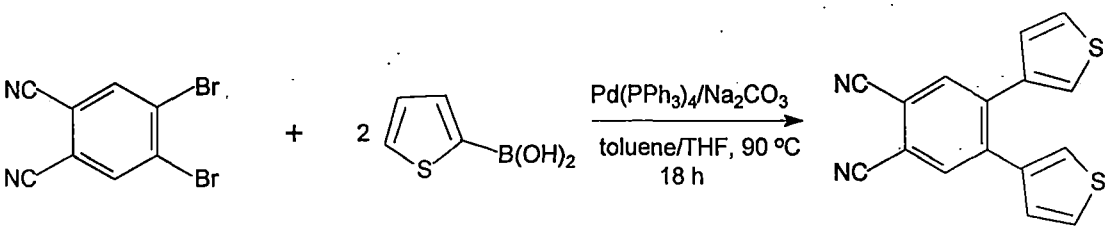


However, although the Suzuki coupling reaction is one of the most useful methods yet developed for the syntheses of both symmetrical and unsymmetrical biaryls, there are still improvements and further applications that could be made to render it more effective. The recent literature shows a vast number of studies on Suzuki reaction parameters including its ample applications after the first report by Suzuki et al. in 1981. Surprisingly, little attempt has been made to investigate consecutive cross-couplings in a one-pot reaction. A few sporadic examples of bis-Suzuki couplings are known in the literature[13,19] and therefore much new research should be extended towards the scope and the amelioration of the economical and ecological parameters of the Suzuki reaction.

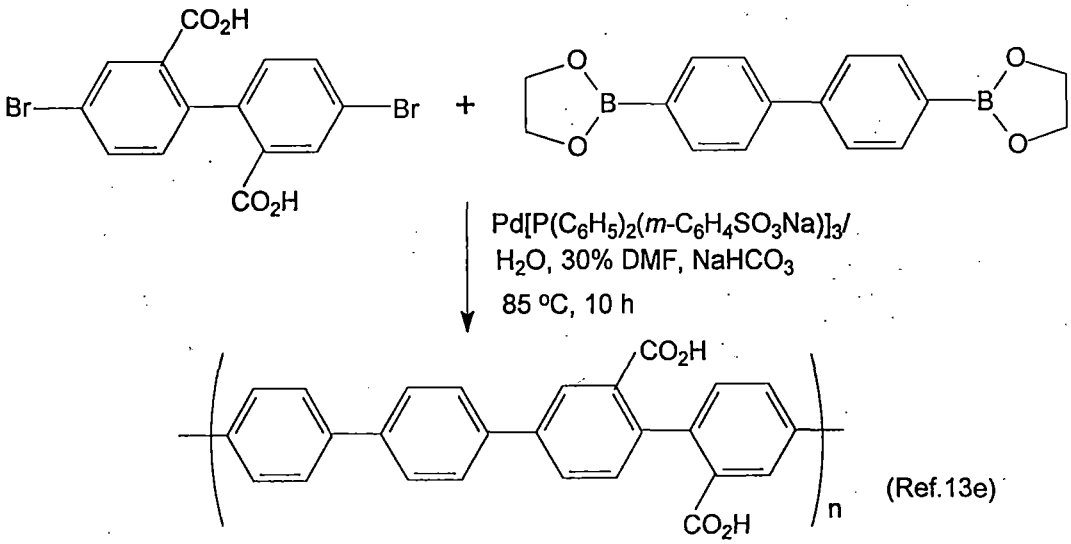
A few examples on bis-Suzuki coupling are given below:



(Ref.13b)

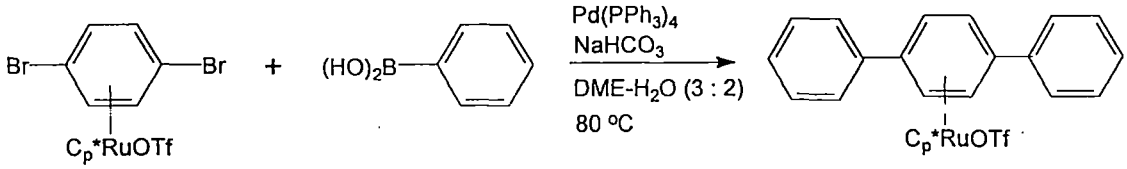


(Ref.3a,c,d)



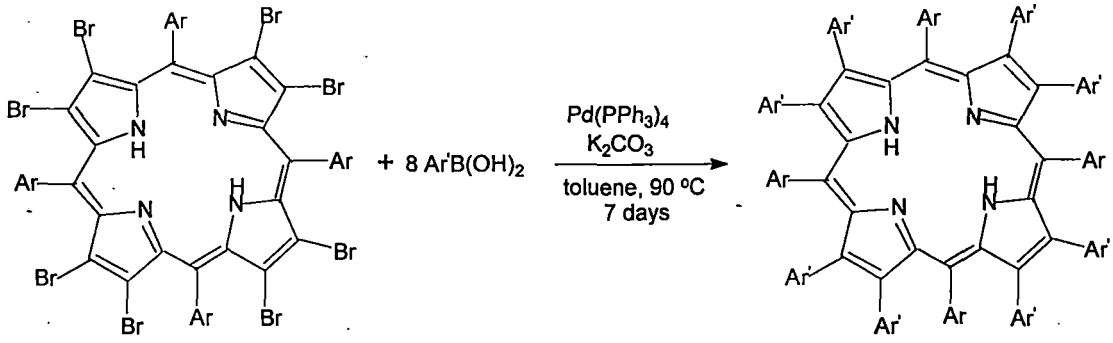
(Ref.13e)

M.W 50,000 (approx) g/mol [Determined by polyamide gel electrophoresis



(Ref.13f)

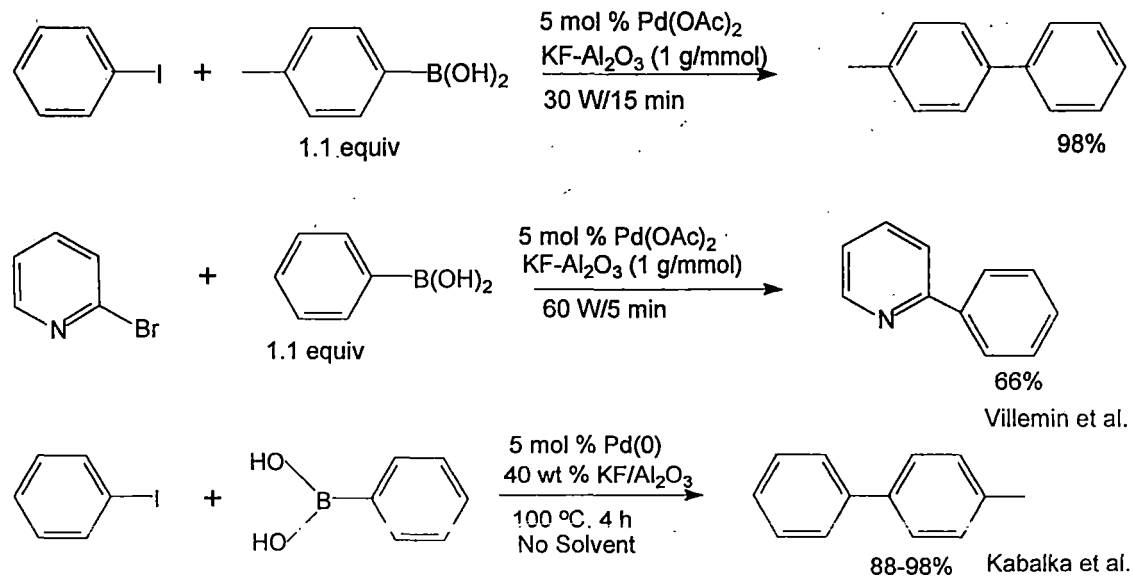
One example of Multi-Suzuki Coupling in one-pot



Ar = 2,4,6-$Me_3C_6H_2$

Ar'	Yield (%)	
p-CF_3Ph	78	(Ref. 13a,19)
p-ClPh	88	

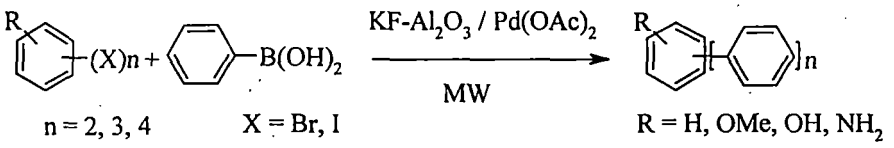
We envisaged that a multi-Suzuki coupling of di-, tri- or tetra-haloaromatics with aryl boronic acids could lead to terphenyls and higher homologues in a one-pot reaction. Kabalka et al.[20] and Villemin et al.[1] reported that Suzuki cross-coupling reactions could be efficiently performed on the surface of KF-alumina with microwave irradiation.



I-B.2: Present Work: Results and Discussion

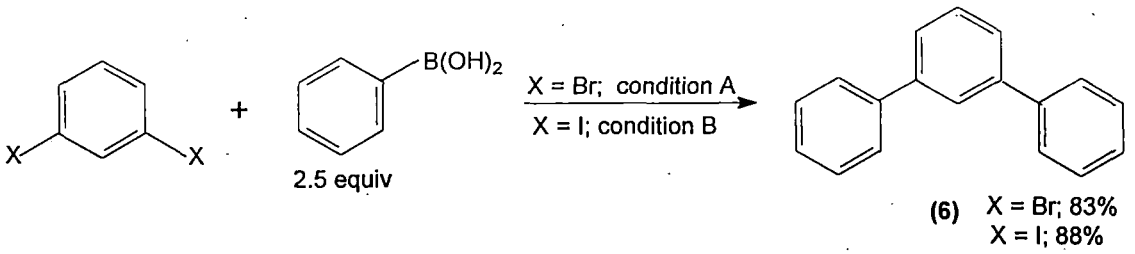
In conjunction with our interest in hetero cross-coupling reactions on KF-alumina surfaces,[21] we investigated microwave-assisted palladium-catalyze coupling of polyhaloaromatics with arylboronic acids on KF-alumina and other inorganic oxides (Scheme 2). In this part of the dissertaion, we report our results, which expand the scope of the Suzuki reaction on a solvent-free inorganic surface leading to the synthesis of a large variety of polyaromatics.

Scheme 2



We initially focused our attention on the cross coupling of dibromoaromatics with phenylboronic acids on KF-alumina using microwave irradiation. The application of microwave in organic reactions is well documented and in many cases, a remarkable activity differences has been noticed.[22] Villemin et al.[1] employed mono-mode irradiation to effect palladium-catalyzed Heck, Stille, Trost–Tsuji and Suzuki coupling reactions promoted on a solvent-free surface of KF-alumina. As expected, they obtained better yields of the biphenyl derivatives from aryl iodides as compared to aryl bromides or chlorides. Palladium acetate was used as the precursor of the catalyst.

As can be seen from the results presented in Table 1, the dibromobenzenes afforded the corresponding terphenyls as the major products (entries 1-3). Varying amounts of mono-substituted biaryls (15-20%) were detected on TLC, which could be easily separated from the terphenyls by column chromatography. While comparing the reaction rate between dibromo- and diiodoarenes (entries 2 and 4), the latter afforded the corresponding terphenyl **6** in a slightly better yield. However, different conditions were required to accomplish the desired bis-coupling.

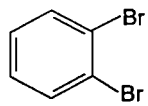
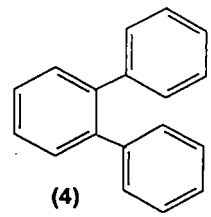
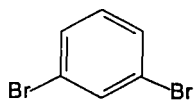
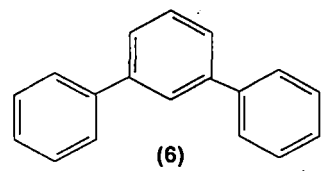
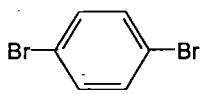
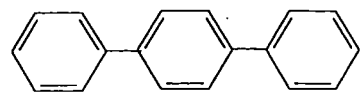
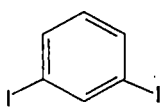
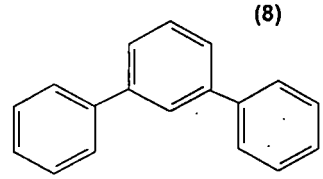
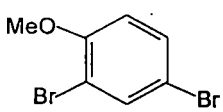
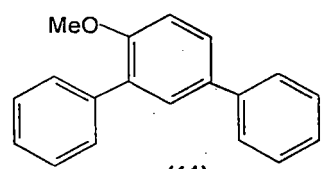
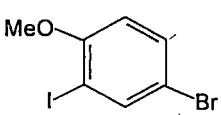
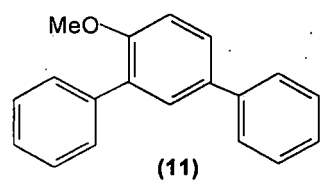
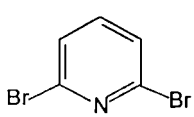
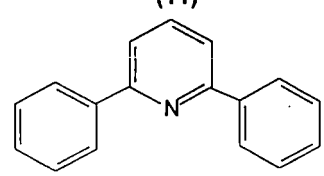
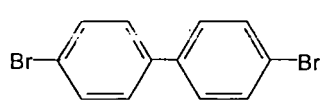
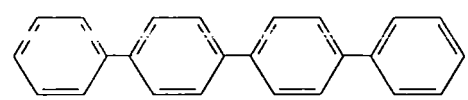


(6) X = Br; 83%
X = I; 88%

Conditions A: $Pd(OAc)_2$ (4 mol %), KF-Al_2O_3 (1.5 g/mmol), 80 W/15 min; B: $Pd(OAc)_2$ (4 mol %), KF-Al_2O_3 (1.5 g/mmol), 320 W/7 min.

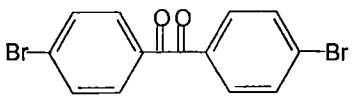
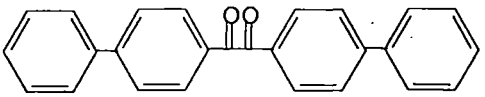
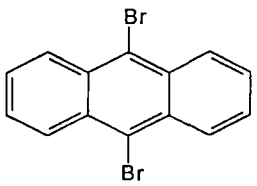
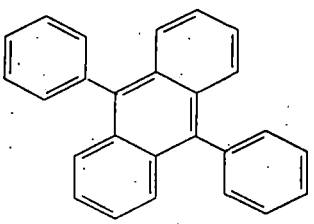
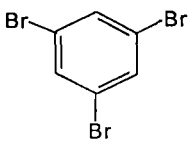
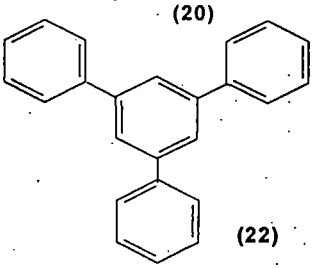
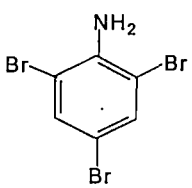
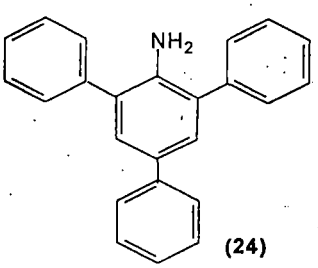
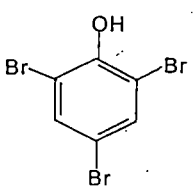
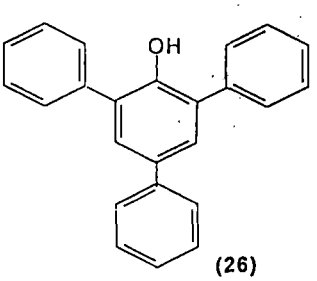
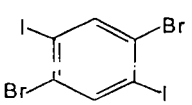
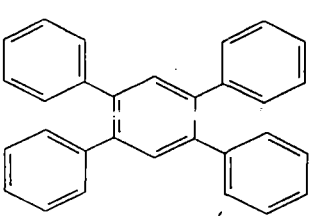
2,4-Dibromoanisole (**10**) and 4-bromo-2-iodoanisole (**12**) afforded the terphenyl (**11**) in almost comparable yields. Thus, no significant reactivity difference between bromo- and iodo- substituents was observed. Among the other dibromoarenes, 2,6-dibromopyridine (entry 7) and 9,10-dibromoanthracene (entry 10) yielded the desired products (**14**) and (**20**) respectively, in excellent yields. The biphenyl systems (entries 8 and 9) produced the corresponding products (**16**) and (**18**) in yields of 50-60%. In the case of tribromoaromatics (entries 11–13), the corresponding tris-coupled compounds (**22**), (**24**) and (**26**) were isolated as the major products (Table 1). Small amounts of mono- or bis-coupled products were detected by TLC. The 1,4-dibromo-2,5-diiodobenzene (**27**) yielded the tetraphenylbenzene (**28**) in 55% yield (entry 14). Villemin and co-workers obtained their best results on Suzuki couplings with aryl iodides using mono-modemicrowave irradiation.[1] Our conditions using KF-alumina (1 : 4) and irradiation from a domestic microwave oven, however, enabled polyarylations in good to excellent yields.

Table 1. Solid-supported [KF-Al_2O_3] polyarylations of polyhaloaromatics with phenyl boronic acid using catalytic $Pd(OAc)_2$ under microwave irradiation.

Entry	Haloaromatics	Conditions Power (W)/ Time	Products [a]	% Isolated Yield[b]
1.	 (3)	80 W / 10 min	 (4)	58
2.	 (5)	80 W / 15 min	 (6)	83
3.	 (7)	160 W / 15 min	 (8)	63
4.	 (9)	320 W / 7 min	 (6)	88
5.	 (10)	80 W / 20 min	 (11)	63
6.	 (12)	80 W / 20 min	 (11)	65
7.	 (13)	160 W / 10 min	 (14)	91
8.	 (15)	400 W / 5 min	 (16)	53

Continued.....

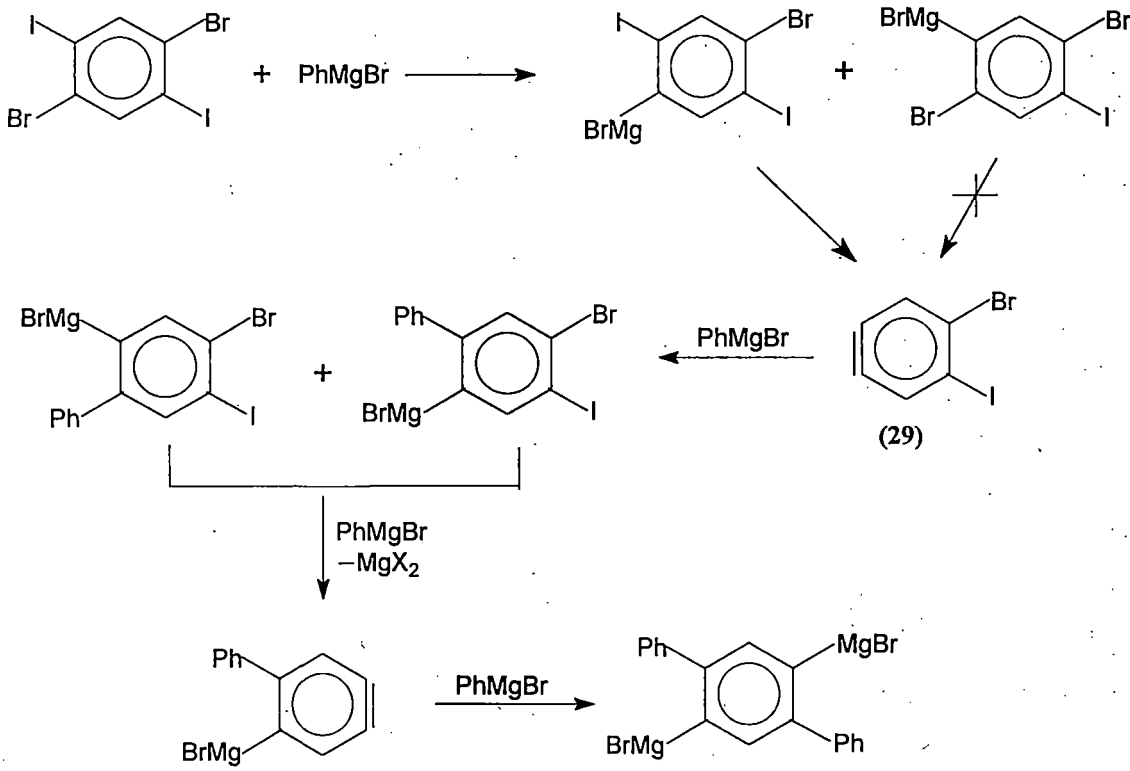
Continued..... **Table 1**

Entry	Haloaromatics	Conditions Power (W)/ Time	Products [a]	% Isolated Yield [b]
9.	 (17)	240 W / 10 min	 (18)	58
10.	 (19)	320 W / 10 min	 (20)	88
11.	 (21)	240 W / 7 min	 (22)	90
12.	 (23)	240 W / 10 min	 (24)	75
13.	 (25)	240 W / 10 min	 (26)	76
14.	 (27)	320 W / 7 min	 (28)	55

All the products gave satisfactory spectral data (^{1}H- and ^{13}C-NMR) and the unknown compounds were compared with reported mps;[b] Yields refer to the average from 2-3 runs.

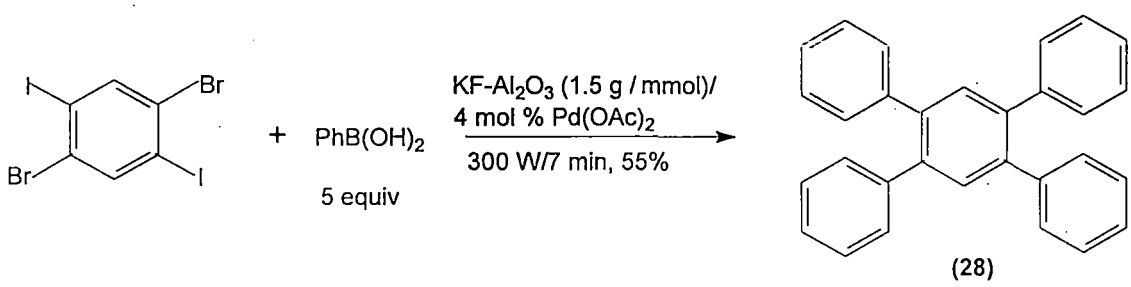
The reaction of 1,4-dibromo-2,5-diiodobenzene with an excess of aryl Grignard reagent gives *p*-terphenyl instead of 1,2,4,5-tetraarylbenzene (**28**). Hart and coworkers[23] explained this experimental finding assuming the formation of benzyne intermediate (**29**) (Scheme 3). On the other hand, reaction of 1,4-dibromo-2,5-

Scheme 3



diiodobenzene with an excess of arylboronic acid using our conditions furnished (**28**) in 55% yield (Scheme 4).

Scheme 4



In order to test the effective role of KF-alumina, we also examined such poly-Suzuki couplings on other inorganic surfaces (Table 2). The results were best on the surface of KF-alumina (1 : 4). The reactions were carried out in air. All the reactants were intimately mixed with the inorganic surface before being placed in a domestic microwave oven (Kenstar; Model OM-9925E) and irradiated at the appropriate power (W) and time (Table 1). In many Suzuki cross-couplings, a crucial role is played by the ligands,[24] which complex with palladium salts. The above solvent-free conditions, however, required no such ancillary ligands, which is advantageous in view of atom economy in the reaction.

Table 2. Multi-Suzuki reactions on different inorganic surfaces under microwave irradiation without solvent [A/B/$Pd(OAc)_2$ = 1/ 2.5/ 0.04 mmol on 1.5 g of B]

Entry	Substrate (A)	Surface (B)	Conditions	Yield (%)
1	1,3-Dibromobenzene	KF-Al_2O_3 (1:4)	80 W/15 min.	83
2	1,3-Dibromobenzene	Al_2O_3	80 W/15 min.	20-25
3	1,3-Dibromobenzene	MgO	80 W/15 min.	25
4	1,3-Dibromobenzene	MgO-K_2CO_3 (3:2)	80 W/15 min.	30

I-B.3: Conclusion

In summary, it is possible to perform palladium-catalyzed Suzuki couplings of polyhaloaromatics with phenyl boronic acid on a surface of KF-alumina with the aid of microwave irradiation from a domestic microwave oven. The method is fast, operationally simple, and allows rapid access to a variety of polyaromatic hydrocarbons. Further applications of this reaction conditions would be studied with aromatic halides bearing more labile functional groups as well as with aryl diboronic acids. The latter studies might produce oligomeric polyaromatic compounds via consecutive aryl-aryl bond formations. Efforts are underway in this laboratory.

I-B.4: Experimental

Representative procedure for a multi-Suzuki coupling: 1,3-Dibromobenzene **5** (236 mg, 1.0 mmol), phenyl boronic acid (305 mg, 2.5 mmol) and palladium acetate (10 mg, 0.04 mmol) were intimately mixed with 1.5 g of KF-alumina (prepared according to ref. 21) and the mixture was irradiated in a domestic microwave oven at 80 Watt for 15 min. The solid mixture was then placed on a silica gel column and eluted with petroleum ether : EtOAc (99 : 1) to furnish *m*-terphenyl **6** (190 mg, 83%); mp 87-88 °C (lit.[25] 89 °C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.30–7.84 (m, 14H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 126.1, 127.2, 127.4, 128.8, 129.2, 141.1, 141.7.

The other compounds (**4**, **8**, **11**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**) were prepared following the above procedure and their characterization data are given below.

1,2-Diphenylbenzene (**4**)

Yield: 58%, m.p. 54-56 °C [lit.[26] 58 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.43-7.37 (m, 4H), 7.18-7.10 (m, 10H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 141.5, 140.5, 130.6, 129.8, 127.8, 127.4, 126.4.

1,4-Diphenylbenzene (**8**)

Yield: 63%, m.p. 210-212 °C [lit.[15] 215-217 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.67-7.63(m, 8H), 7.48-7.43 (m, 4H), 7.38-7.32 (m, 2H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

2,4-Diphenylmethoxybenzene (**11**)

Yield: 63%, m.p. 88-90 °C

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.58-6.99 (m, 13H), 3.80 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 156.0, 140.6, 138.4, 133.8, 131.0, 129.7, 128.7, 128.0, 127.0, 126.7, 111.5, 55.6.

2,6-Diphenylpyridine (**14**)

Yield: 91%, m.p. 78-81 °C [m.p.[27] 82 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.17-8.13 (m, 4H), 7.85-7.80 (m, 1H), 7.71-7.68 (m, 2H), 7.53-7.40 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 156.8, 137.5, 129.0, 128.7, 127.0, 118.7.

4,4′-Diphenylbiphenyl (**16**)

Yield: 53%, m.p. 318-320 °C [lit.[28] 320 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.72–7.37 (m, 18H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 131.9, 128.8, 128.6, 127.6, 127.5, 127.4, 127.3, 127.0.

4,4′-Diphenylbenzil (**18**)

Yield: 58%, m.p. 140-142 °C

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, 4H, J = 8.25), 7.76-7.73 (d, 4H, J= 8.22 Hz), 7.66-7.62 (m, 4H), 7.52-7.42 (m, 6H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.6, 139.5, 132.5, 131.7, 131.3, 130.5, 129.0, 128.6, 127.7

9,10-Diphenylanthracene (**20**)

Yield: 88%, m.p. 245-247 °C [lit.[5] 245-248 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.71–7.31 (m, 18H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 131.3, 129.8, 128.4, 127.5, 126.9, 125.0

1,3,5-Triphenylbenzene (**22**)

Yield: 90%, m.p. 169-171 °C [lit.[29] 172 °C]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.79–7.69 (m, 9H), 7.51-7.39 (m, 9H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 142.3, 141.1, 128.8, 127.5, 127.3, 125.1.

2,4,6-Triphenylaniline (**24**)

Yield: 90%, m.p. 118-120 °C

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.60-7.24 (m, 17H), 3.56 (s,2H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 140.7, 139.4, 131.6, 129.4, 128.9, 128.8, 128.7, 128.4, 127.5, 126.4.

2,4,6-Triphenylphenol (**26**)

Yield: 76%, m.p. 142-144 °C

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.65-7.34 (m, 17H), 5.48 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 148.9, 140.5, 137.5, 133.8, 129.4, 129.2, 129.1, 128.8, 128.6, 128.1, 127.8, 127.0, 126.9, 126.8

1,2,4,5-Tetraphenylbenzene (**28**)

Yield: 55%, m.p. 240-245 °C

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.46 (m, 4H), 7.18–7.16 (m, 18H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 140.9, 139.6, 133.0, 129.9, 127.9, 126.6.

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Part - II: Section - A

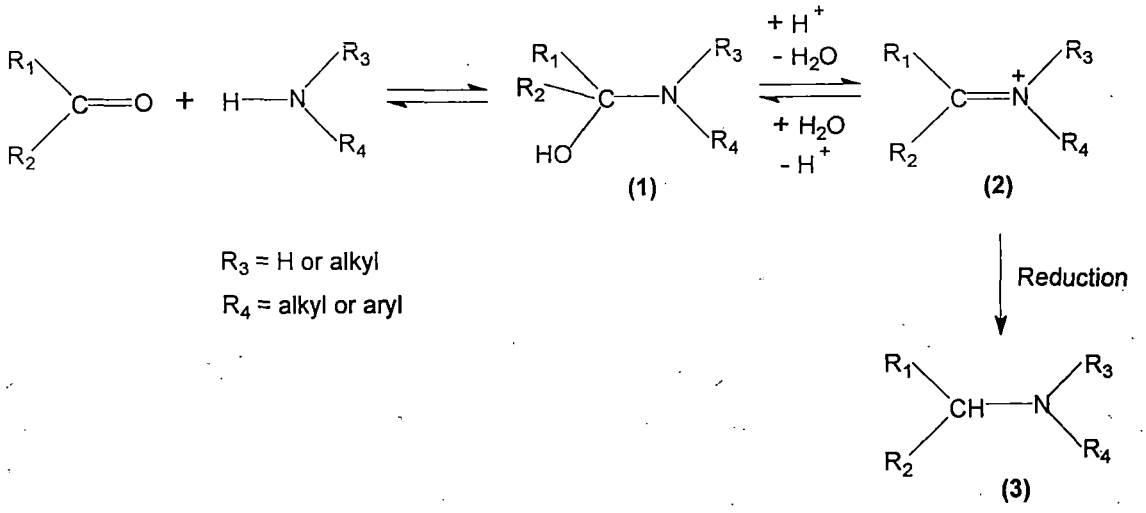
II-A: Direct Reductive Amination of Aldehydes and Ketones Using Potassium Formate and Catalytic Palladium Acetate: Development of a New and Simple Protocol

II-A.1: Reductive Amination: A Brief Review

The synthesis of amines and their derivatives has long been of interest because of their versatile utility as medicinal agents and agrochemicals.[1] Alkyldiarylamines are common structural elements found in many biologically active compounds. Examples include the antipsychotic agent mosapramine, the coronary vasodilator pretiadil, and the anti-inflammatory agent mepheclocine.[2] Tertiary amines are an extremely important class of compound from the drug discovery perspective. Indeed no less than a quarter of registered drugs contain tertiary amines.[3] The *N,N*-dimethylalkylamines are particularly useful as ligands[4] in homogeneous catalytic asymmetric transformation, as a modifier[5] for reversed phase chromatography, and as a buffer[6] in sequential analysis of proteins and peptides.[7]

In both biological systems and chemical synthesis the reductive amination of aldehydes and ketones is an important transformation which allows the direct conversion of carbonyl compounds into amines. The reductive amination reaction is described as a direct reaction when the carbonyl compound and the amine are mixed with proper reducing agent in a single operation (Scheme 1). The reaction involves the initial formation of the intermediate carbinol amine (**1**), which dehydrates to form an imine (**2**). Under the reaction conditions, which are usually weakly acidic to neutral, the imine is protonated to form an iminium ion (**2**),[8] which is subsequently reduced to produce the alkylated amine (**3**). However, there are some reports that provide evidence suggesting a direct reduction of the carbinol amine as a possible pathway leading to alkylated amine (3).[9] A stepwise or indirect reaction involves the pre-formation of the intermediate imine followed by reduction in a separate step.

Scheme 1

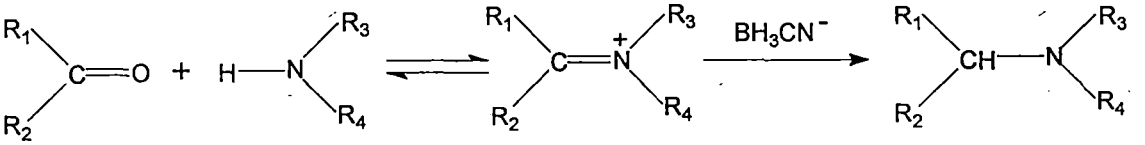


Since the iminium ion (**2**) is reduced much faster than a carbonyl group, it is possible to reductively aminate an aldehyde or ketone by simply reacting the carbonyl compound with an amine at pH 6-8 in the presence of a reducing agents. Several reagents which effect direct reductive amination have been recently developed, include the following: Hydrogen in presence of metal catalyst (catalytic hydrogenation),[8a,10] sodium cyanoborohydride,[11] titanium(IV) isopropoxide-sodium cyanoborohydride,[12] sodium borohydride-magnesium perchlorate,[13] zinc-acetic acid,[14] borohydride exchange resin (BER),[15] zinc bororohydride-zinc chloride,[16] borane-pyridine,[17] sodium triacetoxyborohydride,[18] silica gel-zinc borohydride,[19] zinc chloride-sodium borohydride,[20] titanium(IV) isopropoxide-sodium borohydride,[21] nickel chloride-sodium borohydride,[22] titanium(IV) isopropoxide-polymethylhydrosiloxane,[23] decaborane,[24] tributyltin hydride,[25] dibutyltin chloride hydride and dibutyltin iodide hydride,[26] dibutyltin dichloride-phenylsilane,[27] Et_3SiH-trifluoroacetic.[28] In addition, there are some reports of electrochemical reductive amination reactions.[29] Reductive *N*-alkylation of amides with carbonyl compounds using Et_3SiH-trifluoroacetic acid has also been described.[30]

The catalytic hydrogenation of C-N double bond with platinum, palladium or nickel catalysts[10] is economical and effective reductive amination method, particularly in large scale reactions. However, the reaction may give a mixture of products and low

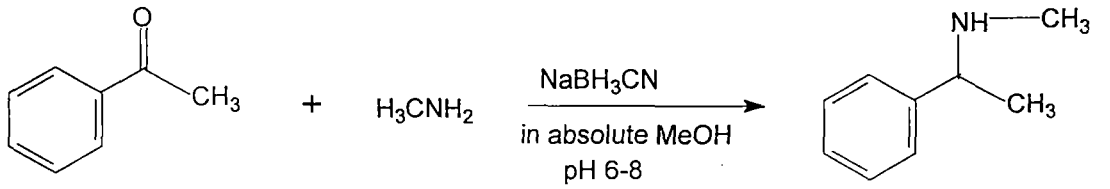
yields depending on the molar ratio and the structure of the reactants[31]. Hydrogenation has limited use with compounds containing C-C multiple bonds and in the presence of reducible functional groups such as nitro[32,33] and cyano[33] groups. The catalyst may be inhibited by compounds containing divalent sulfur.[34] The Borch reduction,[35a] using sodium cyanoborohydride [$NaBH_3CN$] has been the most popular and general method to carry out reductive amination of aldehydes and unhindered ketones with ammonia, primary and secondary amines (Scheme 2). Hindered and diaryl ketones fail to react and aromatic amines react somewhat sluggishly. Reductive amination of acetophenone and methylamine with sodium cyanoborohydride afforded *N*-methyl-1-phenylethylamine (**4**) in 78% yield. Due to its different selectivities at different pH values sodium cyanoborohydride is allowed for a convenient direct reductive amination procedure. At pH 3-4 it reduces aldehydes and ketones effectively, but this reduction becomes slow at higher pH values.[35b] At pH 6-8, the more basic imines are protonated preferencially and reduced faster than aldehydes or ketones.[35a] It has also been successfully used due to its stability in relatively strong acid solutions (~pH 3), its solubility in hydroxylic solvents such as methanol. The reaction of a dicarbonyl compound with an amine in the presence of sodium cyanoborohydride provided an interesting synthesis of nitrogen-heterocycles, as illustrated by the preparation of **5, 6.**

Scheme 2

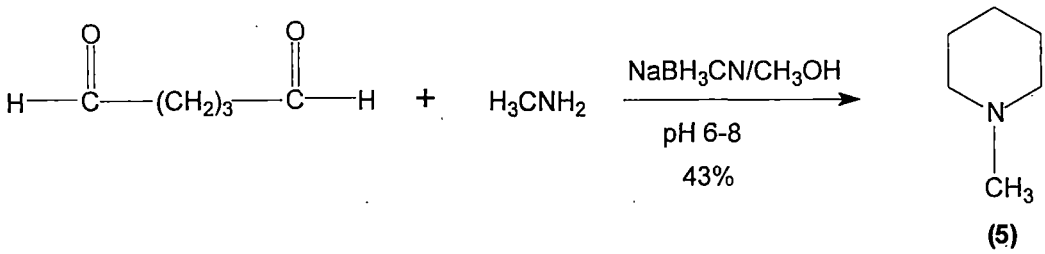


R_1 = H or alkyl R_3 = H or alkyl

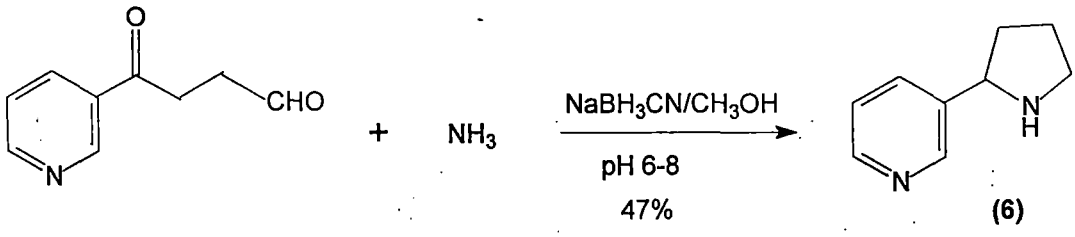
R_2 = alkyl or aryl R_4 = H, alkyl or aryl



(4) 78%



(5)

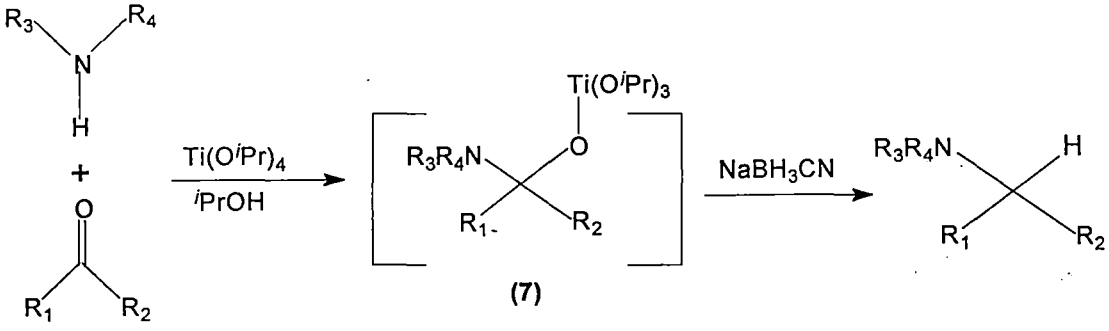


(6)

Limitations are that the reaction may require up to a fivefold excess of the amine,[35] is usually slow and sluggish with aromatic ketones[35] and with weakly basic amines,[36] and may result in the contamination of the product with cyanide.[17b] The reagent is highly toxic[37] and produces toxic byproducts such as HCN and NaCN upon workup.

The Borch reductive alkylation method[35a,c,d] works well provided the intermediate iminium adduct forms readily. For this reason the Borch procedure usually requires an excess of amine to favor the formation of iminium intermediates. When both the ketone and amine starting materials are valuable or the iminium intermediate is difficult to form, the Borch method can be less than satisfactory. Titanium(IV) chloride has been used as a Lewis acid catalyst in cases when the formation of enamines has proven to be difficult,[38] however, an excess of amine is still needed[39] and the presence of acid-sensitive functionality is limited. Titanium(IV) isopropoxide has been used as a trans-esterification catalyst compatible with variety of functional groups, such as lactam, acetonide, and *tert*-butyl dimethylsilyl ether.[40] The research group of Mattson[13] reported that titanium(IV) isopropoxide is a mild and effective Lewis acid catalyst for the reductive alkylation of amines with ketones and aldehydes in the presence of acid-sensitive functional groups (Scheme 3). This one-pot procedure proved to be compatible with carbamate, urea, acetal, ketal, ester, and amide groups. After studying IR spectra of the amine/ketone/titanium(IV) isopropoxide mixtures they suggested that an iminium species is, at most, a transient

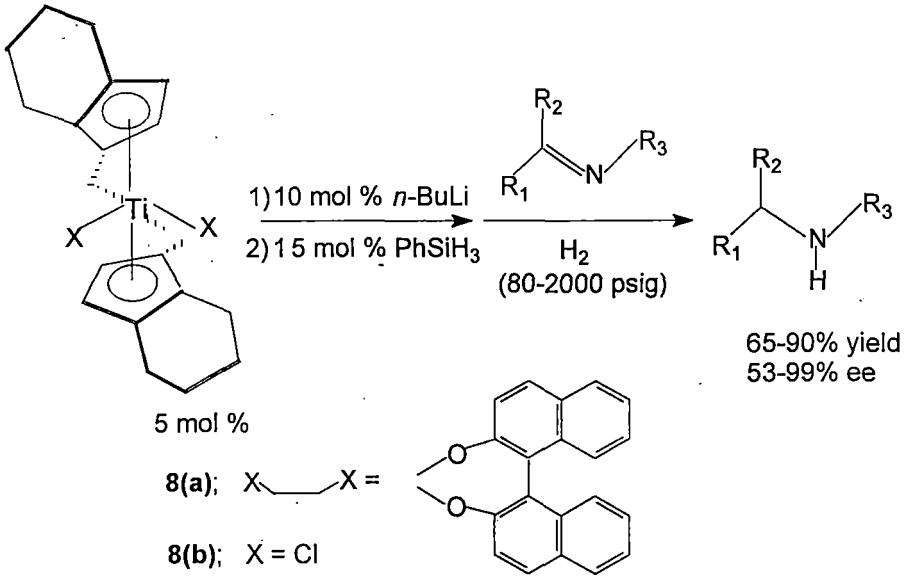
Scheme 3



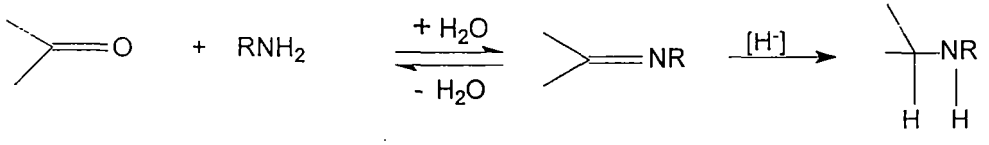
intermediate in this reaction. In one possible mechanism, the stable complex (7) is formed, which then is reduced either directly or via a transient iminium species.

The development of asymmetric catalysts for the hydrogenation of achiral substrates to form enantiomerically enriched products represents a major area of research[41]. With the growing importance of enantiomerically pure nitrogen containing compounds in the pharmaceutical and agrochemically enriched amines has received much attention recently[42]. Processes have been developed using titanium,[43] ruthenium,[44] iridium[45] and rodium[46] complexes as catalysts and hydrogen or silanes[47] as stoichiometric reducing agents. Virtually all of the systems employed for this reaction have been derived from late transition metals and in general substrates must possess a coordinating ligand such as a carbonyl group for high levels of reactivity and selectivity to be realized. As part of an ongoing study of the viability of titanium catalysts for the reduction of unsaturated organic compounds,[48] Buchwald et al have discovered a titanocene catalyst (8) system for the asymmetric hydrogenation of imine (Scheme 4).[49] A feature of this system is that no coordinating group is necessary for high levels of enantioselectivity to be achieved. The catalyst (8) is particularly effective for the reduction of cyclic imines. For these substrates enantiomeric excesses were observed. The reason for this is likely due to the fact that the acyclic imines are mixtures of anti and syn isomers which interconvert during the reaction. The system exihibits tolerance to several common organic functional groups including trisubstituted olefines, acetals and alcohols.

Scheme 4



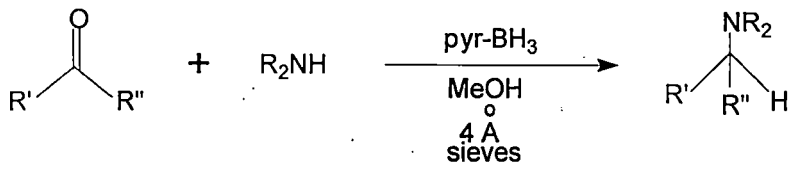
The *in situ* reductive amination of ketones or aldehydes has been an important part of the synthetic chemist's repetoire since the introduction of a procedure based on cyanobohydride,[35b,d,36] yet the toxicity and disposal problems associated with this material has led to a continuing search for alternative reductants.[11c,15,16,50] A successful reductive amination procedure for ketones and aldehydes hinges on rapid imine formation and imine selective reductants. As imine formation is usually rate-determining for *in situ* reductive aminations, catalyzing this reaction is desirable.[51] Typical catalysts are harse, for example, PCl_5,[52] $BF_3{\cdot}OEt_2$,[53] and $ZnCl_2$,[54] with at least one exception - molecular sieves. The *in situ* application of molecular sieves to imine synthesis is logical given the equivalent of water generated during imine formation.[55] Westheimer, however, recognized that molecular sieves display a catalytic role,[56] although the origin of this effect has been contested.[57]



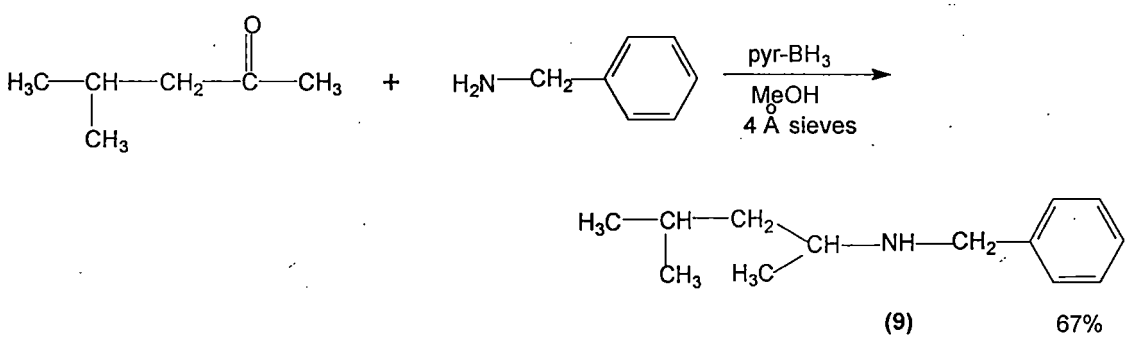
A member of the amine-borane family of reducing agents,[58] pyridine-borane has the selectivity necessary for reductive aminations. Two applications of pyridine-borane to

direct reductive amination have appeared. The study of Moormann was limited to reductive amination of piperidines with aldehydes.[17b] The older and broader study of Pelter exploited an unusual two-phase reaction medium of acetic acid, presumably a catalyst for imine formation, and petroleum ether (2:7).[17a] DiMare et al[17c] reported that *in situ* reductive aminations of aldehydes and ketones with methanolic pyridine-borane in the presence of 4 Å molecular sieves offer a mild, convenient and effective alternative to cyanoborohydride-based procedures (Scheme 5).

Scheme 5



This procedure works well in case of aliphatic ketones. For example, the reaction of 4-methyl-2-pentanone and benzylamine under this condition afforded the amine (**9**) in 67% isolated yield. Secondary amines give consistently low yields with ketones.

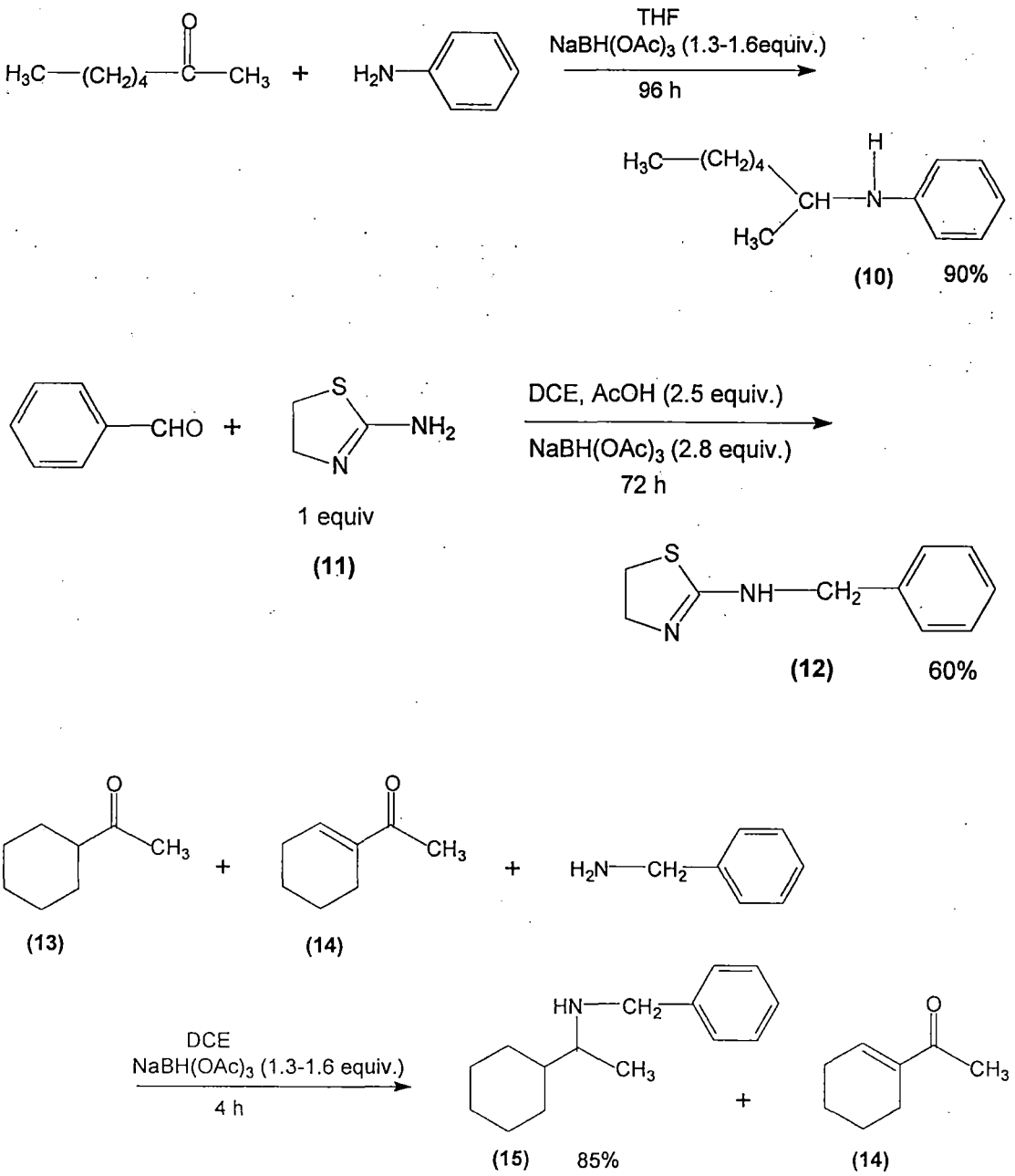


(9) 67%

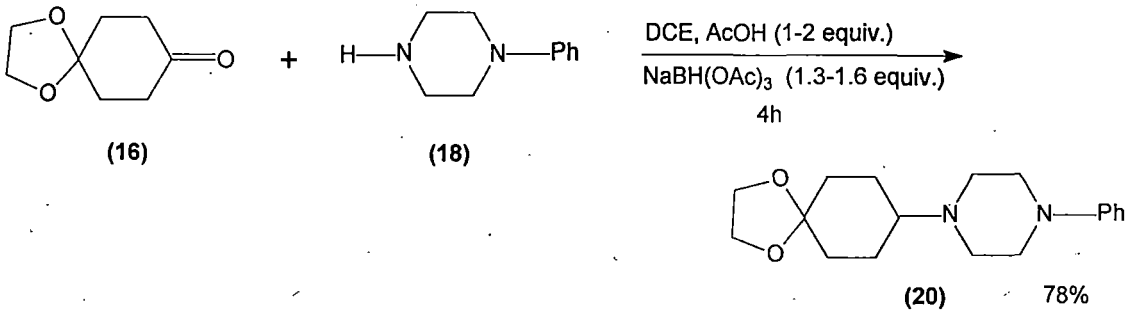
The research group of Abdel-Magid[18] discovered that sodium triacetoxyborohydride is synthetically useful reagent for reductive amination of aldehydes and ketones. Procedures for using this mild and selective reagent have been developed for a wide variety of substrates. The reaction of acyclic ketone 2-heptanone and aniline for 96 h in the presence of sodium triacetoxyborohydride afforded 90% isolated yield of *N*-phenyl-2-aminoheptane (**10**) as outlined in Scheme 6. The scope of the reaction includes aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, and primary and secondary amines including a variety of weakly basic and nonbasic amines. For example, the reductive amination of benzaldehyde and 2-aminothiazole

(**11**) using sodium triacetoxyborohydride gave compound (**12**) in 60% yield. Aliphatic ketones (and aldehydes) can be selectively reductively aminated in the presence of aromatic and α,β-unsaturated ketones. The mixture of 1-acetylcyclohexane (**13**) and 1-acetylcyclohexene (**14**) was reacted with benzylamine to give only *N*-[1-(cyclohexyl)-ethyl]benzylamine (**15**) without aminating 1-acetylcyclohexene (**14**). Acetic acid may be used as catalyst with ketone reactions, but it is generally not needed with aldehydes.

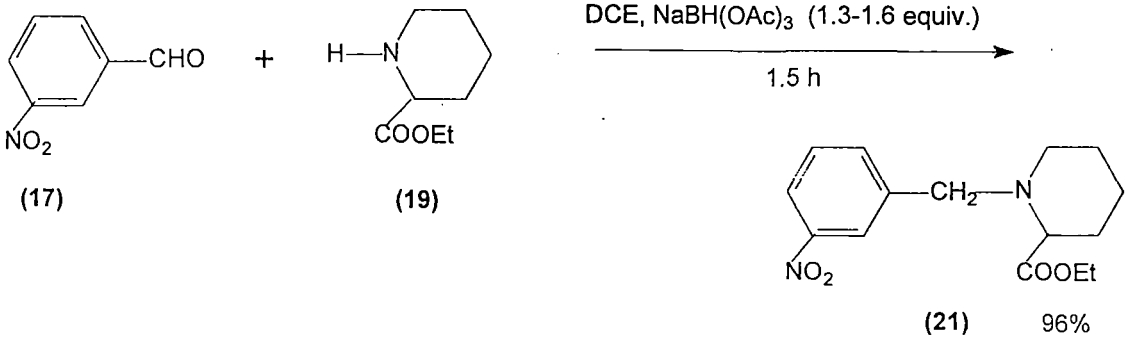
Scheme 6



This borohydride reagent is mild and exhibits remarkable selectivity as a reducing agent. This borohydride reduces aldehydes selectively over ketones,[59] except for β-hydroxy ketones which can be reduced selectively to give 1,3-trans diols.[60] The steric and the electron-withdrawing effects of the three acetoxy groups stabilize the boron-hydrogen bond and are responsible for its mild reducing properties.[61] The selection was also based on the results of reductive alkylation of amines using sodium borohydride in neat liquid carboxylic acids reported earlier by gribble et al.[62] The procedure is carried out in the presence of acid sensitive functional groups such as acetals and ketals; it can also be carried out in the presence of reducible functional groups such as C-C multiple bonds and cyano and nitro groups. Reductive amination of carbonyl compounds (**16** & **17**) with *sec*-amines (**18** & **19**) under the same condition afforded compounds **20** & **21** respectively. In comparison with other reductive amination procedures such as $NaBH_3CN/MeOH$, borane-pyridine and catalytic hydrogenation, $NaBH(OAc)_3$ gave consistently higher yields and fewer side products.



(16) (18) (20) 78%

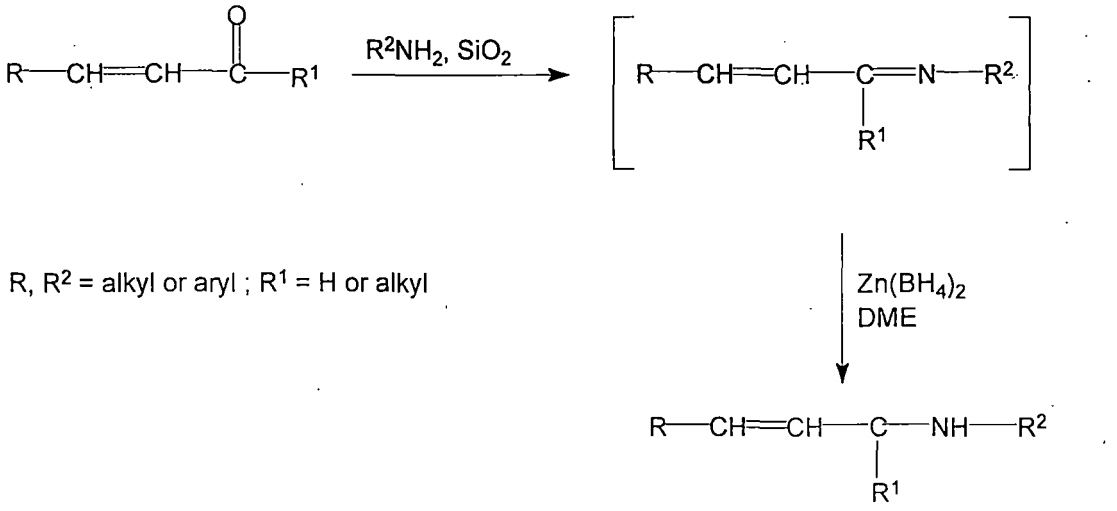


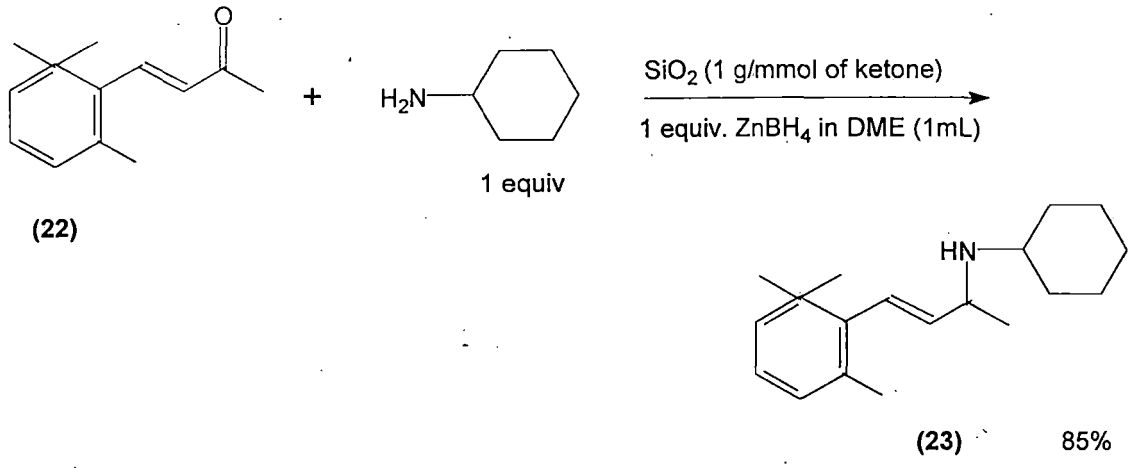
(17) (19) (21) 96%

Limitations include reactions with aromatic and unsaturated ketones some sterically hindered ketones and amines.

In fact, reductive amination of conjugated carbonyl compounds has not been addressed in details in any of the reported methods–hydrogen in presence of metal catalysts, $NaBH_3CN$, BH_3-pyridine, borohydride exchange resin, Zn-AcOH, $NaBH_4$-$Mg(ClO_4)_2$, $ZnBH_4$-$ZnCl_4$, and $NaBH(OAc)_3$; only two exaples, 1-acetylcyclohexene and cinnalmaldehyde, have been included in $NaBH(OAc)_3$ procedure.[18] Although imines are, in general, prepared by the condensation of the carbonyl compound with an amine in the presence of a lewis or protic acid,[63] the research group of Ranu attempts to obtain the imines of conjugated carbonyl compounds, particularly ketones following reported procedures[63] using zinc chloride, boron trifluoride-etherate, *p*-toluenesulfonic acid, molecular sieves, failed. Ranu et al[19] have discovered that reductive amination of conjugated aldehydes ketone is achieved by treatment of the corresponding carbonyl compound with an appropriate amine in the presence of silica gel followed by addition of zinc borohydride in a one-pot operation (Scheme 7). This procedure does not affect nitro and cyano groups. Moreover, zinc borohydride is neutral in nature and, in general is compatible with many sensitive functionalities[19] like acetal[64a] and silyl ether.[64b] The reaction of compound (**22**) and cyclohexylamine under this condition afforded compound (**23**) in 85% yield.

Scheme 7





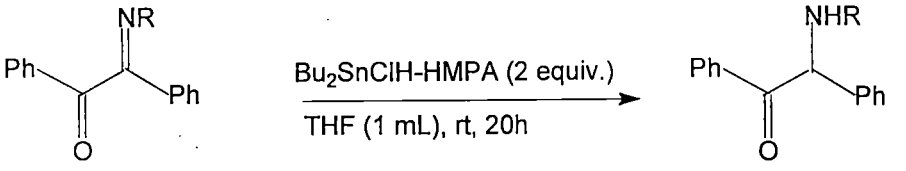
(22)

(23) 85%

The advantages of this procedure are (a) operational simplicity, (b) use of less costly or toxic chemicals, (c) low environmental pollution from waste, (d) mild conditions, (e) fast reaction, and (f) high yield.

Chemoselective reductions of imino groups are very important for the synthesis of multifunctionalized amines. Nevertheless, little attention has been paid to iminoselective reductions by metal hydrides in the presence of carbonyl groups because of the lower electrophilicity of imino groups.[65] Baba et.al. have developed a set of organotin hydrides that reduce polar multiple bonds such as C = O and C = N in an ionic manner,[66] and with which chemoselective reductions of bifunctional substrates could be achieved.[67] The introduction of a halogen substituent or a ligand onto the tin atom can change the character of the original tin hydrides[67c] to provide different chemoselectivities in the reduction of multifunctional substrates. For example, in the reaction with 2,3-epoxy ketones, Bu_2SnFH-HMPA selectively reduce the carbonyl group to furnish predominantely the *anti*-2,3-epoxy alcohol,[67a] whereas Bu_2SnIH-HMPA preferentially reduced the epoxy group to provide 3-hydroxy ketones.[67c] Baba et al[27c] have presented use of Bu_2SnClH-HMPA as a chemoselective reductant of imines in the presence of carbonyls (Scheme 8).

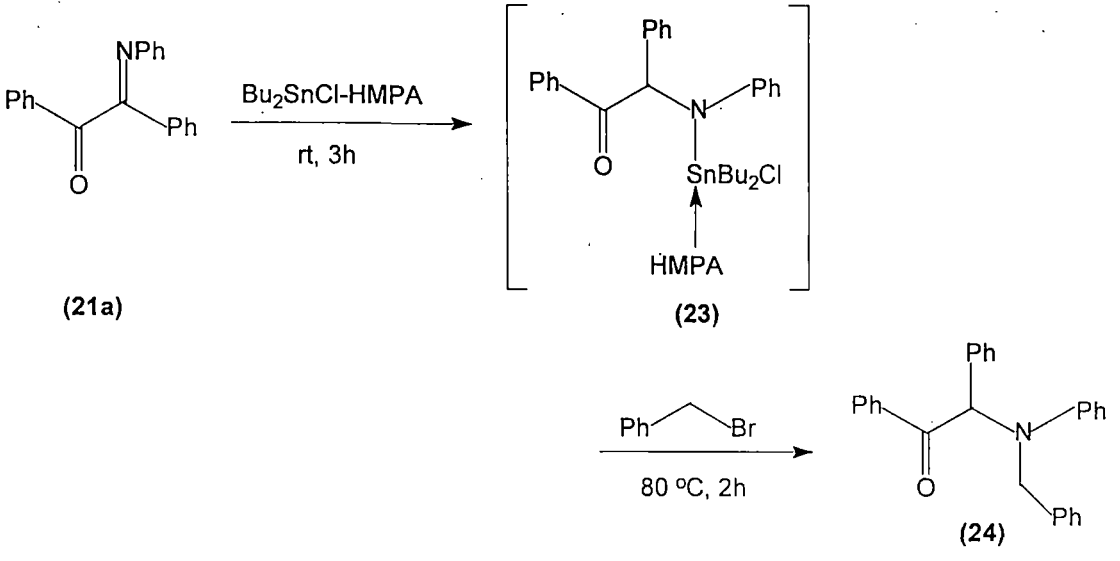
Scheme 8



(21) **(22)**

(a) R = Ph
(b) *p*-ClC_6H_4
(c) *p*-BrC_6H_4
(d) *p*-$OMeC_6H_4$

Further, Bu_2SnClH-HMPA possessed higher iminoselectivity compared with other conventional reductants such as $LiAlH_4$, DIBAL, and $NaBH_4$ which reduced the carbonyl group predominantly. 2-amino ketone (**22**) was obtained by the reduction of (**21**) with Bu_2SnCl-HMPA at room temperature followed by treating with methanol. The reduction progress stoichometrically, where the adducts bearing a nucleophilic Sn-N bond are generated in *situ* without protonation by tin hydride (Bu_2SnCl-HMPA). Moreover, the resulting tin amides from hydrostannation of imines subsequently react with organic halides to furnish unsymmetrical tertiary amines in a one-pot procedure. Multifunctionalized unsymmetrical amines (**24**) could be prepared directly by the subsequent *N*-alkylation of the tin amide (**23**) with benzyl bromide to afford unsymmetric tertiary amine (**24**).

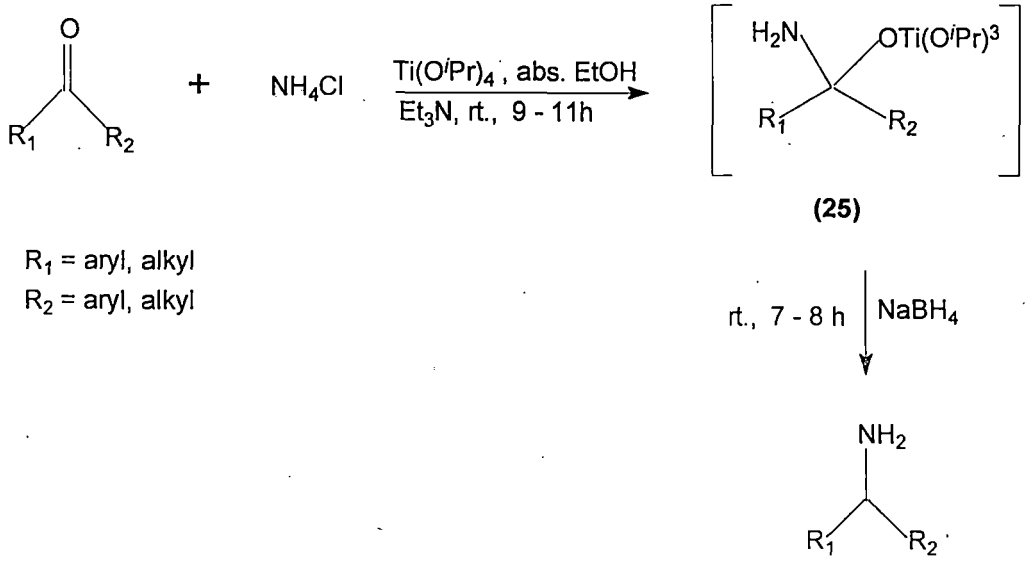


(21a) **(23)** **(24)**

Noteworthy is that highly chemoselective reactions were achieved with the co-existence of other functionalities such as halogen, C-C double bond and hydroxy groups.

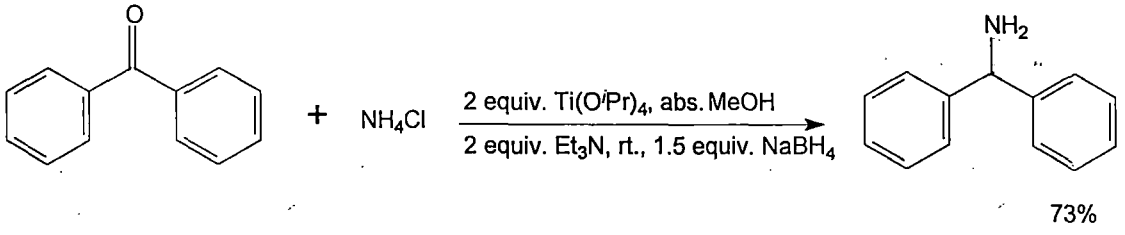
Though many of the reported protocols for reductive amination reactions work well for the preparation of tertiary and secondary amines, synthesis of primary amines by reductive alkylation of ammonia is mostly comprised by over alkylation reaction.[18,35b,36,68] The formation of variable amounts of secondary and tertiary amines along with primary amines is common. The synthesis of primary amines is, therefore, mostly addressed indirectly by using ammonia equivalents[69] such as tritylamine, diallylamine or allylamine. These protocols routinely require a subsequent deprotection step to get primary amines. Accordingly, development of a straightforward route for the synthesis of primary amines via selective monoalkylation of ammonia is an important objective. Bhattacharyya and coworkers[21] developed an efficient one-pot reagent system for the synthesis of primary amines by selective monoalkylation of ammonia with alkyl and aryl ketones using titanium(IV) isopropoxide and sodium borohydride (Scheme 9).

Scheme 9



A mixture of ammonium chloride and triethylamine has been employed as the ammonia equivalent; this requires no special handling techniques and alleviates the use of excess gaseous ammonia. They used a combination of titanium(IV) isopropoxide and sodium borohydride in the reductive alkylations of primary and secondary amines.[70] Because this one-pot reagent system allows easy, direct access to diverse primary amines, it should find widespread application. Under these reaction conditions, only primary amines are formed - the traditional problem of over-alkylation of the product amines was not observed. The reaction may proceed through an intermediate aminocarbinolatotitanium(IV) complex (**25**), which is either reduced directly or via equilibration of **25** to form a transient iminium species.[71] The compatability[70,72] of titanium(IV) isopropoxide with a variety of acid- or base-sensitive groups provides an additional advantage for targeting the syntheses of amines with reagent-sensitive motifs.

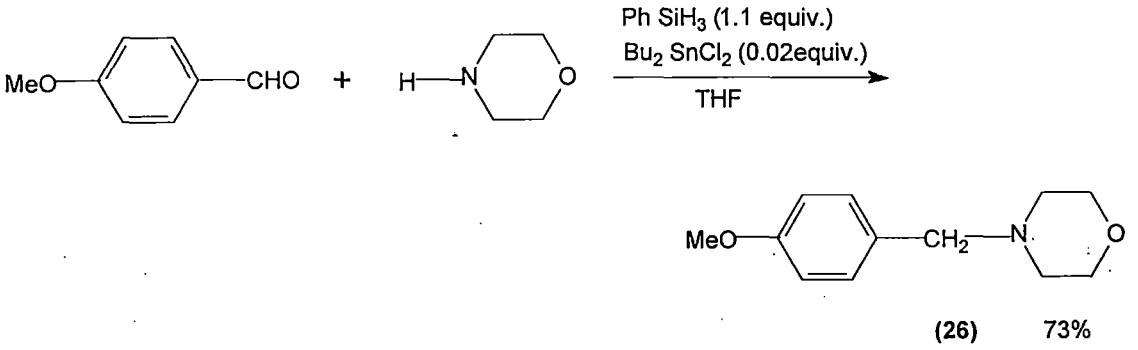
The relevance of this protocol has been demonstrated on a structurally varied set of ketonic substrates. Benzophenone was allowed to react with a mixture of ammonium chloride, triethylamine and titanium (IV) isoproxide, followed by the treatment sodium borohydride at room temperature.



Apodaca et al[27] reported a direct reductive amination procedure which employs phenylsilane as a stoichiometric reductanrt and dibutyltin dichloride as a catalyst. Both aldehydes and ketones were reductively aminated with anilines and secondary alkylamines (acyclic, cyclic), although the reaction failed with primary alkylamines. Reductive amination of 4-methoxybenzyldehyde with morpholine in the presence of 2 mole % dibutyltin dichloride afforded 78% isolated yield of *N*-(4-methoxybenzyl) morpholine (**26**) (Scheme 10). Reactions with substrates bearing potentially reducible functional groups including aryl iodide, cinnamyl, nitro, benzyloxy gave the

anticipated products, without detectable reduction side products. Potentially acid-labile groups were also well tolerated.

Scheme 10

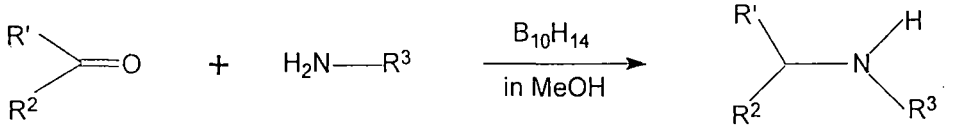


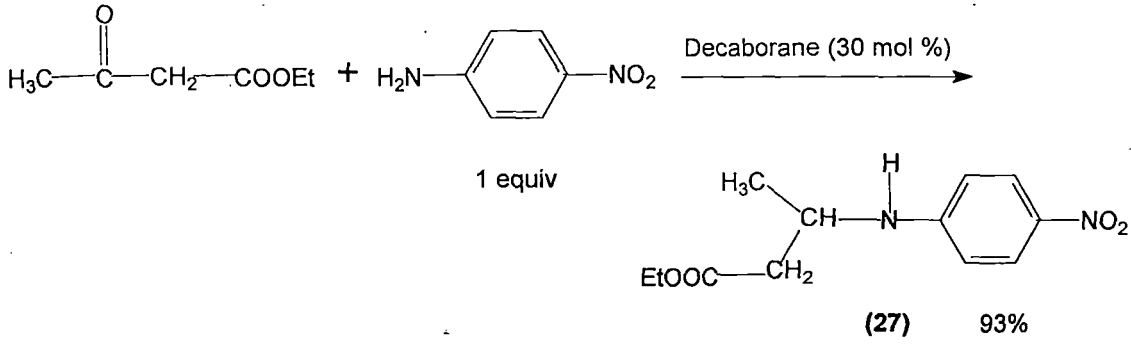
(26) 73%

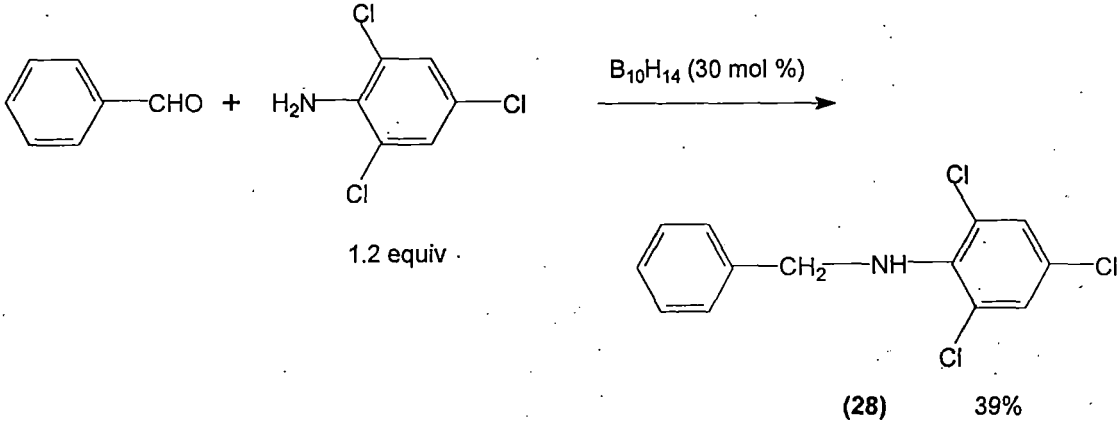
This reported procedure offers some advantages over other methods. Because little, if any competitive carbonyl reduction was observed in these reactions, the use of excess aldehyde or ketone is unnecessary. Because of its catalytic nature, reaction rates can be increased by simply adding more catalyst or through the potential development of more active catalysts.

During the study of decaborane as a mild reducing reagent,[73] Yoon et al[24] found that carbonyls and amines undergo reductive amination in the presence of decaborane (Scheme 11). The treatment of ethyl acetoacetate with 4-nitroaniline usings decaborane in methanol at room temperature under nitrogen, gave the corresponding amines (**27**) in 93% yield. This reaction is efficient, even with a relatively poor nucleophilic amine and is compatible with other functional groups such as nitro groups, olefins and halogen groups. The reaction benzaldehyde with 2,4,6-trichloroaniline under this condition the amine (**28**) in 39% yield, a reaction known to fail using sodium triacetoxyborohydride.[19]

Scheme 11

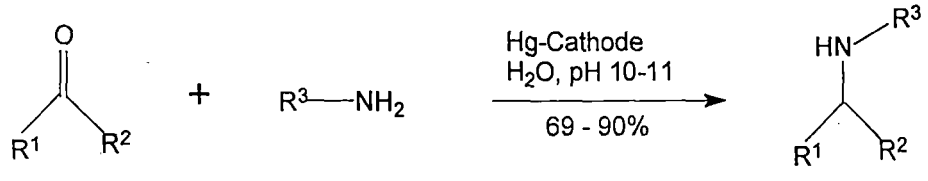


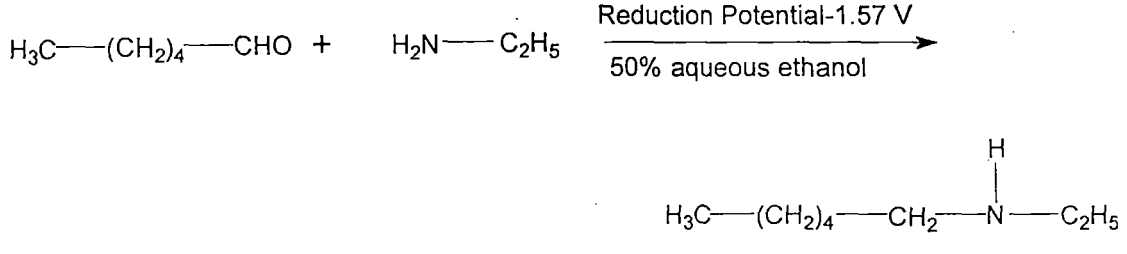




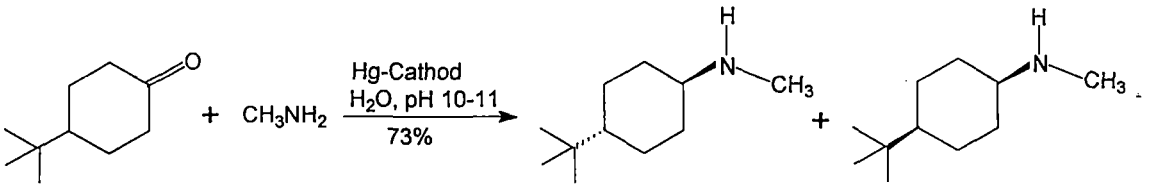
Schäfer et al[29b] have found that secondary amines may be prepared in good yields by potential-controlled reduction of aldehydes or ketones at a mercury cathode in an aqueous solution containing a primary amine (Scheme 12).

Scheme 12

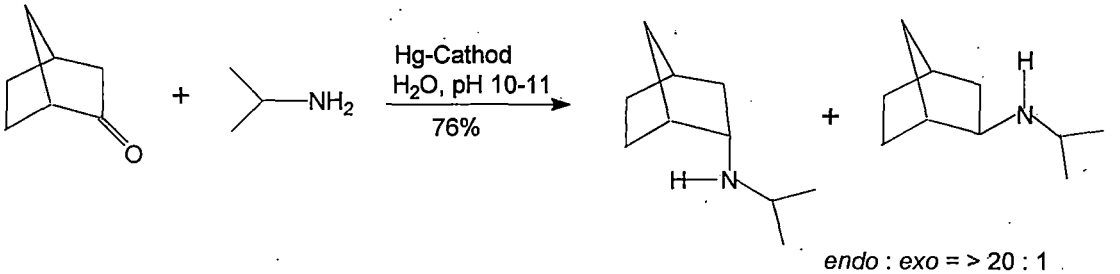




In aqueous medium, an aldehyde or ketone and a primary amine equilibrate to the corresponding schiff base. Because of its lower reduction potential compared with the aldehyde or ketone, the schiff base may be reduced selectively to yield a secondary amine after electron- and proton-transfers. For cyclic ketones, high diastereo-selectivities are obtained in some cases.



trans : cis = 14 : 1

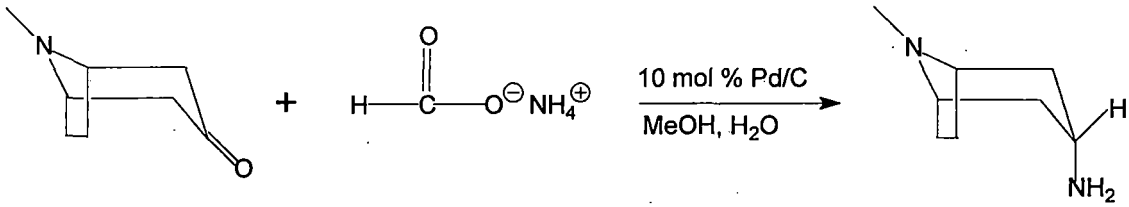


endo : *exo* = > 20 : 1

Cathodic reductive amination may be considered as a good alternative of existing methods for the preparation of secondary amines, because of its high chemoselectivity, good yields, simple work-up and low reagent costs.

The research group of Allgrette[74] first reported a new versatile method for the reductive amination of carbonyl compounds in which ammonium salts are employed together with a palladium catalyst .The use of a cheap and versatile hydrogen source coupled with the catalyst in an aqueous medium, advances the previous methods due to the mild conditions and to the handy and cheap reagents required. This method advances the usual reductive amination processes in terms of yield and shows high stereoselectivity whether applied to constrained carbonyl compounds. This is a new method for the synthesis of a wide range of primary, secondary and tertiary amines. The reaction of 8-methyl-8-azabicyclo-[3.2.1]octa-3-one (**29**) was treated with ammonium formate in the presence 10% Pd/C catalyst to give 3-endo-amino-8-methyl-8-azabicyclo-[3.2.1]octane (**30**) in 83% yield (Scheme 13).

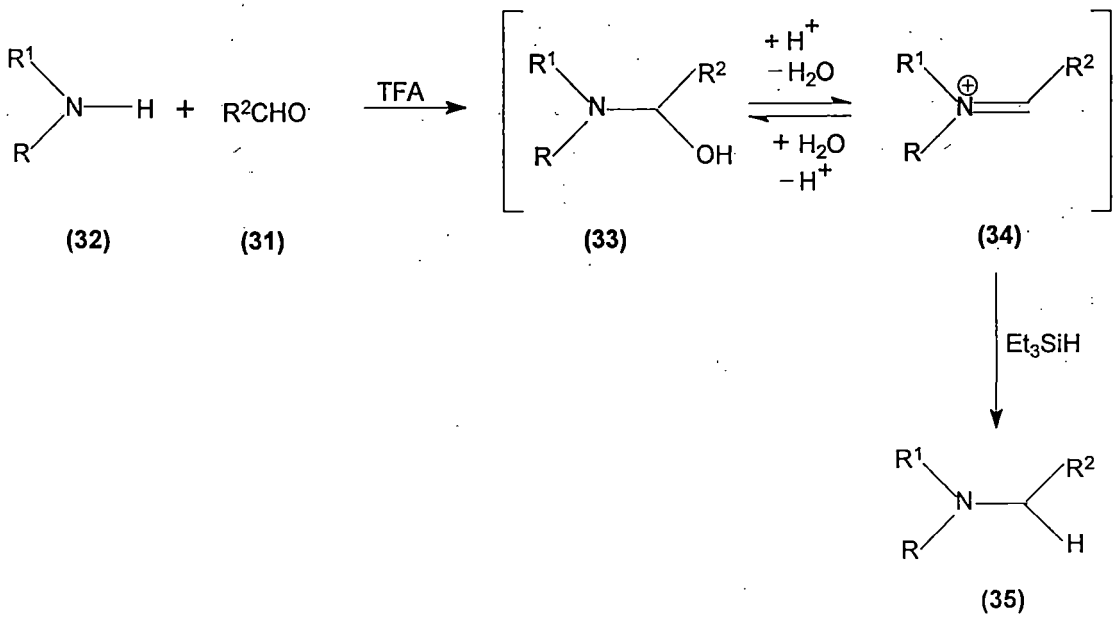
Scheme 13



(29) (30) 83%

Hydrosilanes such as triethylsilane in the presence of Lewis acid are mild and useful reducing reagents in organic synthesis.[30,75-79] They have been used in the reduction of imines to secondary amines,[76] In the reductive N-methylation of amino acids via oxazolidines,[77] In the N-alkylation of anthranilamides via oxazolidines,[78] and recently in the *N*-alkylation of amides, carbamates and ureas.[79] The research group of Chen envisioned[28] that a secondary amine **32** would react with an aldehydes **31** to give a hemiaminal **33** (scheme 14). This in hemiaminal **33** may undergo reduction with triethylsilane and trifluoroacetic acid through an iminium ion **34** affording the *N*-alkylated product **35**.

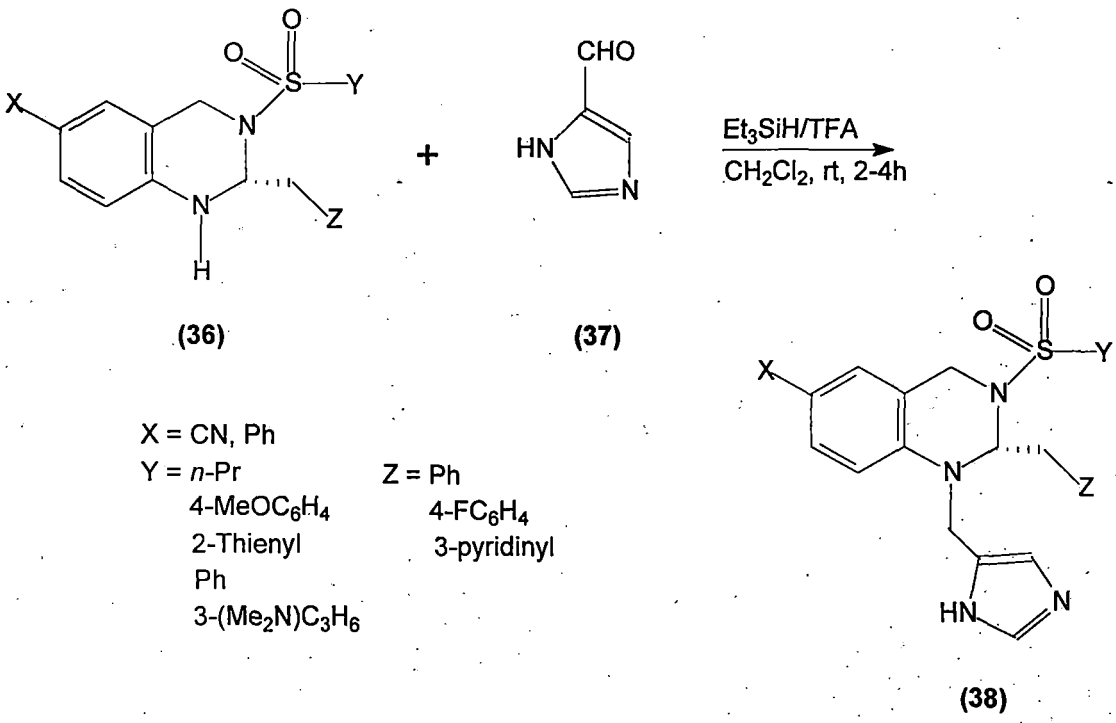
Scheme 14



(32) (31) (33) (34)

(35)

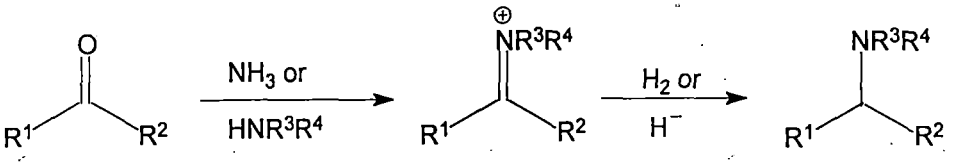
An improved synthesis of 1-(imidazolyl)methyl-4-sulfonylbezodiazapines (**38**), new farnesyltransferase inhibitors, from the corresponding carbonyl compound (**36**) and amine (**37**) was developed using this novel reductive N-alkylation method.



II-A.2.1: Present Work: Background, Objectives and Strategy

As described in the introduction, the reductive amination is a useful organic transformation for preparing primary, secondary and tertiary amines. The carbonyl compounds initially react with ammonia or amine to form an imine, which then undergoes reduction in presence of hydrogen or hydride ion (Scheme 15). when the overall two-step procedure is performed in a one-pot operation, such protocol is described as "direct reductive amination".

Scheme 15



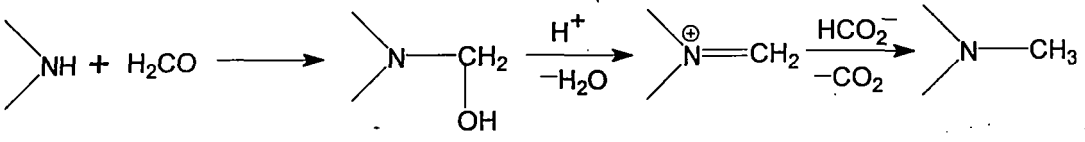
$R^1 = R^2 = H$, alkyl, aryl $R^3 = R^4 = H$, alkyl, aryl

Several reductive systems are known to effect the reduction of C-N double bond of the imine. Use of molecular hydrogen in presence of a metal-catalyst is one of classical methods to perform this reduction. However, the reaction conditions are not compatible with a number of otherwise reducible groups such as nitro, cyano, double or triple bonds. Secondly, such reduction requires a special set of apparatus and is always associated with usual risks of using hydrogen gas.

On the other hand, several hydride containing reagents are much common to have been employed in imine reduction. A few of them are: $[NaBH_3CN]$;[11] $ZnCl_2$-$Zn(BH_4)_2$;[16] pyridine-BH_3;[17] $[NaBH(OAc)_3]$;[18] silica gel-$Zn(BH_4)_2$;[19] $Ti(^iPrO)_4$-$NaBH_4$;[21] $NiCl_2$-$NaBH_4$;[22] $Ti(^iPrO)_4$-polymethylhydro-siloxane;[23] decaborane;[24] Bu_3SnH;[25] Bu_2SnClH and Bu_2SnIH;[26] phenylsilane-dibutyltin dichloride;[27] Et_3SiH-trifluoroacetic acid.[28] All these methods require stoichiometric or excess quantities of the hydrides, which are generally highly reactive and expensive as well. Furthermore, use of tin hydrides in some protocols are not recommended for large-scale preparation as the residual insoluble tin comopounds pose a great risk in its elimination. There are some well-known organic reactions which appear to proceed via transfer of hydrogen as hydride species, although the reagents themselves are not immediately obvious hydride donors. Formic acid and formates are recognized as

hydride donors in such reactions as the methylation of amines using formaldehyde/ammonium formate (Scheme 16; Leuckart reaction).[80] The reduction of multiple bonds with the aid of a hydrogen donor in the presence of a

Scheme 16



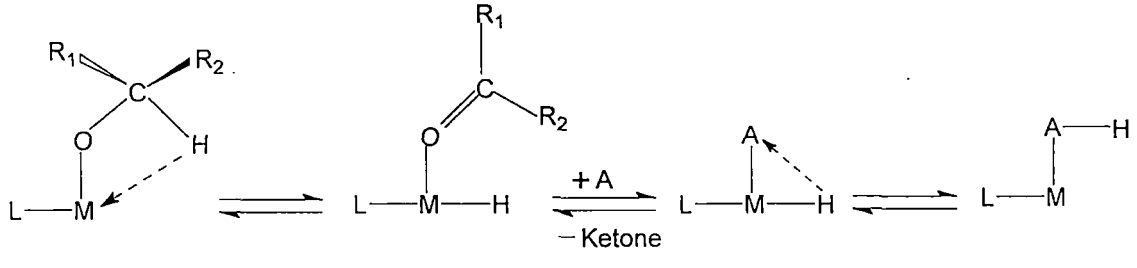
catalyst is known as hydrogen-transfer reaction or transfer hydrogenation (H-transfer).[81] The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of the catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor). This can be generalized as in eq. 1. In hydrogen-transfer reactions the hydrogen source must be

$$DH_2 + A \underset{}{\overset{cat}{\rightleftharpoons}} D + AH_2 \qquad (1)$$

DH_2 = hydrogen donor ; A = hydrogen acceptor

different from dihydrogen. Formic acid and its salts have been successfully used for this purpose. The use of hydrogen donors had some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with this reagent as well as the necessity of pressure vessels. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.

From a mechanistic point of view, two general reaction paths cans be envisaged for hydrogen transfer:[82] a step-wise process, called "hydridic route", and a concerted process, called "direct hydrogen transfer" (Figure 1). The "hydridic route" involves



"hydridic route"

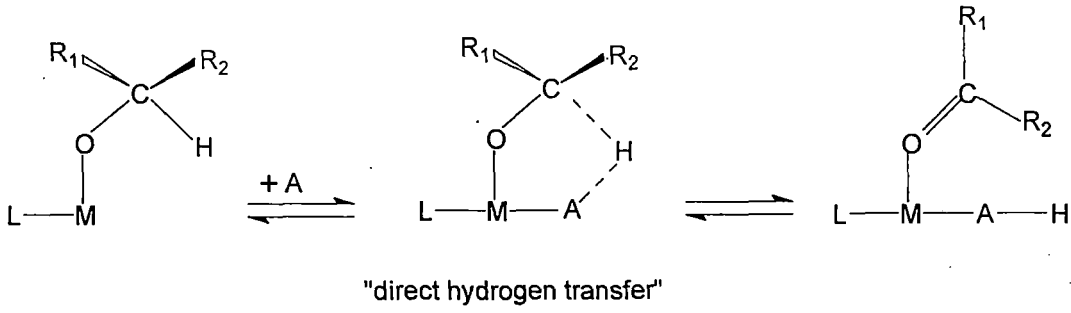


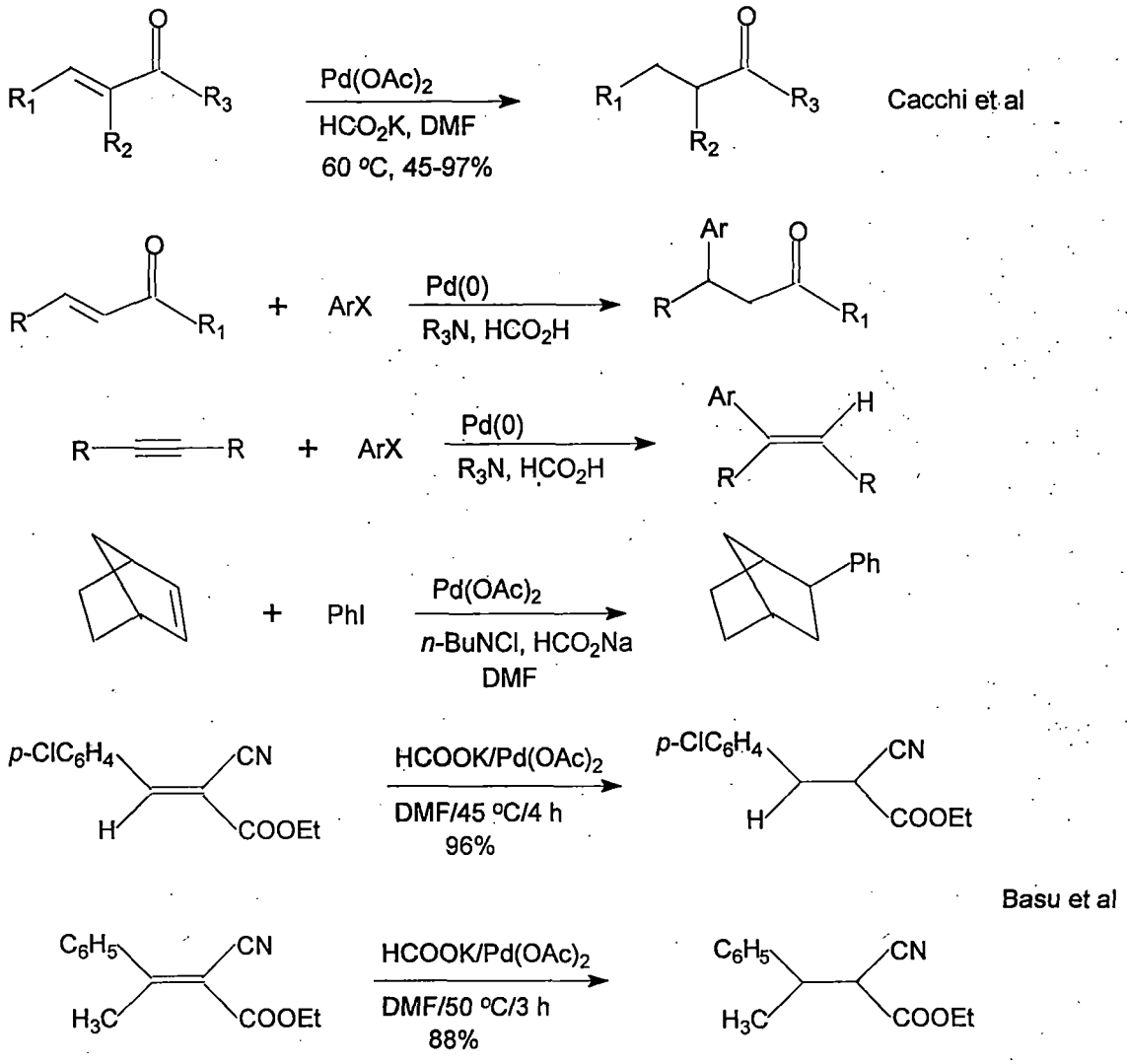
Figure 1. Possible paths for the hydrogen-transfer reactions.

the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and the H-acceptor are held together in close proximity by the catalyst. A cyclic transition state such as the one proposed for Meerwein-Pondorf-Varely reduction is possibly involved.

The most popular H-donors are alcohols, including chiral ones, and formic acid.[83] More recently, alkyl-ammonium formates, in particular triethylammonium formate (TEAF), have proven to be useful sources of hydrogen, due to their solubility in organic solvents.[84] Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[85] this usually overwhelms the energetic requirement of the reduction process. The use of such H-donors is recommended in reactions where unfavorable energetic balances are expected. The use of formic acid as hydrogen donor appears to have advantages over cyclohexene, cyclohexadiene and hydrazine. A further elaboration in the use of formate anion as a donor has been reported. During the early nineties, Cacchi[86a] and others[87] reported use of different combinations of formic acid and its salts such as, HCOOH/$NaHCO_3$/*n*-Bu_4NCl; HCOOH/*n*-Bu_3N; HCOOK in palladium-catalyzed reduction of electron-deficient alkenes and reductive arylation of alkenes (Scheme 17). They also observed that differences in the nature of formate salt and of the reaction medium can significantly affect the course of reaction.[87] Use of formic acid as the source of hydrogen, called the Wallach reaction, or ammonium salts of formic acid, called the Leuckart reaction, often yields the *N*-formyl derivative of the amine instead of the free amine.[68b] On the other hand, we[86b]

and other groups[86a] have recently shown that potassium formate promoted by palladium acetate can reduce

Scheme 17

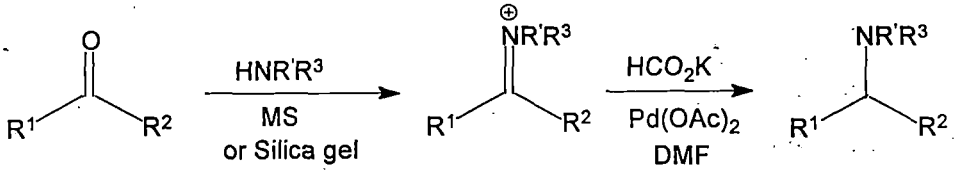


efficiently the conjugated C-C double bond. It therefore appeared reasonable to investigate whether potassium formate, which is soluble in polar organic solvents and in water, with activation by palladium salt could significantly reduce the C-N double bond of the imine formed in the direct reductive amination reaction.

II-A.2.2: Present Work: Results and Discussion

We report herein our observation, which finally constitutes a one-pot reductive amination protocol for aldehydes and ketones, including conjugated ones, with the aid of potassium formate and catalytic palladium acetate (Scheme 18).

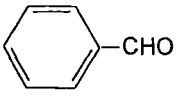
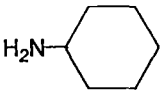
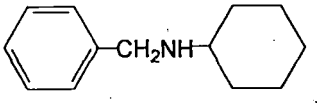
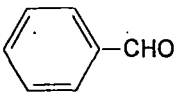
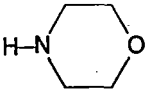
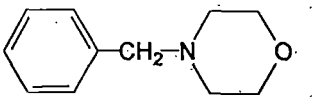
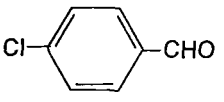
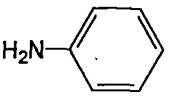
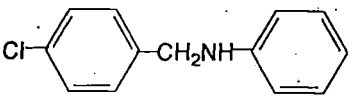
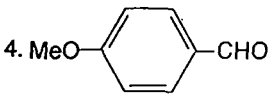
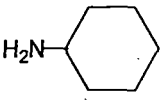
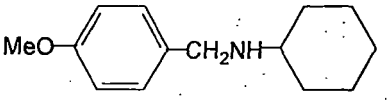
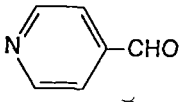
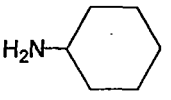
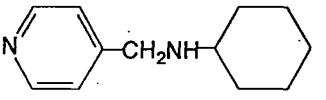
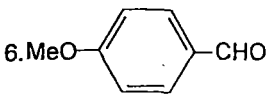
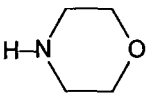
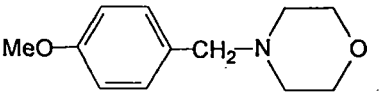
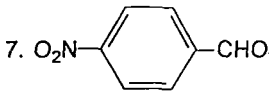
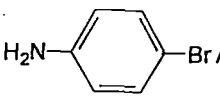
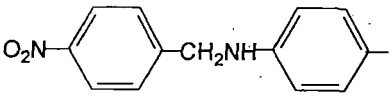
Scheme 18



R^1 = alkyl or aryl
R^2 = H, alkyl
R^3 = H, alkyl
R' = alkyl

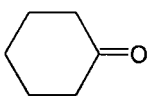
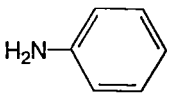
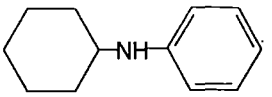
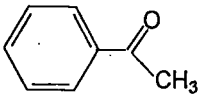
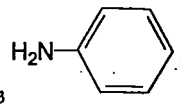
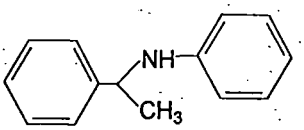
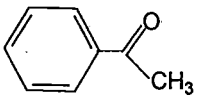
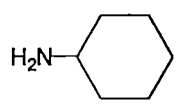
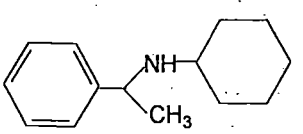
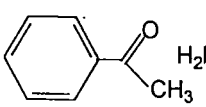
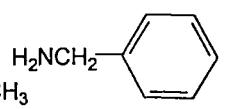
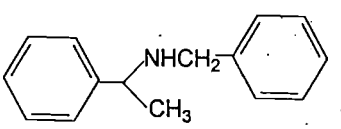
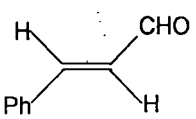
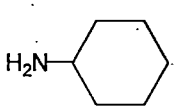
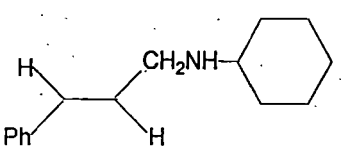
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 1). Both primary and secondary amines, such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including chloro (entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. The reaction of pyridine-4-aldehyde with cyclohexylamine was reductively at 40 °C for 3 h and the desired product (**43**) was isolated after column chromatogric purification in 86% yield. Similarly, *p*-methoxybenzaldehyde underwent reductive amination (entries 4 and 6) efficiently with both primary and secondary aliphatic amines affording the desired products (**42**) and (**44**) in 75% and 67% yields respectively. The reaction of *p*-nitrobenzaldehyde with aromatic amine (*p*-bromoaniline) was also studied (entry 7). The reaction also proceeded under fairly mild condition to furnish the compound (**45**) in 56% yield. Among the ketones, we first studied the reaction of cyclohexanone with aniline (entry 8). The desired product, *N*-cyclohexylaniline (**46**) was isolated as colourless oil (70%). Although acetophenone is a difficult case for some reductive amination protocols, use of excess potassium formate (2-4 mmol) and a slight excess of palladium acetate (5 mol %) gave reductive amination of the ketones at a rate comparable to that of other substrates. Thus, acetophenone was subjected to reaction with both aliphatic and

Table 1. Direct reductive amination of aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

Entry	Substrate	Amine	Condition [a]/Temp Time	Product	%Yield [b]
1.			A / 40 °C/ 3 h	 **(39)**	68
2.			A / 40 °C/ 4 h	 **(40)**	62
3.			A / 50 °C/ 5 h	 **(41)**	67
4.			A / 40 °C/ 3 h	 **(42)**	75
5.			A / 40 °C/ 3 h	 **(43)**	86
6.			A / 50 °C/ 5 h	 **(44)**	67
7.			A / 50 °C/ 5 h	 **(45)**	56

Continued.....

Continued..... **Table 1**

Entry [b]	Substrate	Amine	Condition [a]/Temp Time	Product	%Yield
8.			B / 50 °C/ 5 h	 (46)	70
9.			B / 60 °C/ 6 h	 (47)	76
10.			B / 60 °C/ 6 h	 (48)	83
11.			B / 60 °C/ 6 h	 (49)	80
12.			B / 50 °C/ 5 h	 (50)	69

[a] Conditions A: Aldehyde + Amine in DMF with MS (4Å) and stirred at room temparature for 3-5 h; B: Ketone + Amine intimately mixed on activated silica gel and stirred at room temperature for 5-6 h.

[b] Yields are reported after chromatographic purification (2-3 runs). Satisfactory spectral data were obtained for all the amines (products) and given in the experimental section.

aromatic primary amines (entries 9-11) to afford the desired *N*-aryl or *N*-alkyl amines in 76-83% yields. Reductive amination of cinnamaldehyde (entry 12) with cyclohexyl amine, however, proceeded with concomitant reduction of the C-C double bond. Unlike the Leuckart reaction or the Wallach reaction, no *N*-formyl derivatives were formed in this protocol.

It is well known that aldehydes generally form imines faster than ketones. In this protocol, separate conditions were employed for imine preparation prior to addition of reducing agent. Whereas the aldehydes (except cinnamaldehyde) were reacted with amines in presence of activated molecular sieves (4 Å), the imines from the ketones were prepared on a surface of silica gel following the procedure of Ranu et al.[19] However, the imines prepared by using either molecular sieves or silica gel were directly taken in dimethyl formamide and subjected to reduction by adding palladium acetate (2-5 mol %) and potassium formate (2-3 equiv) and heated at 40-60°C for 3-6 h (see experimental section). The products were obtained after purification on column chromatography. In general, the reaction procedure is very simple and the reaction procedure appears to be mild.

II-A.3: Conclusion:

In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium-catalyzed hydride addition is probably the cause of the C-N double bond reduction, the possibility for asymmetric reductive amination in presence of a chiral ligand might be explored.

II-A.4: Experimental

II-A.4.1: Preparation of activated Silica Gel (HF_{254})

Silica gel (HF_{254}) was purchased from SRL, India, and was activated by heating at 150 °C under vacuo (0.5 Hg) for 1 h and then cooled under N_2 before use.

II-A.4.2: *General procedure for Aldehydes (except Cinammaldehyde)*

A solution of *p*-anisaldehyde (0.680 g, 5 mmol) and cyclohexylamine (0.500 g, 5 mmol) in dry DMF (5 mL) was magnetically stirred at room temperature for 4 h, in presence of molecular sieves (4 Å). To the resulting reaction mixture were added HCOOK (0.840 g, 10 mmol) and palladium acetate (22 mg, 0.1 mmol). The mixture was then heated at 40 °C for 3 h to complete the reaction (TLC) and after cooling it was diluted with ice-cold water (15 mL). The mixture was extracted with diethyl ether (3 x 20 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography over silica gel using EtOAc : hexane (1 : 19; R_f 0.26) affording *N*-cyclohexyl-*p*-methoxybenzylamine (**42**).

Yield: 75% (0.815 g), liquid

IR (neat): ν_{max} 2925, 2851, 1610, 1510, 1456, 1300, 1246, 1178, 1035, 821 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, 2H, *J* = 8.3 Hz), 6.85 (d, 2H, *J* = 8.3 Hz), 3.78 (s, 3H), 3.73 (s, 2H), 2.47 (br.s, 1H), 1.92-1.70 (m, 4H), 1.62-1.59 (m, 1H), 1.31-1.05 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 158.4, 132.9, 129.2, 113.7, 56.0, 55.2, 50.3, 33.4, 26.2, 24.9.

Similarly compounds **39**, **40**, **41**, **43**, **44** and **45** were prepared from corresponding aldehydes and amines.

N-Cyclohexylbenzylamine (**39**)

Yield: 68% (0.644 g), liquid

IR (neat): ν_{max} 3400 (N-H), 1600, 1450, 1321 (C-N) cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.31-7.06 (m, 5H), 3.80 (s, 2H), 2.48 (br, 1H), 1.92-1.70 (m, 1H), 1.61-1.54 (m, 4H), 1.31-1.07 (m, 6H)

N-Benzylmorpholine (**40**)

Yield: 62% (0.550 g), liquid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.32-7.25 (m, 5H), 3.70 (t, 4H), 3.49 (s, 2H), 2.44 (t, 4H).

N-(4-Chlorobenzyl)aniline (**41**)[88]

Yield: 67% (0.730 g), liquid

IR (neat): ν_{max} 3380 (N-H), 1600, 1490, 1320 (C-N), 1095 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.54 (d, 2H, J = 7.9 Hz), 7.32 (d, 2H, J = 7.9 Hz), 7.15 (t, 2H, J = 7.2 Hz), 6.71 (t, 1H, J = 7.2 Hz), 6.64 (d, 2H, J = 8.81 Hz), 4.29 (s, 2H), 3.97 (br s, 1H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.8, 138.0, 133.0, 129.3, 128.7, 128.2, 117.8, 112.8, 47.6.

N-(Pyridin-4-yl-methyl)cyclohexylamine (**43**)

Yield: 86% (0.818 g), liquid.

IR (neat): ν_{max} 2940, 1603, 1547, 1455, 1383 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.52 (d, 2H, J = 4.8 Hz), 7.26 (d, 2H, J = 4.8 Hz), 3.83 (s, 2H), 2.86 (br, 1H), 1.92-1.82 (m, 4H), 1.62-1.60 (m, 1H), 1.27-1.06 (m, 6H).

N-(4-Methoxybenzyl)morpholine (**44**)

Yield: 67% (0.694 g), liquid.

IR (neat): ν_{max} 2954,2852, 1612, 1514, 1456, 1245, 1116, 1033 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, 2H, J = 8.34 Hz), 6.85 (d, 2H, J = 8.34 Hz), 3.78 (s, 3H), 3.69 (t, 4H), 3.43 (s, 2H), 2.42 (t, 4H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.7, 130.4, 129.5, 113.6, 66.9, 62.8, 55.2, 53.4.

4-Bromo-*N*-(4-nitrobenzyl)aniline (**45**)

Yield: 56% (0.860 g), liquid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.19 (d, 2H, J = 8.5 Hz), 7.50 (d, 2H, J = 8.5 Hz), 7.23 (d, 2H, J = 8.6 Hz), 6.44 (d, 2H, J = 8.6 Hz), 4.45 (s, 2H), 4.22 (br, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.8, 146.2, 132.1, 127.6, 123.9, 114.5, 114.4, 109.8, 47.5.

Anal. Calcd. for $C_{13}H_{11}BrN_2O_2$ (307.15): C, 50.84; H, 3.61.

Found: C, 50.66; H, 3.69.

II.-A.3.3: *General Procedure for Ketones and Cinnamaldehyde*

A mixture of acetophenone (0.601 g, 5 mmol) and benzyl amine (0.535 g, 5 mmol) was uniformly absorbed on the surface of activated silica gel (5 g) by dropwise addition under stirring, and the mixture was then stirred at room temperature (25 °C) under nitrogen for 4 h to allow complete conversion of the corresponding imine. HCOOK (0.840 g, 10 mmol), palladium acetate (22 mg, 0.1 mmol) and DMF (5 mL) were added and the reaction mixture was then heated at 60 °C a for 6 h. After completion (TLC) the reaction mixture was cooled, diluted with ice-cold water and extracted with diethyl ether (3 x 20 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated with solvent to leave the crude product, which was purified by column chromatography over silica gel using EtOAc : hexane (1 : 9) affording *N*-(1-phenylethyl)benzylamine (**49**).

Yield: 80% (0.845 g), liquid.

IR (neat): ν_{max} 3380, 1602, 1452, 1305 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34-7.23 (m, 10H), 3.79 (q, 1H, J = 6.57 Hz), 3.60 (q, 2H, J = 13.1 Hz), 1.86 (br, 1H), 1.35 (d, 3H, J = 6.57 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 145.4, 140.5, 128.3, 127.3, 125.5, 57.4, 51.5, 24.4.

Anal. Calcd. for $C_{15}H_{17}N$ (211.31): C, 85.26; H, 8.11.

Found: C, 85.11; H, 8.43.

Using the same method compounds **46**, **47**, **48 and 50** were prepared from the corresponding carbonyls and amines.

N-Cyclohexylaniline **(46)**[14]

Yield: 70% (0.614 g), liquid.

IR (neat): ν_{max} 3400, 3085, 3055, 1602, 1560, 1462, 1450,1367, 1321 (C-N), 1255, 1179,1148 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.22-7.14 (m, 2H), 6.71-6.61 (m, 3H), 3.27 (m, 1H), 1.81-1.62 (m, 5H), 1.45-1.10 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.1, 129.2, 117.0, 113.3, 51.9, 33.4, 25.9, 25.0.

N-(1-Phenylethyl)aniline **(47)**

Yield: 76% (0.844 g), liquid.

IR (neat): ν_{max} 3416 (N-H), 3053, 1603, 1506, 1450, 1322 (C-N), 1260 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.36-7.31 (m, 5H), 7.06 (t, 2H, J = 7.3 Hz), 6.6 (t, 1H, J = 7.3 Hz), 6.48 (d, 2H, J = 1.92 Hz), 4.46 (q, 1H, J = 6.7 Hz), 3.81 (s, 1H), 1.47 (d, 3H, J = 6.7 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.2, 145.2, 129.0, 128.2, 126.8, 125.8, 117.1, 113.2, 53.3, 24.9.

N-(1-Phenylethyl)cyclohexylamine **(48)**

Yield: 83% (0.750 g), liquid.

IR (neat): ν_{max} 3380, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.35-7.20 (m, 5H), 3.96 (q, 1H, J = 6.6 Hz), 2.28 (br, 1H), 1.72-1.65 (m, 4H), 1.55 (m, 1H), 1.33 (d, 3H, J = 6.6 Hz), 1.14-1.01 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 146.0, 128.3, 126.6, 125.4, 54.3, 53.5, 34.4, 33.0, 26.0, 24.8.

N-(3-Phenylpropan-1-yl)cyclohexylamine **(50)**

Yield: 69% (0.743 g), liquid.

IR(neat): ν_{max} 3320, 2930, 1629, 1496, 1440, 1378, 1127 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.35-7.16 (m, 5H), 2.8-2.62 (m, 1H), 2.64 (t, 4H, J = 7.4 Hz), 2.38 (m, 1H, NH), 1.87-1.59 (m, 8H), 1.30-1.02 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 142.1, 128.3, 128.2, 125.6, 56.8, 46.4, 34.2, 33.6, 31.9, 26.1, 25.0.

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Part – II: Section – B

II-B: Chemoselective Reduction of Functionalized Alkenes Using HCOOK and Catalytic $Pd(OAc)_2$

II-B.1: Present Work: Background, Objectives and Strategy

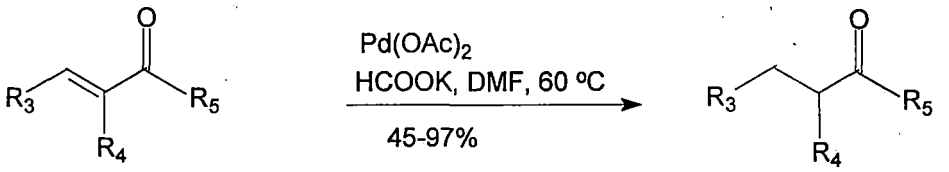
Prior to using the combination of potassium formate and catalytic palladium acetate in the reduction of C–N double bonds of the imines (described in Part–II: Section–A of this dissertation), we employed this reductant in reducing the C–C double bonds of highly functionalized alkenes. In this section (Part–II: Section–B), a new procedure for chemoselective reduction of α,β–unsaturated cyanoesters using potassium formate as hydrogen donor and palladium (II) acetate as homogeneous catalyst is described.

The reduction of multiple bonds with the aid of a hydrogen donor in the presence of catalyst is defined as "transfer hydrogenation" and has been known for a long time.[1] Apart from the reduction procedure using molecular hydrogen, transfer hydrogenation offers some palpable benefits, as detailed by Noyori[2] and others.[3] These includes procedural simplicity, avoidance of hazardous reagents such as molecular hydrogen and borane (thereby removing the need for specialized, expensive facilities for the handling of such reagents) and a distinct reactivity and chemo- and enantioselectivity, which may well compliment other methods. Over the last decades, transfer hydrogenations have been achieved with high degree of enatioselctivity.[3,4] Inevitably, there are drawbacks, the most serious being the unfavourable thermodynamics associated with the transfer hydrogenation of ketones using alcohols, especially propan-2-ol, as hydrogen source.[5] Judicious choice of hydrogen donor and reaction conditions are needed in such cases if good conversions are to be achieved.

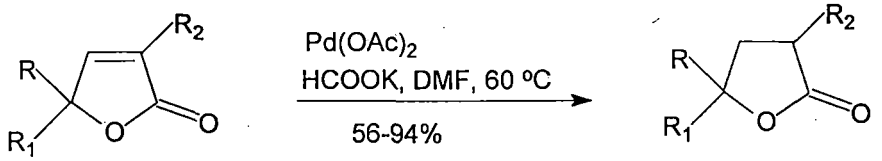
From the mechanistic point of view, formic acid and formates are believed to transfer hydrogen as hydride in presence of the transition metal catalysts (e.g. palladium catalyst) and such process is referred to as catalytic transfer hydrogenation (CTH) via "hydridic route" (p. 115).[3] As stated by Noyori, transition metal complexes "prefer the hydride mechanism".[2] Several excellent reviews on catalytic transfer

hydrogenations (CTH) are available in the literature[1b-d;3-5] and therefore not discussed here.

Chemoselective reduction of C–C multiple bonds in conjugated syetems is an important process in organic synthesis.[6] Despite the bewildering variety of reducing agents available to synthetic chemists, new and selective reductants are in constant demand. Transition metal-catalyzed hydrogen transfer reaction with the aid of a hydrogen donor, such as trialkyl ammonium formate,[7] and other hydrides like *n*-Bu_3SnH,[8] NaH_2PO_3/H_2O,[9] $Ph_2SiH_2/ZnCl_2.H_2O$,[10] triethoxysilane–water,[11] are some of the examples employed for selective conjugate reduction. In most cases, direct source of hydride is used for conjugate addition to the more nucleophilic β–carbon, whereas formic acid and its salts are believed to be a source of hydride *in situ*,[12] which eventually adds to the β–carbon. As mentioned earlier, Cachhi et al.[13] has reported a combination of $Pd(OAc)_2$/HCOOK as a convenient alternative reductant for conjugate reduction of α,β–carbonyl compounds. A few examples are given below.



R_5 = alkyl, aryl, OR

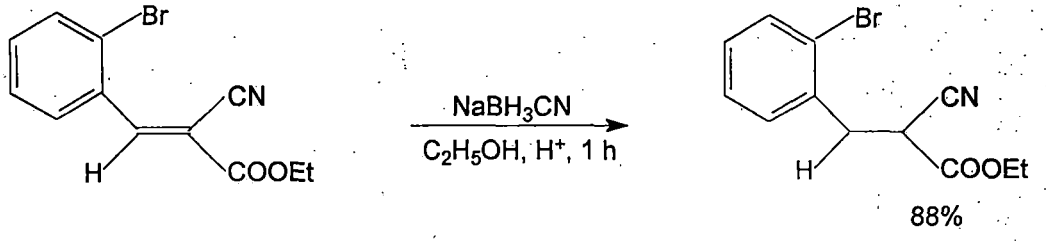


Cacchi et al.

R = $-(CH_2)_5-$, Me, Et, Ph, *n*-C_7H_{15}
R_1 = $-(CH_2)_5-$, Me, H
R_2 = C_6H_4-OMe-4, C_6H_4-OH-4, C_6H_4-Me-2, Ph

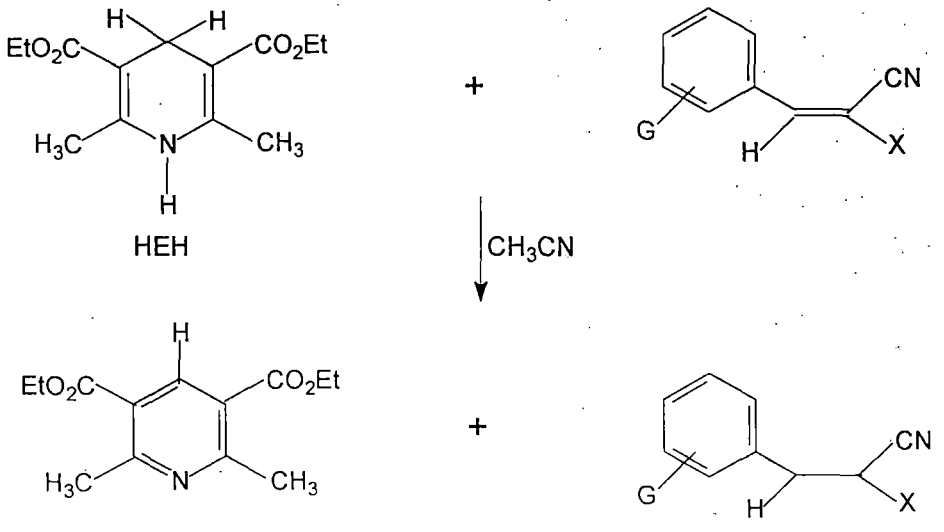
On the other hand, palladium-catalyzed reduction of conjugated nitriles and cyano esters using molecular hydrogen or hydrogen donor afforded with reduction of the cyano group as well.[1c] For example, reduction of reduction of α,β–unsaturated cyano esters in presence of Pd/C and *p*-menthene (as hydrogen donor) led to reduction of not only the C–C double bonds, but also of the nitrile group to a methyl group.[14]

Moreover, reduction of nitrile using a combination of Pd/C and formic acid seemed to be very variable in many other examples.[1d,15] Early studies on reduction of alkylidenecyanoacetic esters using sodium borohydride at room temperature led to reduction of C–C double bonds as well as reduction of the ester to alcohol.[16] Sodium borohydride has however been successfully worked in reducing ethyl benzylidenecyanoacetate[17] and sodium cyanoborohydride has selectively reduced α,β–unsaturated esters, nitriles and nitro compounds.[18] However, metal hydrides are generally highly reactive and expensive reagents and cyanoborohydride generates toxic byproducts upon workup.



Recently, Hantzsch 1,4-dihydropyridines (HEH) has been employed for selective reduction of α,β–unsaturated cyanoesters.[19] This procedure, however, involves specific reagent (Hantzsch 1,4-dihydropyridines) and after the reaction the redox products require separation (Scheme 1).

Scheme1

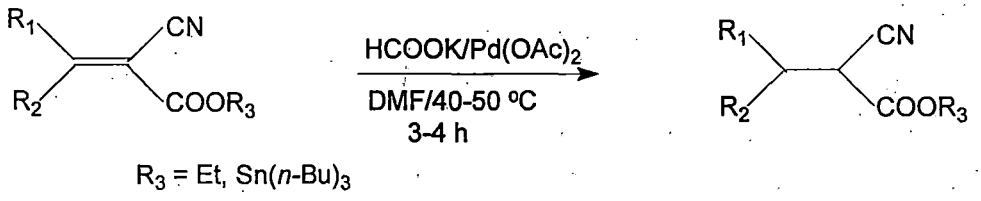


X = CO_2Et, CN

G = *p*-OCH_3, *p*-CH_3, *p*-Cl, *p*-CN

Consequently, it appeared to us of interest to check the efficacy of $Pd(OAc)_2$/HCOOK combination in the reduction of more functionalized α,β–unsaturated cyano esters (Scheme 2). The study could be of further importance, as the homogeneous chiral transition metal-catalyzed hydrogen transfer reactions are known to induce asymmetry in the reduction of ketones (C=O) and imines (C=N). A review by Palmer and Wills illustrated many examples.[3,4] The chiral Pd-complex catalyzed conjugate reduction without any concomitant reduction of other functional groups might produce asymmetric compounds for further elaboration to useful synthetic intermediates. The results of our studies are discussed below.

Scheme 2



R_3 = Et, Sn(*n*-Bu)$_3$

II-B.2: Present Work: Results and Discussion

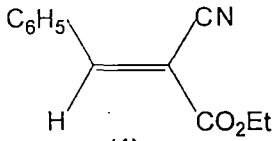
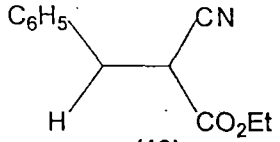
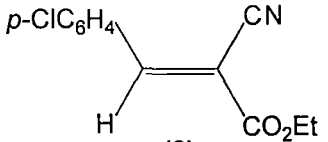
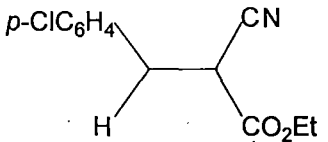
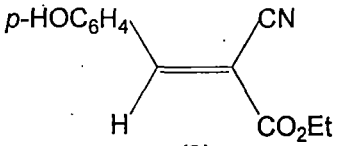
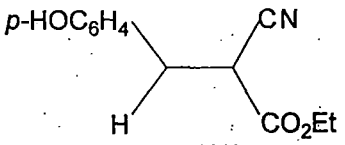
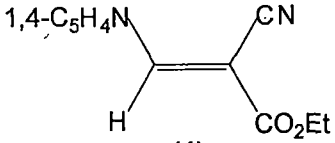
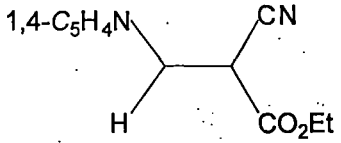
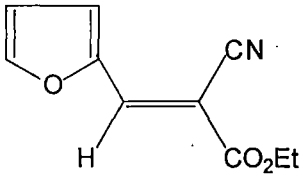
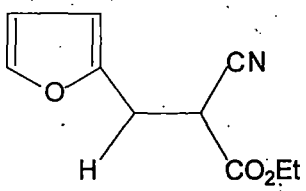
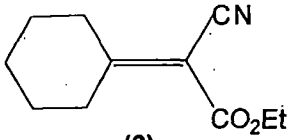
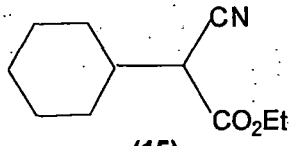
In the present work, a series of functionalized α,β–unsaturated cyano esters (**1-9**) have been prepared for the reduction study and to develop optimized conditions. The unsaturated compounds were prepared by condensation of their carbonyl substrates with ethyl cyanoacetate under Knoevenagel conditions.[20] The tri-*n*-butyl stannyl ester of benzylidene derivative (**8**) was prepared its ethyl ester (**1**) by transesterification with *bis*-tri-*n*-butyltin oxide, according to the conditions developed in this laboratory.[21] The condensed products were purified either by vacuum sublimation or by column chromatography. The NMR spectra were in accord with the reported data and/or appeared to be consistent.

The reductions of the functionalized alkenes were carried out as follows. To a solution of the unsaturated cyano ester (1 mmol) in DMF (3 ml) was added $Pd(OAc)_2$ (2 mol%) and HCOOK (2 equivalent) and the mixture was stirred at 45-50 °C for 3-4 h under N_2 to obtain complete reduction, as monitored on TLC. After usual workup, the reduced products (**10-18**) were purified by column chromatography over silica gel. The pure products were isolated in good to excellent yields.

The results are summarized in Table 1. Some of the salient features may be noted. Although dehalogenation of haloaromatics is known under transfer reduction using heterogeneous catalyst,[1b] the present method did not proceed with cleavage of carbon–halogen bond. Thus ethyl 2-cyano-3-(4-chlorophenyl)acrylate (**2**) underwent reduction of the olefinic bond without any concomitant removal of the chloride. At the same time, any other products originating from the reduction of the nitrile group was detected. The heteroaromatic systems such as pyridyl or furano derivatives (**4** and **5**) afforded the desired products in 87% and 79% yields respectively. The tri-*n*-butyl stannyl ester (**8**) gave the reduced product (**17**) in 75% yield and no demetallation was observed.[22]

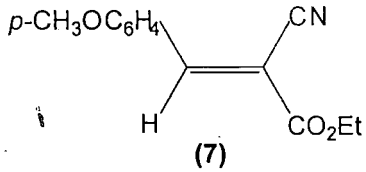
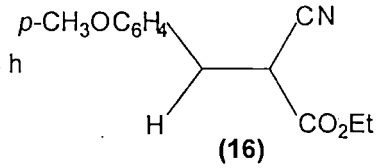
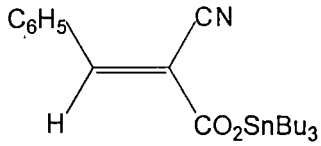
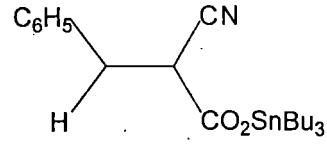
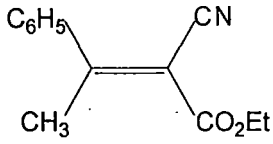
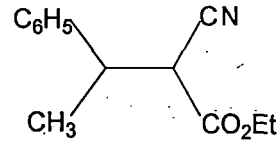
To observe any effect of ligand participation in the catalytic process, the reduction of ethyl 2-cyano-3-phenyl-2-butenoate (**9**) was carried out in presence of various

Table 1. Reduction of α,β-unsaturated cyano esters by using HCOOK and catalytic $Pd(OAc)_2$

Entry	Olefin	Temp./time	Product	%Yield[a]
1a.	 **(1)**	45 °C/ 3 h	 **(10)**	92
1b.	 **(2)**	45 °C/ 4 h	 **(11)**	96
1c.	 **(3)**	50 °C/ 4 h	 **(12)**	95
1d.	 **(4)**	50 °C/ 3 h	 **(13)**	87
1e.	 **(5)**	45 °C/ 4 h	 **(14)**	79
1f.	 **(6)**	50 °C/ 4 h	 **(15)**	76

Continued.....

Continued..... **Table 1.**

Entry	Olefin	Temp./time	Product	%Yield[a]
1g.	 **(7)**	45 °C/ 4 h	 **(16)**	95
1h.	 **(8)**	50 °C/ 3 h	 **(17)**	75
1i.[b]	 **(9)**	50 °C/ 3 h	 **(18)**	88

[a]Yields refer to single runs and are for pure, isolated products; all compounds were fully characterized by IR, UV, and ^{1}H- and ^{13}C-NMR spectra.

[b]The reaction was also carried out in presence of PPh_3, P(*o*-tolyl)$_3$, and TMEDA.

ligand such as triphenylphosphine (PPh_3), tri-*o*-tolylphosphine [P(*o*-tolyl)$_3$], and tetramethyl ethylenediamine (TMEDA). In all the experiments, a smooth conversion to the reduced product with excellent yield was observed. Choice of solvent is an important factor governing the activity of soluble catalyst in transfer reduction.[1d,15] As most soluble catalysts are often coordinated to solvent, DMF was found to be superior in comparison to non-polar solvents like toluene or carbon tetrachloride.

II-B.3: Conclusion

The present study constitutes a useful condition for chemoselective reduction of C–C double bonds of α,β–unsaturated cyano esters with the aid of potassium formate in presence of catalytic palladium acetate. The reaction possibly involves the "hydridic route" and adds to the β–carbon of conjugated systems. Unlike the other transfer hydrogenation reactions, the halogen, cyano or ester functions remain unchanged during the reduction process. The ability of this reductant to perform conjugate reduction on functionalized alkylidenecyanoacetate in a controlled fashion is noteworthy. The homogeneous catalytic condition offers further use of chiral ligands to promote asymmetric induction. As compared to formic acid or other formate salts, potassium formate exhibited better chemoselectivity and being a cheap and environmentally benign reagent; the reductant system might be able to draw interest of synthetic chemists and industries.

II-B.4: Experimental

II-B.4.1: Preparation of α,β-unsaturated cyanoesters

A series of α,β-unsaturated cyano esters have been prepared from their carbonyl substrates by condensing with ethyl cyanoacetate under Knoevenagel condition.

General Procedure

Ethylcyanoacetate (56.8 g, 50 mmol), aldehyde or ketone (50-70 mmol), ammonium acetate (7.7 g, 10 mmol) and glacial acetic acid (24 g, 40 mmol) was mixed in dry benzene (50 mL) and heated under reflux for 12-24 h in a Dean-Stark water seperator. The cold reaction mixture was washed with (3 x 25 mL) 10% sodium chloride and removed the benzene on a water bath under reduced pressure. The residue was transferred in a 1-litre bottle containing a solution of sodium metabisulphite (65 g) in water (250 mL) and shaked mechanically for 2-6 h. The turbid was diluted with water (400 mL). The unsaturated cyano ester was extracted with (3 x 50 mL) of benzene and dried with anhydrous sodium sulphate. The benzene was removed by distilling at atmospheric pressure until the temperature rises to 90 °C. The crude product was either recrystallized from petroleum ether or was distilled under reduced pressure.

Ethyl 2-cyano-3-phenylacrylate (1)

Colourless crystals, m.p. 48-49 °C [lit.[23] 49 °C].

UV (MeOH): λ_{max} 305 nm.

IR (Nujol): ν_{max} 3020, 2400, 2226, 1727, 1608, 1268, 1215, 1104, 754, 686 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 7.98 (dd, 2H, J = 7.32; 0.96 Hz), 7.56-7.48 (m, 3H), 4.39 (q, 2H, J = 7.12 Hz), 1.40 (t, 3H, J = 7.12 Hz).

Ethyl 2-cyano-3-(4-chlorophenyl)acrylate (2)

Colourless crystals, m.p. 89-90 °C [lit.[23] 90 °C].

UV (MeOH): λ_{max} 311.6 nm

IR(Nujol):ν_{max} 3019, 2400, 2226, 1726, 1609, 1591, 1492, 1269, 1214, 754, 670 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1H), 7.93 (d, 2H, *J* = 8.6 Hz), 7.48 (d, 2H, *J* = 8.6 Hz), 4.39 (q, 2H, *J* = 7.14 Hz), 1.40 (t, 3H, *J* = 7.14 Hz).

Ethyl 2-cyano-3-(4-hydroxyphenyl)acrylate **(3)**

Coourless crystals, m.p. 165-166 °C.

UV (MeOH): λ_{max} 347.0 nm.

IR (Nujol): ν_{max} 3400, 2224, 1720, 1608 cm^{-1}.

Ethyl 2-cyano-3-(pyridin-4-yl)acrylate (**4**)

Pale brown crystals, m.p. 93-94 °C

UV(MeOH): λ_{max} 271.6 nm

IR(Nujol): ν_{max} 2222, 1715, 1605 cm^{-1}.

Ehtyl 2-cyano-3-(furan-2-yl)acrylate (**5**)

Yellow crystals, m.p. 91-92 °C [lit.[23] 93 °C]

UV(MeOH): λ_{max} 335.6 nm.

IR(Nujol): ν_{max} 2410, 2222, 2090, 1739, 1635, 779 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.75 (d, 1H, *J* = 1.6 Hz), 7.39 (d, 1H, *J* = 4.0 Hz), 6.67 (dd, 1H, *J* = 4.0; 1.6 Hz), 4.39 (q, 2H, *J* = 7.14 Hz), 1.38 (t, 3H, *J* = 7.14 Hz).

Ethyl 2-cyano-2-cyclohexylideneacetate (**6**)

Liquid, b.p. 117-121 °C/2 mm Hg.

IR (neat): ν_{max} 2220, 1710, 1598, 907, 732 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.27 (q, 2H, *J* = 7.14 Hz), 2.98 (t, 2H, *J* = 6.0 Hz), 2.66 (t, 2H, *J* = 6.2 Hz), 1.82-1.79 (m, 2H), 1.75-1.70 (m, 2H), 1.69-1.64 (m, 2H), 1.36 (t, 3H, *J* = 7.14 Hz).

Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (7)

Yellow crystals, m.p. 77-78 °C [lit.[24] 79-80 °C]

UV (MeOH): λ_{max} 346.2 nm.

IR (Nujol) : ν_{max} 2361, 1728, 1659, 1528, 757, 669 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.85 (s, 1H), 7.7 (d, 2H, J = 6.6 Hz), 6.7 (d, 2H, J = 6.6 Hz), 4.1 (q, 2H, J = 5.4 Hz), 3.6 (s, 3H), 1.1 (t, 3H, J = 5.4 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 164.1, 162.9, 154.6, 134.0, 124.7, 116.6, 115.1, 99.7, 62.7, 56.0, 14.6.

Tri-*n*-butylstannyl 2-cyano-3-phenylacrylate (8)

The title compound was prepared by transesterification method[21] from ethyl 2-cyano-3-phenylacrylate (1) and *bis*-tri-*n*-butyltin oxide in carbon tetrachloride using a Dean-Stark water separator as gummy syrup in 72% yield.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.15 (s, 1H), 7.95 (m, 2H), 7.47 (m, 3H), 1.70-1.65 (m, 6H), 1.39-1.31 (m, 12H), 0.94 (t, 9H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$, 75MHz): δ 166.6, 153.8, 133.6, 132.5, 131.0, 129.4, 116.7, 105.9, 27.5, 26.9, 17.0, 13.6.

Ethyl 2-cyano-3-phenyl-2-butenoate (9)

Liquid, b.p. 135-137 °C/2 mm Hg [lit.[24] 136-138 °C/2 mm Hg].

UV (MeOH): λ_{max} 279.0 nm.

IR (neat): ν_{max} 2088, 1743, 1646, 1215, 756, 669 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.57-7.40 (m, 5H), 4.37 (q, 2H, J = 7.14 Hz), 2.59 (s, 3H), 1.39 (t, 3H, J = 7.14 Hz).

I-B.4.2: Catalytic trnsfer hydrogenation of α,β-unsaturated cyano esters

A representative procedure

Ethyl 2-cyano-3-(furan-2-yl) propionate (**14**)

To a solution of ethyl 2-cyano-3-furan-2-yl-acrylate (**5**) (500 mg, 2.62 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (12 mg, 2 mol %), HCOOK (440 mg, 5.24 mmol) and stirred the reaction mixture in a sealed tube (screw-cap) under N_2 at 45 °C for 4 h . The mixture was cooled, diluted with water and extracted with ether (3 x 15 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel and elution with ethyl acetate-light petroleum (1 : 9) afforded the desired product (**14**) as colourless oil in 79% (400 mg) yield.

UV (MeOH): λ_{max} 222.0 nm.

IR (neat): ν_{max} 2244, 1747 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 3.79 (m, 1H), 3.28 (m, 2H), 1.31 (t, 3H, *J* = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.4, 149.3, 142.8, 115.9,b 110.9, 108.7, 63.3, 37.3, 36.1, 14.3.

Anal. Calcd, for $C_{10}H_{11}NO_3$ (193.20): C, 62.17; H, 5.74.

Found: C, 62.32; H, 5.96.

Similarly compounds (**10**), (**11**), (**12**), (**13**), (**15**), (**16**), (**17**) and (**18**) were prepared as mentioned in Table 1.

Ethyl 2-cyano-3-phenylpropionate (**10**)

Yield: 92%, liquid.

UV (MeOH): λ_{max} 258.0 nm.

IR (neat): ν_{max} 2989, 2349, 2256, 1746, 1262, 1208, 701 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHZ): δ 7.36-7.25 (m, 5H), 4.21 (q, 2H, J = 9 Hz), 3.72 (dd, 1H, J = 9; 6 Hz), 3.29-3.13 (m, 2H), 1.24 (t, 3H, J = 9 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.5, 135.3, 129.1, 128.8, 127.8, 116.2, 62.9, 39.6, 35.7, 13.9.

Ethyl 2-cyano-3-(4-chlorophenyl)propionate (**11**)

Yield: 96%, liquid.

UV (MeOH): λ_{max} 225.0 nm.

IR (neat): ν_{max} 2372, 2244, 1745, 1674, 1495 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 2H, J = 8.3 Hz), 7.20 (d, 2H, J = 8.3 Hz), 4.22 (q, 2H, J = 7.1 Hz), 3.68 (dd, 1H, J = 8.0; 5.9 Hz), 3.23-3.15 (m, 2H), 1.27 (t, 3H, J = 7.1 Hz)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.0, 133.7, 130.4, 128.9, 127.7, 115.7, 62.8, 39.3, 34.9, 13.9.

Ethyl 2-cyano-3-(4-hydroxyphenyl)propionate (**12**)

Yield: 95%, liquid

UV (MeOH): λ_{max} 242.0 nm.

IR (neat): ν_{max} 3338, 2244, 1742 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, 2H, J = 7.9 Hz), 6.79 (d, 2H, J = 7.9 Hz), 4.25 (q, 2H, J = 7.2 Hz), 3.73 (dd, 1H, J = 8.1; 5.8 Hz), 3.22-3.08 (m, 2H), 1.26 (t, 3H, J = 7.2 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.7, 155.6, 133.9, 130.2, 126.6, 116.3, 63.0, 40.0, 34.8, 13.8.

Ethyl 2-cyano-3-(pyridin-4-yl)propionate (**13**)

Yield: 87%, liquid.

UV (MeOH): λ_{max} 257.4 nm.

IR (neat): ν_{max} 2226, 1720 cm^{-1}.

^{1}H-NMR($CDCl_3$, 300 MHz): δ 8.6 (d, 2H, *J* = 4.5 Hz), 7.23 (d, 2H, *J* = 4.5 Hz), 4.26 (q, 2H, *J* = 7.1 Hz), 3.77 (dd, 1H, *J* = 8.1; 5.9 Hz), 3.27-3.21 (m, 2H), 1.29 (t, 3H, *J* = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.3, 150.2, 129.4, 124.1, 116.2, 63.4, 38.3, 34.7, 13.9.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92.

Found: C, 64.34; H, 5.83.

Ethyl 2-cyano-2-2cyclohexylacetate (**15**)

Yield: 76%, liquid.

IR(neat): ν_{max} 2932, 2360, 2232, 1743, 1451 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.27 (q, 2H, *J* = 7.2 Hz), 3.4 (d, 1H, *J* = 5.7 Hz), 2.07 2.04 (m, 1H), 1.78-1.65 (m, 6H), 1.35 (t, 3H, *J* = 7.2 Hz), 1.29-1.20 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.8, 115.7, 62.5, 44.5, 38.8, 31.0, 29.3, 25.5, 14.5

Ethyl 2-cyano-3-(4-methoxyphenyl)propionate (**16**)

Yield: 95%, liquid.

UV (MeOH): λ_{max} 228.6 nm.

IR (neat): ν_{max} 2226, 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, 2H, *J* = 6.7 Hz), 6.86 (d, 2H, *J* = 6.7 Hz), 4.2 (q, 2H, *J* = 7.14 Hz), 3.78 (s, 3H), 3.68 (dd, 1H, *J* = 8.3; 6.06 Hz), 3.24 – 3.09 (m, 2H), 1.26 (t, 3H, *J* = 7.14 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.5, 159.0, 130.1, 127.2, 116.2, 114.1, 62.7, 55.1, 39.8, 34.9, 13.8.

Tri-*n*-butylstannyl 2-cyano-3-phenylpropionate (**17**)

Yield: 75%, highly viscous liquid.

UV (MeOH): λ_{max} 257.8 nm.

IR (neat): ν_{max} 2230, 1730 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.50-7.12 (m, 5H), 3.71-3.66 (m, 1H), 3.1-2.91 (m, 2H), 1.74-1.58 (m, 6H), 1.41-1.16 (m, 12H), 0.72 (t, 9H, J = 7.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.0, 135.7, 129.4, 128.4, 127.3, 116.3, 62.4, 47.9, 42.3, 27.4, 16.9, 13.3.

Ethyl 2-cyano-3-phenylbutanoate (**18**)

Yield: 88%, liquid.

UV (MeOH): λ_{max} 242.4 nm.

IR (neat): ν_{max} 2243, 1747, 1595, 1446, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.43-7.22 (m, 5H), 4.12 (q, 2H, J = 7.1 Hz), 3.70-3.61(m, 1H), 3.55-3.48 (m, 1H), 1.50 (d, 3H, J = 7.0 Hz), 1.17 (t, 3H, J = 7.1 Hz).

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TETRAHEDRON LETTERS

Palladium-catalysed amination of halopyridines on a KF-alumina surface

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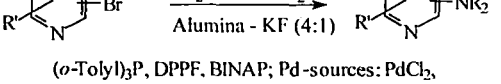
Abstract—Palladium-catalysed C–N hetero cross-coupling reactions between bromopyridines and amines (both primary and secondary) can be efficiently performed on a KF-alumina (basic) surface, thus negating the use of strong bases such as sodium *tert*-butoxide. The reaction conditions are optimised with reference to catalytic systems, solvents and the surface.

Aminopyridines are versatile intermediates for synthetic transformations to biologically active compounds[1] and are known to act as central nervous system stimulants.[2] Their derivatives are often used as ligands in coordination and organometallic chemistry,[3] and have found industrial applications as fluorescent dyes.[4] Most of the early preparative methods for aminopyridines involve aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[5] 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. Buchwald and others[6] have recently developed chelating bis-phosphine-palladium catalysed cross-coupling reactions that allow the preparation of aminopyridines from their corresponding halopyridines.[7] The method involves Pd(0)/bis-phosphine complexes as the effective catalyst for oxidative addition to the carbon–halogen bond, followed by coupling with the amine. The amination is catalyst-specific (Pd–ligand complexes) and very sensitive to the nature of the base.[6a,d] Although this reaction efficiently produces aminopyridines in the presence of chelating bis-phosphine/Pd(0) complexes, the use of strong bases such as sodium *tert*-butoxide is not desirable and remains associated with problems such as in the case of direct amination using NaNHR or $NaNR_2$.[5,8] Furthermore, the use of strong bases greatly limits the functional group tolerance of the process.[9]

The weaker base (Cs_2CO_3) has been employed fo haloaromatics[9] and halothiophenes,[10] but not in th case of halopyridines and its use is limited due to hig solubility in organic solvents and its hygroscopi nature. Since the use of a base is one of the keys to th success of this coupling reaction, we investigated palla dium-catalysed cross coupling of bromopyridines an amines on a KF-alumina (basic) surface. KF-alumin has been successfully employed in many other cases s as to exploit its basicity on the surface[11] and ver recently Pd-catalysed C–C couplings (Suzuki, Heck Stille, Trost-Tsuji) have been reported using KF-alu mina under mono-mode microwave irradiation.[12] Th report describes our results, which constitute a conve nient and efficient heterogeneous method for C–N cou pling by Pd-catalysed amination of halopyridines o KF-alumina (basic) surface (Scheme 1).

As can be seen from the results presented in Table the amination on KF-alumina surface works with di ferent bromopyridines. While 2-bromopyridine (entri 1 and 2) reacts with different amines smoothly, 3-bro mopyridine (entry 7) undergoes amination in relative poor yield. Amination of dibromopyridines affor only monoamine derivatives in good to excellent yield In the case of 2,5-dibromopyridine (entries 8 and 9 amination occurs selectively at the 2-position. Buch



(*o*-Tolyl)$_3$P, DPPF, BINAP; Pd-sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$

Scheme 1.

Keywords: aminopyridines; palladium catalyst; carbon–nitrogen cross coupling; KF-alumina.

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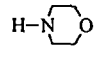
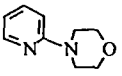
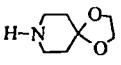
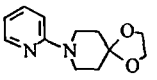
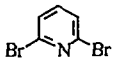
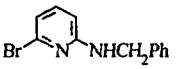
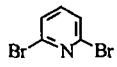
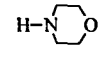
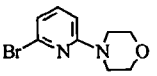
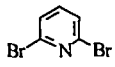
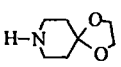
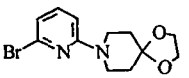
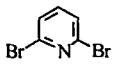
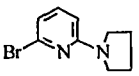
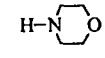
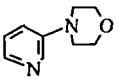
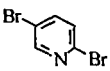
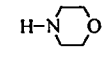
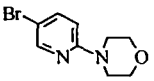
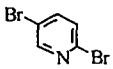
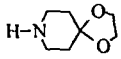
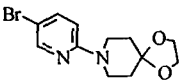
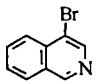
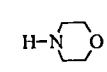
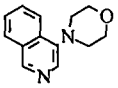
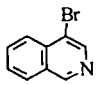
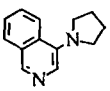
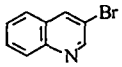
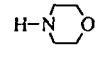
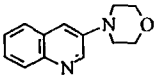
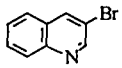
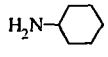
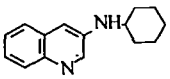
PII: S0040-4039(02)01852-X

Table 1.

Entry	Bromoarene	Amine	Catalyst[a]	Conditions[b]/ time (h)	Product	Yield(%)[c]
1			[A]	2 / 8		70
2			[A]	2 / 8		58
3		H_2NCH_2Ph	[H]	2 / 8		90
4			[A]	1 , 2 / 5		78
5			[A]	2 / 5		62
6			[A]	2 / 5		91
7			[F]	1 , 2 / 9		48
8			[A]	1 , 2 / 5		92
9			[A]	2 / 5		73
10			[E], [F]	1 , 2 / 6		86
11			[F]	2 / 6		90
12			[F]	2 / 6		78
13			[F]	2 / 8		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, 9).

wald observed complete bis-amination of 2,6-dibromopyridine using Pd$_2$(dba)$_3$-dppe catalyst in the presence of excess amine.[7a] Our conditions, however, yielded monoamines as the major products even after prolonged reaction times and in the presence of excess amine (entries 3–6). This selectivity offers an advantage for further reaction with the other halogen substituents. In the bicyclic systems, 4-bromoisoquinoline (entries 10 and 11) and 3-bromoquinoline (entries 12 and 13) undergo amination efficiently.

A great deal of experimentation on the cross couplin of bromopyridines with primary and secondary amine was carried out in order to optimise the reaction condi tions. Palladium sources, ligand, solvent and the sup port (KF-Al$_2$O$_3$) were optimised and several details ar worthy of comment. Firstly, different palladium source like PdCl$_2$, Pd(OAc)$_2$, Pd$_2$(dba)$_3$, Pd(acac)$_2$ an Pd[PPh$_3$]$_4$ complexing with either mono-phosphine [(*o* tolyl)$_3$P] or bis-phosphines (BINAP and DPPF) wer employed as the catalytic systems. The Pd[(*o*

tolyl)$_3$P]$_2$Cl$_2$ and Pd$_2$(dba)$_3$/BINAP complexes were found to be most effective in this amination process (Table 1). The formation of bis-(pyridyl) complexes using monophosphine ligands, as proposed by Buchwald,[7a] 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-Al_2O_3 surface with a slight excess of amine and without solvent. Toluene and xylene have been used as solvents with almost similar effects, whilst the presence of DMF as a co-solvent induces faster debromination (entry 10). 2-Bromopyridine (entries 1 and 2) 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 that 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) catalysed 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.

Experimental

General procedure

Preparation of activated Al_2O_3/KF: 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 min 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 h, cooled under N_2 and used for reaction.

To a mixture of 2,6-dibromopyridine (473 mg, 2 mmol), benzylamine (856 mg, 8 mmol), Pd(OAc)$_2$ (10 mg, 0.04 mmol) and (±) BINAP (50 mg, 0.08 mmol) was added activated Al_2O_3/KF (2 g). The mixture was intimately stirred at 90–100°C for 8 h under nitrogen. After cooling to room temperature the semi-solid mass was washed repeatedly with ether (4×15 ml), combined and concentrated. The residue was purified by silica gel column chromatography (petroleum-ether:EtOAc= 20:1) to give 2-benzylamino-6-bromopyridine (475 mg, 90%); mp 85°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.46 (d, 2H, J=5.9 Hz), 5.18 (br.s, 1H), 6.24 (d, 1H, J=8.2 Hz), 6.73 (d, 1H, J=7.5 Hz), 7.20 (dd, 1H, J=8.2; 7.5 Hz), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.3, 104.5, 116.1, 127.3, 127.4, 128.7, 138.3, 139.5, 140.2, 158.7.

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Microwave-assisted Suzuki coupling on a KF–alumina surface: synthesis of polyaryls

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Abstract—A range of conjugated polyaryls has been synthesized through one-pot microwave assisted palladium-catalyzed consecutive Suzuki coupling reactions on a KF–alumina surface with notable features including rapid reaction times, solvent-free conditions, high yields, atom economic and air-insensitive reactions.

Biaryls and higher homologues are an important class of conjugated polyaromatic compounds, originating from benzene as unique building blocks. On the one hand, multinuclear aromatics develop the concept of aromaticity and supramolecular benzene chemistry,[1] and on the other hand, lead to wide applications in material and biological sciences.[2] Polyaryls find several applications as liquid crystals,[2a] laser-dyes[2b] and conducting polymers.[2c,d] For example, the terphenyls (*o*-, *m*-, *p*-isomers) are used industrially as heat storage and transfer agents and as textile dye carriers whilst the *p*-isomer has found application as a laser dye. 9,10-Diphenylanthracene is used as a fluorescer in a peroxyoxalate chemiluminescence system.[3] In addition, biaryls and higher homologues are often present as subunits in numerous biologically active natural products, pharmaceuticals and agrochemicals.[4] The synthesis of polyaromatic hydrocarbons (PAHs) and their derivatives has therefore been of considerable interest to organic and physical chemists for many years.

A variety of methods are available for the synthesis of biaryls via coupling of benzene rings promoted by different reagents.[5] The transition metal-catalyzed cross-coupling of Grignard reagents with dihalobenzenes[5b,c] and other methods[5d] produce the desired terphenyls in poor yields. However, most of the classical methods are often complicated by harsh reaction conditions, lack of selectivity and generality, or the requirement of expensive reagents. Moreover, many of the methods are not being recognized from the viewpoint of green chemistry. Recent literature reports confirm that palladium-catalyzed Suzuki coupling reactions of aryl halides with aryl boronic acids (or esters) have become convenient and widely used synthetic methods for regioselective aryl–aryl bond formation.[5,6] The reasons are manifold: ease of access of the organoboronic species, broad range of functional group tolerance, low toxicity of the inorganic residues, etc. However, although the Suzuki coupling reaction is one of the most useful methods yet developed for the syntheses of both symmetrical and unsymmetrical biaryls, there are still improvements and further applications that could be made to render it more effective. Surprisingly, little attempt has been made to investigate consecutive cross-couplings in a one-pot reaction. A few sporadic examples of bis-Suzuki couplings are known in the literature[5e,7] and therefore much new research should be extended towards the scope and the amelioration of the economical and ecological parameters of the Suzuki reaction. We envisaged that a multi-Suzuki coupling of di-, tri- or tetra-haloaromatics with aryl boronic acids could lead to terphenyls and higher homologues in a one-pot reaction. Kabalka et al.[8a] and Villemin et al.[8b] have reported that Suzuki cross-coupling reactions can be efficiently performed on the surface of KF–alumina with microwave irradiation. In conjunction with our interest in hetero cross-coupling reactions on KF–alumina surfaces,[8c] we investigated microwave-assisted palladium-catalyzed coupling of polyhaloaromatics with arylboronic acids on KF–alumina and other inorganic oxides. In this letter, we report our results, which expand the scope of the Suzuki reaction on a solvent-free inorganic surface leading to the synthesis of a large variety of polyaromatics.

Keywords: polyaromatic hydrocarbons; Suzuki coupling; palladium; KF–alumina; microwave assisted reactions.

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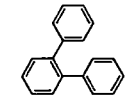
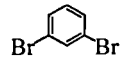
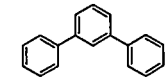
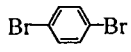
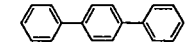
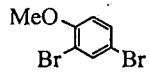
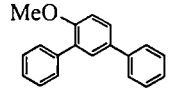
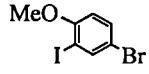
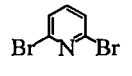
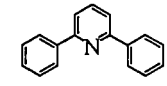
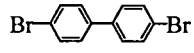
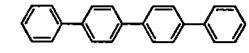
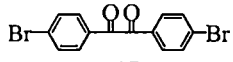
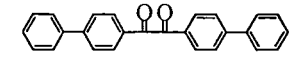
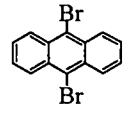
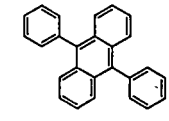
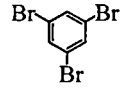
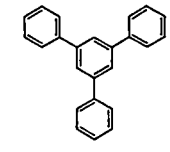
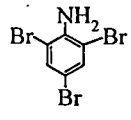
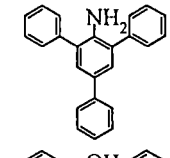
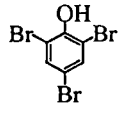
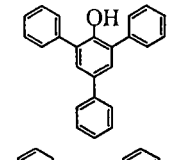
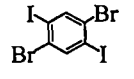
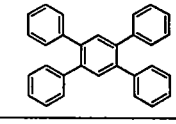
Table 1. Solid-supported [KF–Al_2O_3] polyarylations of polyhaloaromatics with phenyl boronic acid using catalytic $Pd(OAc)_2$ under microwave irradiation

Entry	Haloaromatics	Conditions Power (W)/ Time	Products [a]	% Isolated Yields [b]
1	 **1**	80 W / 10 min	 **2**	58
2	 **3**	80 W / 15 min	 **4**	83
3	 **5**	160 W / 15 min	 **6**	63
4	 **7**	320 W / 7 min	**4**	88
5	 **8**	80 W / 20 min	 **9**	63
6	 **10**	80 W / 20 min	**9**	65
7	 **11**	160 W / 10 min	 **12**	91
8	 **13**	400 W / 5 min	 **14**	53
9	 **15**	240 W / 10 min	 **16**	58
10	 **17**	320 W / 10 min	 **18**	88
11	 **19**	240 W / 7 min	 **20**	90
12	 **21**	240 W / 10 min	 **22**	75
13	 **23**	240 W / 10 min	 **24**	76
14	 **25**	320 W / 7 min	 **26**	55

[a] All the products gave satisfactory spectral data (^{1}H- and ^{13}C-NMR) and the known compounds were compared with reported mps; [b] Yields refer to the average from 2-3 runs.

We initially focused our attention on the cross-coupling of dibromoaromatics with phenylboronic acids on KF– alumina using microwave irradiation. As can be seen from the results presented in Table 1, the dibromobenzenes afforded the corresponding terphenyls as the major products (entries 1–3). Varying amounts of mono-substituted biaryls (15–20%) were detected on TLC, which could be easily separated from the terphenyls by column chromatography. While comparing the reaction rate between dibromo- and diiodoarenes (entries 2 and 4), the latter afforded the corresponding terphenyl **4** in a slightly better yield. However, different conditions were required to accomplish the desired bis-coupling. 2,4-Dibromoanisole (entry 5) and 4-bromo-2-iodoanisole (entry 6) afforded the terphenyl **9** in almost comparable yields. Thus, no significant reactivity difference between bromo- and iodo-substituents was observed. Among the other dibromoarenes, 2,6-dibromopyridine (entry 7) and 9,10-dibromoanthracene (entry 10) yielded the desired products **12** and **18**, respectively, in excellent yields. The biphenyl systems (entries 8 and 9) produced the corresponding products **14** and **16** in yields of 50–60%. In the case of tribromoaromatics (entries 11–13), the corresponding tris-coupled compounds **20**, **22** and **24** were isolated as the major products (Table 1). Small amounts of mono- or bis-coupled products were detected by TLC. The 1,4-dibromo-2,5-diiodobenzene **25** yielded the tetraphenylbenzene **26** in 55% yield (entry 14). Villemin and co-workers obtained their best results on Suzuki couplings with aryl iodides using mono-mode microwave irradiation.[8b] Our conditions using KF–alumina (1:4) and irradiation from a domestic microwave oven, however, enabled polyarylations in good to excellent yields. We also examined such poly-Suzuki couplings on other inorganic surfaces (Table 2). The results were best on the surface of KF–alumina (1:4). The reactions were carried out in air. All the reactants were intimately mixed with the inorganic surface before being placed in a domestic microwave oven (Kenstar; Model OM-9925E) and irradiated at the appropriate power (W) and time (Table 1). In many Suzuki cross-couplings, a crucial role is played by the ligands,[9] which complex with palladium salts. The above solvent-free conditions, however, required no such ancillary ligands, which is advantageous in view of atom economy in the reaction.

Table 2. Multi-Suzuki reactions on different inorganic surfaces under microwave irradiation without solvent [A/B/$Pd(OAc)_2$ = 1/2.5/0.04 mmol on 1.5 g of B]

Entry	Substrate (A)	Surface (B)	Conditions	Yield (%)
1	1,3-Dibromobenzene	$KF–Al_2O_3$ (1:4)	80 W/15 min	83
2	1,3-Dibromobenzene	Al_2O_3	80 W/15 min	20–25
3	1,3-Dibromobenzene	MgO	80 W/15 min	25
4	1,3-Dibromobenzene	$MgO–K_2CO_3$ (3:2)	80 W/15 min	30

In summary, we have demonstrated that it is possible to perform palladium-catalyzed Suzuki couplings of polyhaloaromatics with phenyl boronic acid on a surface of KF–alumina with the aid of microwave irradiation from a domestic microwave oven. The method is fast, operationally simple, and allows rapid access to a variety of polyaromatic hydrocarbons.

Representative procedure for a multi-Suzuki coupling: 1,3-Dibromobenzene **3** (236 mg, 1.0 mmol), phenyl boronic acid (305 mg, 2.5 mmol) and palladium acetate (10 mg, 0.04 mmol) were intimately mixed with 1.5 g of KF–alumina (prepared according to Ref. 8c) and the mixture was irradiated in a domestic microwave oven at 80 W for 15 min. The solid mixture was then placed on a silica gel column and eluted with petroleum ether:EtOAc (99:1) to furnish *m*-terphenyl **4** (190 mg, 83%); mp 87–88°C (lit.[10] 89°C); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.84 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 126.1, 127.2, 127.4, 128.8, 129.2, 141.1, 141.7.

Acknowledgements

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A Simple Protocol for Direct Reductive Amination of Aldehydes and Ketones Using Potassium Formate and Catalytic Palladium Acetate

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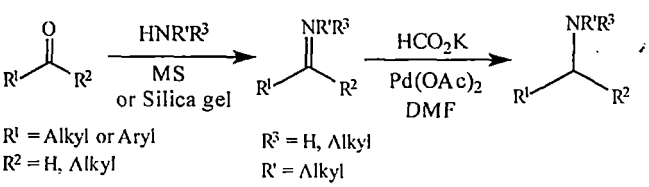
Abstract: A method for direct reductive amination of aldehydes and ketones, including α,β-unsaturated carbonyl compounds, has been developed, which requires potassium formate as reductant and palladium acetate as catalyst. Suitable amines include both primary and secondary aliphatic and aromatic amines.

Key words: reductive amination, potassium formate, palladium acetate, one-pot reaction

The direct reductive amination of carbonyl compounds[1] is a useful organic transformation for preparing primary, secondary and tertiary amines. The carbonyl compound initially reacts with ammonia or amine to form an imine, which then undergoes reduction in presence of hydrogen or hydride ion (Scheme 1). The term 'direct reductive amination' is used to describe a reaction in which a mixture of the carbonyl compound and the amine is treated with suitable reducing agent in a one-pot operation.[1b] Several reductive systems are known to effect the reduction of the C–N double bond of the imine. The Borch reduction,[2] one of the early methods, involves sodium cyanoborohydride, [$NaBH_3CN$], as the reductant. However, use of excess reagent (up to 5-fold) along with toxic cyanide as the by-product limits its wide applications. The alternative sodium triacetoxyborohydride, [$NaBH(OAc)_3$],[3] has not been successful for aromatic and unsaturated ketones. Other reagents include $ZnCl_2$–$Zn(BH_4)_2$;[4] $NiCl_2$–$NaBH_4$;[5] Ti(*i*-PrO)$_4$–polymethylhydrosiloxane;[6] Ti(*i*-PrO)$_4$–$NaBH_4$;[7] Bu_3SnH;[8] Bu_2SnClH and Bu_2SnIH;[9] decaborane;[10] silica gel–$Zn(BH_4)_2$;[11] Et_3SiH–trifluoroacetic acid;[12] pyridine–BH_3;[13] phenylsilane–dibutyltin dichloride.[14] All these methods require stoichiometric or excess quantities of the hydrides, which are generally highly reactive and expensive as well. Furthermore, use of tin hydrides in some protocols is not recommended for large-scale preparation as the residual insoluble tin compounds pose a great risk in its elimination. On the other hand, use of formic acid as the source of hydrogen, called the Wallach reaction, or ammonium salts of formic acid, called the Leuckart reaction, often yields the N-formyl derivative of the amine instead of the free amine.[15] Recently, we[16a] and other groups[16b] have shown that potassium formate promoted by palladium acetate can reduce efficiently the conjugated C-C double bond. It therefore appeared reasonable to investigate whether potassium formate, which is soluble in polar organic solvents and in water, with activation by palladium salt could significantly reduce the C-N double bond of the imine formed in the direct reductive amination reaction. We report herein our observation, which constitutes a one-pot reductive amination protocol for aldehydes and ketones, including conjugated ones, with the aid of potassium formate and catalytic palladium acetate.



Scheme 1

To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 1). Both primary and secondary amines, such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including chloro (entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. Although acetophenone is a difficult case for some reductive amination protocols, use of excess potassium formate (2–4 mmol) and a slight excess of palladium acetate (5 mol%) gave reductive amination of the ketones at a rate comparable to that of other substrates. The process is equally effective for heteroaromatic systems (entry 5). Reductive amination of cinnamaldehyde (entry 12) with cyclohexyl amine, however, proceeded with concomitant reduction of the C–C double bond. Unlike the Leukart reaction or the Wallach reaction, no N-formyl derivatives were formed in this protocol.

It is well known that aldehydes generally form imines faster than ketones. In this protocol, separate conditions were employed for imine preparation prior to addition of reducing agent. Whereas the aldehydes (except cinnamaldehyde) were reacted with amines in presence of activated molecular sieves (4 Å), the imines from the ketones were prepared on a surface of silica gel following the procedure of Ranu et. al.[11] However the imines prepared by using either molecular sieves or silica gel were directly taken in dimethyl formamide and subjected to reduction by adding palladium acetate (2–5 mol%) and potassium formate

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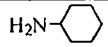
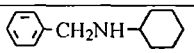
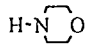
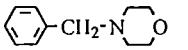
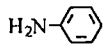
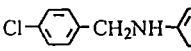
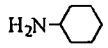
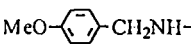
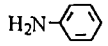
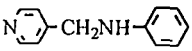
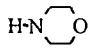
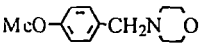
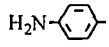
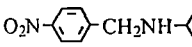
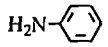
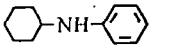
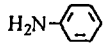
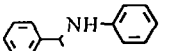
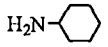
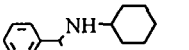
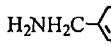
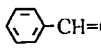
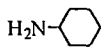
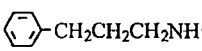
Table 1 Direct Reductive Amination of Aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

Entry	Substrate 1	Amine 2	Condition[a]/Temp./ Time (h)	Product3	Yield (%)[b]
1			A/40 °C/3		68
2			A/40 °C/4		62
3			A/50 °C/5		67
4			A/40 °C/3		75
5			A/40 °C/3		86
6			A/50 °C/5		67
7			A/50 °C/5		56
8			B/50 °C/5		70
9			B/60 °C/6		76
10			B/60 °C/6		83
11			B/60 °C/6		80
12			B/50 °C/5		69

[a] Conditions A: Aldehyde + Amine in DMF with MS (4 Å) and stirred at r.t. for 3–5 h; B: Ketone + Amine intimately mixed on activated silica and stirred at r.t. for 5–6 h.

[b] Yield are reported after chromatographic purification (2–3 runs). Satisfactory spectral data were obtained for all the amines (products).

(2–3 equiv) and heated at 40–60 °C for 3–6 hours.[17] The products were obtained after purification on column chromatography. In general, the reaction procedure is very simple and the reaction condition appears to be mild.

In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium catalysed hydride addition is probably the cause of the C–N double bond reduction, the possibility for asymmetric reductive amination in presence of a chiral ligand might be explored.

Acknowledgement

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(17) **General Procedure for Aldehydes.** For the aldehydes (listed in Table 1) except cinnamaldehyde:
A solution of *p*-anisaldehyde (680 mg, 5 mmol) and cyclohexylamine (500 mg, 5 mmol) in dry DMF (5 mL) was magnetically stirred at r.t. for 4 h, in presence of molecular sieves (4 Å). To the resulting reaction mixture were added HCOOK (840 mg, 10 mmol) and palladium acetate (22 mg, 0.1 mmol). The mixture was then heated at 40 °C for 3 h to complete the reaction (TLC) and after cooling it was diluted with ice-cold water (15 mL). The mixture was extracted with ether (3 × 20 mL). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by column chromatography over silica gel. Elution with ethyl acetate–hexanes (1:19; R_f 0.26) furnished *N*-cyclohexyl *p*-methoxybenzyl amine **4** (815 mg, 75%) as an oil: IR(neat): 1246, 1300, 1510, 1610, 2851, 2925 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.31 (m, 6 H), 1.61 (br, 1 H), 1.70–1.92 (m, 4 H), 2.43–2.50 (m, 1 H), 3.73 (s, 2 H), 3.78 (s, 3 H), 6.84 (d, 2 H, *J* = 8.3 Hz), 7.22 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.2, 33.4, 50.3, 55.2, 56.0, 113.7, 129.2, 132.9, 158.4.

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Palladium Mediated Chemoselective Reduction of α,β-Unsaturated Cyano Esters with Potassium Formate

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ABSTRACT

A number of α,β-unsaturated cyano esters have been chemoselectively reduced with potassium formate as hydrogen donor, and palladium(II) acetate as homogeneous catalyst, in DMF without any concomitant reduction of cyano or carboxylate or halogen groups.

Key Words: Hydrogen transfer reduction; α,β-Unsaturated cyano esters; α,β-Unsaturated tin carboxylate; Palladium acetate; Potassium formate.

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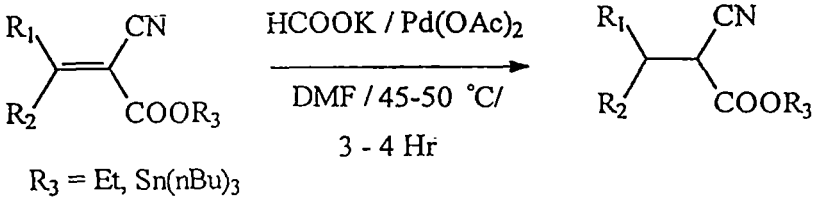
Chemoselective reduction of carbon–carbon multiple bond in conjugated systems is an important process in organic synthesis.[1] Despite the bewildering variety of reducing agents available to synthetic chemists, new and selective reductants are in constant demand. Transition metal-catalyzed hydrogen transfer reaction with the aid of a hydrogen donor, such as trialkyl ammonium formate,[2] and other hydrides like *n*-Bu_3SnH,[3] NaH_2PO_3/H_2O,[4] $Ph_2SiH_2/ZnCl_2 \cdot H_2O$,[5] triethoxysilane–water,[6] are some of the examples employed for selective conjugate reduction. In most cases, direct source of hydride is used for conjugate addition to the more nucleophilic β-carbon, whereas formic acid and its salts are believed to be a source of hydride in situ,[7] which eventually adds to the β-carbon. Cacchi et al.[8] has recently reported a combination of $Pd(OAc)_2$/HCOOK as a convenient alternative reductant for conjugate reduction of α,β-unsaturated carbonyl compounds. On the other hand, reduction of conjugated nitriles and cyano esters using molecular hydrogen or Pd-catalyzed hydride-transfer afforded with reduction of the cyano group as well.[9] For example, reduction of α,β-unsaturated cyano esters in presence of Pd/C and *p*-menthene (as hydrogen donor) led to reduction of not only the C=C double bond, but also the nitrile function to a methyl group.[10] Moreover, reduction of nitrile using a combination of Pd/C and formic acid seemed to be very variable in many other examples.[11] Early studies on reduction of alkylidenecyanoacetic esters using sodium borohydride at room temperature led to reduction of C=C double bond as well as reduction of the ester to alcohol.[12] Sodium borohydride has however been successfully used for reduction of **1a**[13] and sodium cyanoborohydride has selectively reduced α,β-unsaturated esters, nitriles, and nitro compounds.[14] However, metal hydrides are generally highly reactive and expensive reagents and cyanoborohydride generates toxic byproducts upon workup. Very recently, Hantzsch 1,4-dihydropyridines (HEH) has been employed for selective reduction of α,β-unsaturated cyano esters.[15] This procedure, however, involves specific reagent (Hantzsch 1,4-dihydropyridines) and after the reaction the redox products require separation. Consequently, it appeared to us of interest to check the efficacy of $Pd(OAc)_2$/HCOOK combination in reduction of more functionalized α,β-unsaturated cyano esters. The study could be of further importance, as the soluble chiral Pd-catalyzed hydrogen transfer reactions are known to induce asymmetry in the product.[16] The chiral Pd-complex catalyzed conjugate reduction without any concomitant reduction of other functional groups might produce asymmetric compounds for further elaboration to useful synthetic intermediates. We wish to report that α,β-unsaturated

cyanoesters possessing other sensitive functional groups can be smoothly converted into the corresponding saturated cyanoacetates according to Sch. 1. The reduction appeared to be mild and efficient as the nitrile, ester (alkyl and tri-*n*-butyl stannyl), and halogen functions remain unaffected.

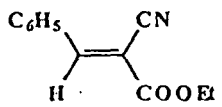
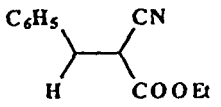
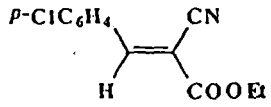
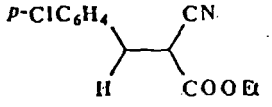
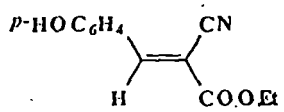
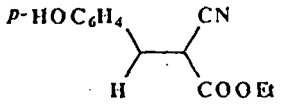
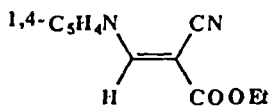
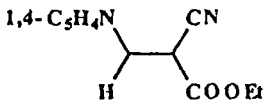
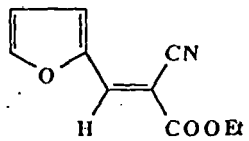
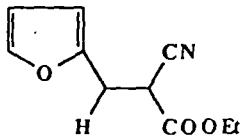
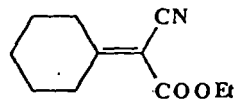
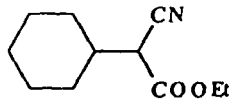
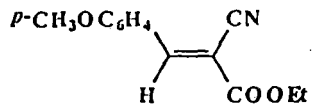
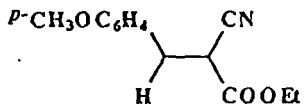
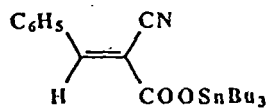
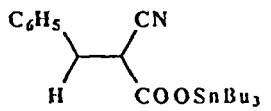
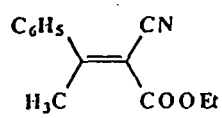
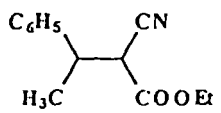
A series of α,β-unsaturated cyano esters (**1a–i**) have been prepared from their carbonyl substrates condensed with ethyl cyanoacetate under Knoevenagel condition.[17] The unsaturated cyano ester was dissolved in DMF and added $Pd(OAc)_2$ (2 mol%), HCOOK (2 equivalent) and stirred at 45–50°C for 3–4 h in a screw-cap sealed tube under N_2. After usual workup, the product was purified by column chromatography over silica gel to afford the reduced product in good to excellent yield (Table 1). Although dehalogenation of halo-aromatics is known under transfer reduction using heterogeneous catalyst,[18] the present method did not proceed with cleavage of carbon–halogen bond (Entry **1b**). The stannyl ester (Entry **1h**), prepared from its ethyl ester by transesterification with *bis*-tri-*n*-butyltin oxide,[19] also survived demetallation under the reaction condition.[20] To observe any effect of ligand participation in the catalytic process, the reaction was carried out in presence of various ligands, such as PPh_3, P(*o*-tolyl)$_3$ and TMEDA with the alkylidenecyanoacetic ester (**1i**). In all the experiments, a smooth conversion to the reduced product with excellent yield was obtained. Choice of solvent is an important factor governing the activity of soluble catalyst in transfer reduction.[11] As most soluble catalysts are often coordinated to solvent, DMF was found to be superior in comparison to non-polar solvents like toluene or carbon tetrachloride.

Thus the present study constitutes a useful condition for selective reduction of C=C double bond of α,β-unsaturated cyano esters using $HCOOK/Pd(OAc)_2$ as simple and inexpensive reductant. The reaction possibly involves hydride transfer in situ at the β-carbon and proceeds without any concomitant reduction of cyano, ester, or halogen groups. The ability of this reductant to perform conjugate reduction on functionalized



Scheme 1.

Table 1. Reduction of α,β-unsaturated cyano esters by using HCOOK and catalytic $Pd(OAc)_2$.

No.	Olefin	Temp./time	Product	Yield (%)[a]
1a		45°C/3 h		92
1b		45°C/4 h		96
1c		50°C/4 h		95
1d		50°C/3 h		87
1e		45°C/4 h		79
1f		50°C/4 h		76
1g		45°C/4 h		95
1h		50°C/3 h		75
1i[b]		50°C/3 h		88

[a]Yields refer to single runs and are for pure, isolated products; all compounds were fully characterized by IR, UV, and ^{1}H- and ^{13}C-NMR spectra.
[b]The reaction was also carried out in presence of PPh_3, P(*o*-tolyl)$_3$, and TMEDA.

alkylidenecyanoacetate in a controlled fashion is noteworthy. The homogeneous catalytic condition offers further use of chiral ligands to promote asymmetric induction. Future studies will be attempted in this direction.

EXPERIMENTAL

A representative procedure (Table 1, Entry **1e**) is as follows: To a solution of the unsaturated cyano ester (0.50 g, 2.62 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (12 mg, 2 mol%), HCOOK (0.44 g, 5.24 mmol) and stirred the reaction mixture in a sealed tube (screw-cap) under N_2 at 45°C for 4 h. The mixture was cooled, diluted with water and extracted with ether (3 × 15 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel and elution with ethyl acetate–light petroleum (1:9) afforded the desired product as colorless oil in 79% yield. IR (neat): ν_{max} 2244, 1747 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3H, J = 7.1 Hz), 3.28 (m, 2H), 3.79 (m, 1H), 4.26 (q, 2H, J = 7.1 Hz), 6.23 (s, 1H), 6.30 (s, 1H), 7.34 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 36.1, 37.3, 63.3, 108.7, 110.9, 115.9, 142.8, 149.3, 165.4.

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PALLADIUM CATALYZED AMINATION OF HALOPYRIDINES ON A KF-ALUMINA SURFACE

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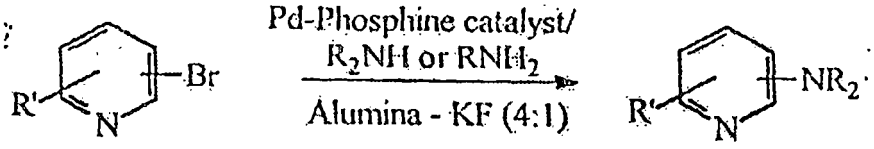
Recent development of palladium catalysis in amination of aryl halides seems to have overwhelmed other synthetic methods for the construction of an aryl-nitrogen bond. The synthesis of arylamines by the reaction of aryl halides (or triflates) with primary and secondary amines in presence of palladium-phosphine catalyst and sodium *tert*-butoxide as a base has become a valuable synthetic tool for a variety of applications. Although this reaction has been employed for preparing aminopyridines, the use of strong base greatly limits tolerance of a wide range of functional groups.

In order to avoid use of strong bases, we investigated amination of halopyridines on a surface of potassium fluoride-alumina. This poster paper describes our results, which constitutes a convenient and efficient heterogeneous method for carbo-nitrogen coupling by palladium-catalyzed amination of halopyridines on KF-alumina surface (Scheme 1).

Scheme 1



Phosphine: (*o*-Tolyl)$_3$, DPPF, BINAP; Pd-sources: $PdCl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd[PPh_3]_4$