Part II

"Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface"

II.1: Introduction

Aromatic amines are important substructures in natural products and organic materials.[1] Arylamines are attractive targets for chemical synthesis because of their prevalence and wide utility. One of their earliest applications was in the production of brightly colored synthetic dyes, introduced in the late nineteenth century.[2] Arylamines have a large number of other applications and are thus attractive targets for chemical synthesis. They are found in biologically active compounds such as pharmaceuticals[3] and agrochemicals.[4] Several commonly occurring DNA lesions are arylamines, and they have been the target of recent synthetic efforts.[5] Arylamines have also been employed as ligands for transition metals,[6] and in the design of conductive polymers[1b] and other electronically interesting materials.[7]

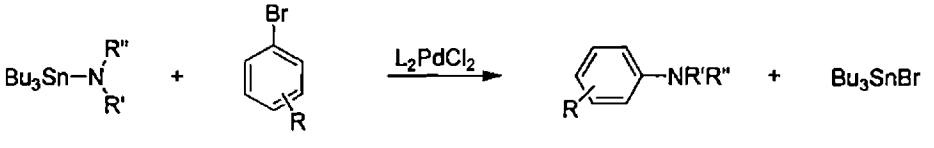
The historical importance of aromatic amines, which is also reflected in their industrial relevance, spurred interest in developing methods for their production. Over the years a number of cleverly designed and extremely useful methods of aryl C–N bond formation have been reported.[6] Most of the early preparative methods for aromatic amines involve electrophilic nitration and subsequent reduction, alkylation and dealkylation of amines, rearrangement, hydrogenolysis, aromatic nucleophilic substitution by S_NAr, benzyne or $S_{RN}1$ reactions.[9]

The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C–N bond formation and has many potential applications for the synthesis of aniline derivatives which are inaccessible through other routes.[10] Palladium–catalyzed amination reactions are fundamentally important organic transformations that have received tremendous attention over the past few years.[11] The transition metal–mediated coupling of amines with aryl halides is regeoselective, does not require activating groups, and occurs under relatively mild conditions. Recently, Buchwald *et al.*[12] and Hartwig *et al.*[13] have demonstrated a valuable palladium catalyzed *N*–arylation of various amines with aryl halides and triflates as a powerful tool for the formation of an aromatic nitrogen bond in the synthesis of a variety of arylamines. The reactions can be carried out at a lower temperature under mild conditions than the copper–mediated classical Ullmann condensation. Elegant work by Buchwald,[12] Hartwig,[13] and others[14] has led to significant improvements in amination methodology since its discovery by Migita and co–workers[15] in 1983. Most of the reported methods employ electron–rich phosphine ligands,[16] possessing either

a ferrocene[17] or a biphenyl backbone,[18] or bulky nucleophilic *N*–heterocyclic carbenes (sometimes referred to as "phosphine mimics").[19] Chelating phosphines such as 1,1'–*bis*(diphenylphosphino)ferrocene (DPPF)[20] and 2,2'–*bis*(diphenylphosphino)1,1'–binaphthayl (BINAP)[21] have been demonstrated to exhibit improved catalytic activity in this type of transformation. Commonly used bases in Pd–catalyzed aminations are *t*–BuONa,[12] Cs_2CO_3,[22] K_3PO_4,[13] MeONa and *i*-PrONa.[23] The combination of Pd / rac. BINAP has been found to be an excellent catalyst system for the coupling of primary amines with aryl bromides.[21] Additionally, the BINAP catalyst system functions well in the presence of the weak base Cs_2CO_3, allowing for a high level of functional group tolerance.[22] Although a general protocol had been developed for the Pd–catalyzed cross coupling of primary and secondary amines with aryl bromides using sodium *tert*–butoxide,[22] this base causes problems with a number of common functional groups such as, esters, aldehydes, enolizable ketones, nitriles and nitro groups. The scope of this method was further expanded by the use of Cs_2CO_3,[22] allowing the coupling of aryl bromides, which were incompatible with *t*–BuONa.

Kosugi and Migita first reported the C–N coupling of aryl halides with tin amides (Scheme 1) using palladium catalysts containing tri–*o*–tolylphosphine as ligand.[15,24] Although these reactions were limited in scope and possessed problems from the toxicity and environmental instability of tin amides, the potential for palladium complexes to catalyze aromatic carbon–nitrogen bond formation in a synthetically valuable fashion was suggested.

Scheme 1

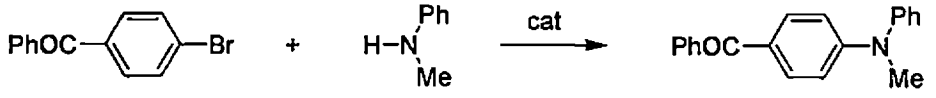


$L_2PdCl_2 = [PdCl_2\{P(o\text{-toyl})_3\}_2]$

Guram and Buchwald[25] subsequently developed methodology in which the Migita process was generalized and greatly simplified. The use of stoichiometric amounts of organo tin compounds is the main disadvantage of this method both for ecological reasons and with regard to practicability. Independently, Buchwald *et al.*[26] and Hartwig *et al.*[27] reported the first catalytic amination of aryl bromides with free amines (Scheme 2). Instead of isolation or generation of a tin amide *in situ*, the amination reactions were conducted by reaction of an aryl halide with the

combination of amine and stoichiometric amounts of sterically hindered base such as, *t*–BuONa or silylamide base in toluene or THF at temperature 65–100 °C.

Scheme 2

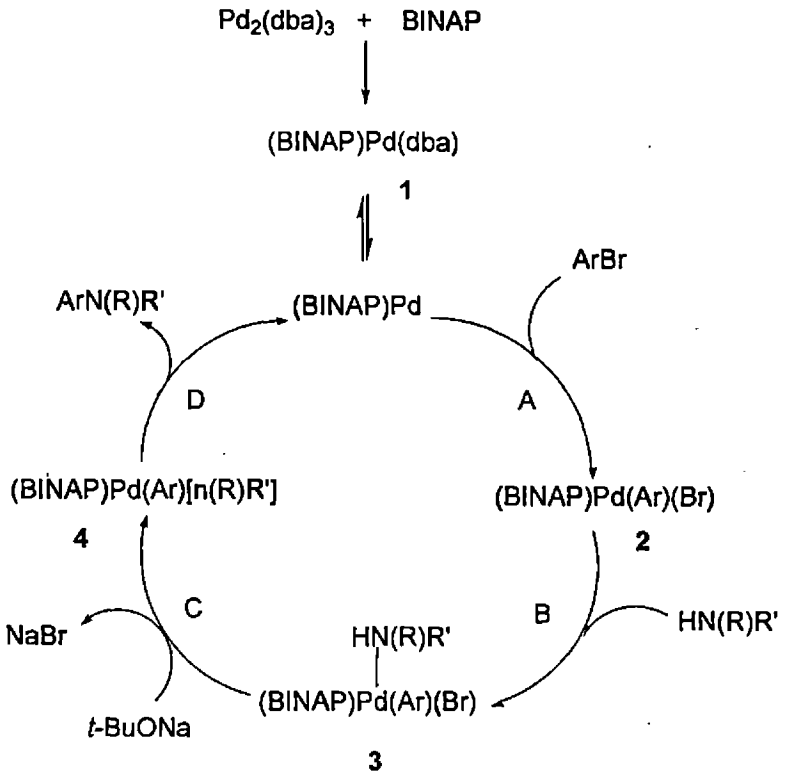


89 %

cat = $Pd_2(dba)_3$ / P(*o*-tolyl)$_3$ or $PdCl_2[P(o\text{-tolyl})_3]_2$

Palladium–catalyzed cross coupling of aryl bromides with amines have stressed the need to employ P(*o*–tolyl)$_3$ as a ligand in order to obtain reasonable yields of the desired aniline products.[15,25–28] The importance of this ligand was attributed to its steric bulk, which is believed to hinder the formation of *bis*(phosphine) palladium complexes as intermediates. Hartwig has demonstrated through kinetics studies that oxidative addition, palladium–nitrogen bond formation, and reductive elimination proceed through mono-phosphine palladium complexes when P(*o*–tolyl)$_3$ is used as the ligand.[29] One drawback of the use of these P(*o*–tolyl)$_3$/Pd catalyst systems is that they typically give poor results when applied to the cross coupling of primary amines with aryl bromides. In general, low yields of the desired aniline are realized, and large amounts of arene side products are produced which result from β–hydride elimination from a palladium–amido intermediate. In a number of transition metal complexes, the use of the chelating *bis*(phosphine) ligand has been found to inhibit β–hydride elimination. Hartwig's results rendered this alternative unattractive since it appeared that a chelating ligand would cause difficulty in accessing the requisite three–coordinate monophosphine complexes. In conjunction, Buchwald et al .[21a] used BINAP as a supporting ligand for palladium–catalyzed carbon–nitrogen bond forming reactions. The use of BINAP as a ligand for coupling secondary amines with ortho–substituted halides also resulted in much higher yields than were obtained when P(*o*–tolyl)$_3$ was employed. The effectiveness of $Pd_2(dba)_3$/BINAP suggests that any or all of steps A–D (Scheme 3) may occur from intermediates without prior phosphine dissociation. In particular, coordination of the amine to **2** would form pentacoordinate **3**.[30] Deprotonation of the coordinated amine by *t*-BuONa would give **4** which reductively eliminates to give (BINAP)Pd and the aniline product. Structural features specific to BINAP may be the key to the success of this catalyst system.

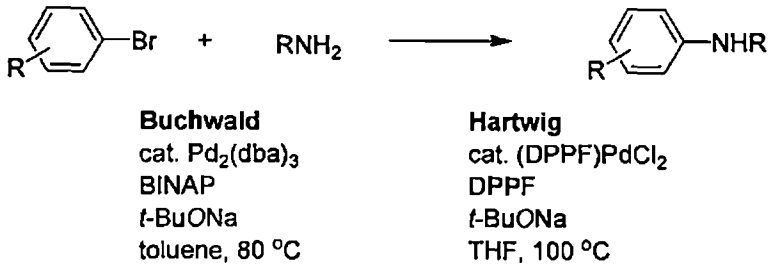
Scheme 3

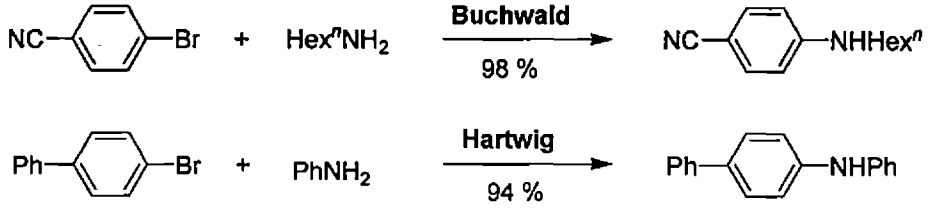


The research groups of Buchwald[21a] and Hartwig[20] reported amination reactions with palladium complexes of BINAP and DPPF as catalysts. These palladium complexes provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary amines, and with anilines. It is ironic that the amination chemistry was first discovered upon use of a particular labile phosphane, but dramatically improved by the use of chelating ligands.

The Buchwald group found that a combination of $Pd_2(dba)_3$ and BINAP in the presence of *t*–BuONa performed as a superior catalyst for the cross coupling of amines with aryl bromides to afford aniline derivatives.[21a] The efficiency of BINAP as a ligand may be attributed to its ability to inhibit the formation of catalytically inactive palladium *bis*(amine) aryl halide complexes. This remarkable protocol is illustrated by the catalytic cross–coupling of 4–cyanobromobenzene with n–hexylamine to give the aminated product in 98% yield using only 0.05 mol% of catalyst.

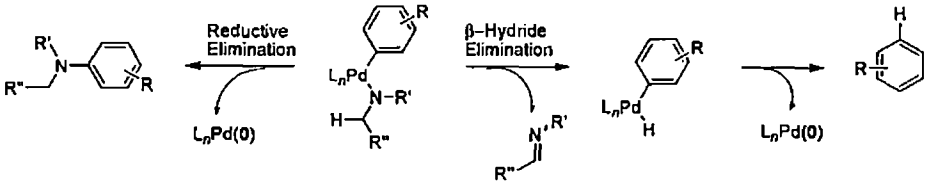
Scheme 4



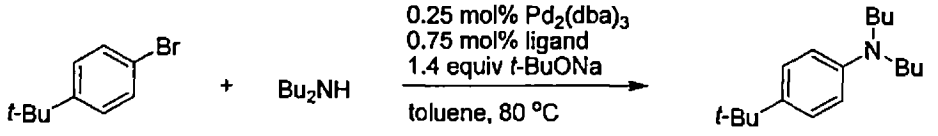


The Hartwig group discovered that $(DPPF)PdCl_2$ catalyst provided high yields of mixed, secondary arylamines from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(*o*–tolyl)$_3$ catalyst system.[20] This study revealed several important concepts; first, the catalytic cycle involves *bis*(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high–yielding, intermolecular amination of aryl halides and finally the favorable selectivity for reductive elimination over β–hydrogen elimination results from chelation and large bite angle, rather than from steric effects. The methods, based on the use of the monophosphine 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.[12b] These reactions are usually plagued by the reduction of the starting aryl bromide, leading to the formation of the byproduct arene via a β–hydride elimination pathway from amido–palladium intermediate (Scheme 5). To surmount such problem Buchwald *et al.*[12b] tested that palladium complexes derived from ligands (*rac*)–PPFA[31] and (*rac*)–PPF–OMe[31,32] are highly effective for the aryl amination reaction of acyclic secondary amines (Scheme 6).

Scheme 5

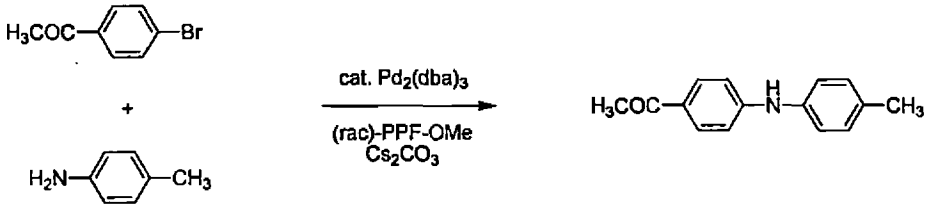


Scheme 6



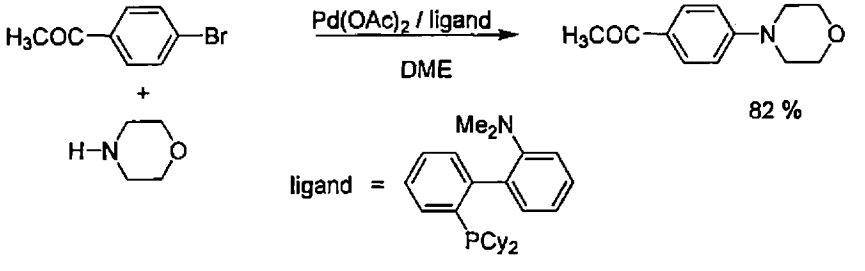
It was noted that the combination of $Pd_2(dba)_3$ and (*rac*)–PPF–OMe allowed the reaction to tolerate the presence of methyl and ethyl esters aldehydes, enolizable ketones and nitro groups, which are incompatible with reaction conditions which employ *t*–BuONa as the stoichiometric base (Scheme 7).[22]

Scheme 7



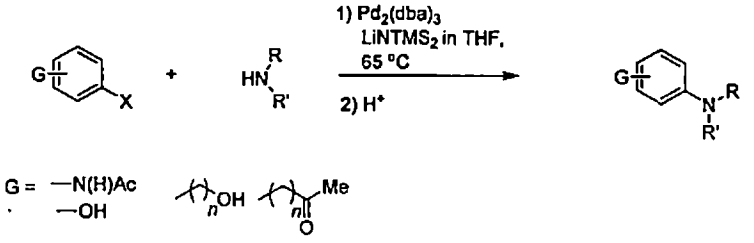
Buchwald *et al.*[18a,33] reported the palladium catalyzed amination of 4–bromoacetophenone with morpholine in the presence of $Pd(OAc)_2$, ligand, K_3PO_4 in DME(Scheme 8).

Scheme 8



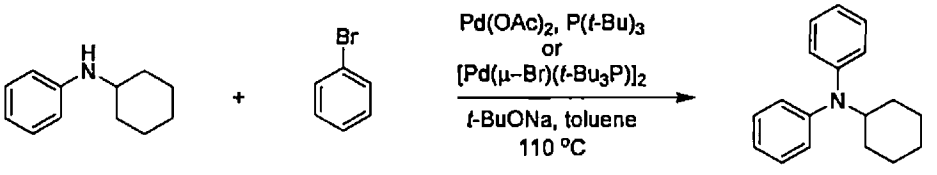
Recently, Buchwald *et al.*[34] described a method for the coupling reaction of amines with aryl halides containing alcohol, phenol, amide, or keto groups in the presence of $LiN(TMS)_2$ (Scheme 9).

Scheme 9



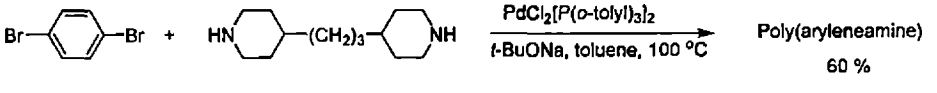
Very recently, Prashad *et al.*[35] reported an efficient palladium catalyzed amination of aromatic bromides with hindered N–alkyl substituted anilines either using the combination of $Pd(OAc)_2$ and P(*t*–Bu)$_3$ or a palladium(I) tri–*tert*–butylphosphine bromide dimer (Scheme 10), $[Pd(\mu\text{–}Br)(t\text{–}Bu_3P)]_2$, a new, commercially available, and easily handled catalyst.

Scheme 10



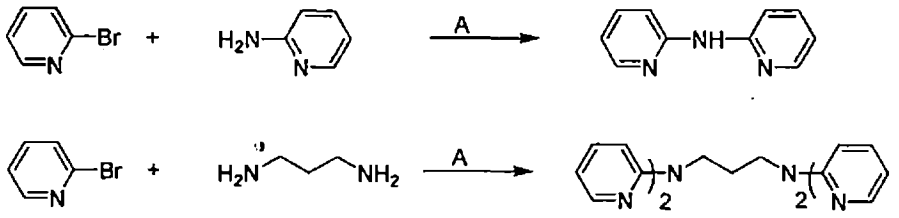
The amination methodology has recently found application in polymer synthesis. The reaction of aryl dibromide with secondary amine (Scheme 11) proceeds smoothly in the presence of stoichiometric *t*–BuONa and catalytic $PdCl_2[P(o\text{–tolyl})_3]_2$ to give new poly(aryleneamine).[38]

Scheme 11



The Buchwald groups have revealed that the palladium catalyzed amination strategy can be effectively applied to the synthesis of amino pyridines and this protocol represents a significant improvement relative to existing procedures which often require activated substrates and harsh reaction conditions.[37] The reaction of 2–bromopyridine with 2–aminopyridine (sheme 12) produced the interesting product in 87% yield. This was also an effective strategy for preparing diarylated diamines.

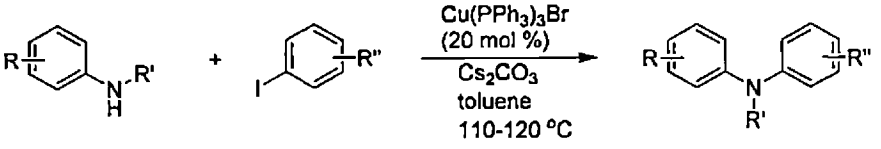
Scheme 12



A = $Pd_2(dba)_3$, BINAP, $NaOBu^t$, toluene, 70 °C

One of the most widely used methods for the synthesis of arylamines is the Ullmann condensation, in which an amine is condensed with an aryl halide in the presence of base and a copper catalyst.[8e] Traditionally, copper–catalyzed Ullmann coupling protocols necessitate the use of high temperature (200 ^{0}C) providing low to moderate yield of amines and often require the use of stoichiometric amounts of copper reagents, which, on scale, leads to problems of waste disposal.[38] Additionally, they have been plagued by poor substrate scope. However, there has been a resurgence of more economical copper–mediated systems that circumvent or overcome the limitations of classical Ullmann–Goldberg type couplings, which are known to require harsh reaction conditions.[39] Recently, milder Ullmann–type processes for C–N bond formation such as N–arylation of anilines,[40] amides,[41] imidazoles,[42] indoles,[43] and hydrazines[44] have been reported. Progress in the arylation of aliphatic amines, however, has been realized only in the context of chelating substrates,[39b] such as α– and β–amino acids[45] and β–amino alcohols[48] or in strategies utilizing less convenient or more costly arylating agents.[47] Gujadhur *et al.*[40b–c] have found that the copper complex $Cu(PPh_3)_3Br$, is active for amination of mono– and diarylamines to di– and triarylamines, respectively, using Cs_2CO_3 as a base at 120 ^{0}C (Scheme 13).

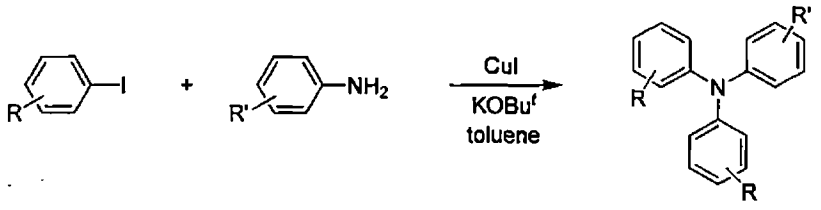
Scheme 13



Similarly Goodbrand and Hu[39a] 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 ^{0}C. Chaudhari *et al.*[40a]

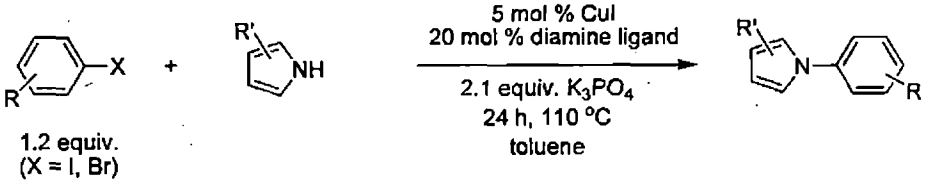
described a simple and efficient methodology for the synthesis of triarylamines in a single step using a ligand–free CuI catalyst and potassium tertiary butoxide as the base (Scheme 14).

Scheme 14



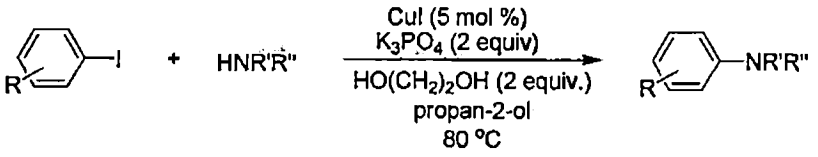
Kang *et al.*[47a] demonstrated the Cu–catalyzed *N*–arylation of amines with hypervalent iodonium compounds with secondary aliphatic amines, at room temperature in presence of weak base. Later on they[41b] also described the Cu–catalyzed N–arylation of benzamides or nitrogen heterocycles with catalytic CuI (10 mol %) in the presence of ethylene diamine (10 mol %) as a ligand and K_3PO_4 or Cs_2CO_3 as a base under mild conditions. After that a variety of diamine ligands have been used by Buchwald group[48] for copper–catalyzed N–arylation of π–excessive nitrogen heterocycles (Scheme 15). The coupling of either aryl iodides or aryl bromides with common nitrogen heterocycles (pyrroles, pyrazoles, indazoles, imidazoles, and triazoles) was successfully performed in good yield with catalysts derived from diamine ligands and CuI. It has been found that the functional groups such as aldehydes, ketones, alcohols, primary amines, and nitriles on the aryl halide or heterocycle remain unaffected after reaction.

Scheme 15



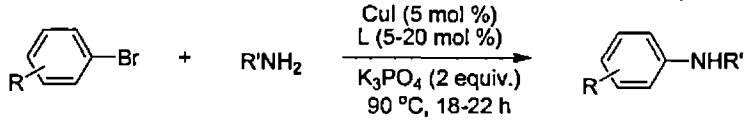
Recently, Buchwald *et al.*[43c] reported a mild, practical Cu–catalyzed amination of functionalized aryl iodides using air stable CuI as the catalyst, ethylene glycol as the ligand and unpurified propan–2–ol as the solvent (Scheme 16). These reactions can be performed without protection from air or moisture.

Scheme 16



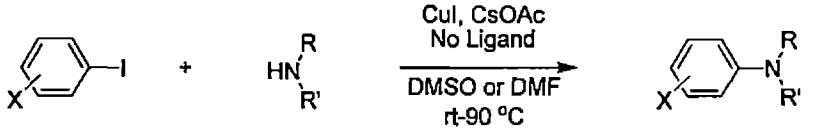
Very recently, Kwong and Buchwald[49] reported a mild Cu–catalyzed coupling of primary amines to functionalized aryl bromides using air–stable CuI as the catalyst and structurally simple salicylamides as ligands (Scheme 17).

Scheme 17



A unique combination of CuI and cesium acetate was found to mediate intermolecular amination of aryl halides under mild conditions (Scheme 18).[50]

Scheme 18



R, R = H, alkyl, aryl, Ns

II.2: Present work: Background, Objective and strategy

The palladium–catalyzed amination of aryl halides[12,13b,21a,20,26,27] has become an important method for the synthesis of arylamines found in pharmaceuticals,[51] materials with important electronic properties,[36,52] and ligands for early metal catalysts.[6] Because of the importance of this synthetic method, there has been extensive effort to find catalysts that provide high turnover numbers,[16a,53] fast reaction rates,[17b,33] high functional group compatibility,[22] and increased scope of the aromatic C–N bond formation. The Buchwald–Hartwig reaction has emerged during the last decade as a very powerful tool for the synthesis of aryl amines. The hetero cross–coupling reaction is normally carried out in presence of a palladium catalyst, most commonly a *bis*–phosphine ligand and a base (3–5 equiv), preferably sodium *tert*–butoxide.[26] Many advances have been made in this palladium–catalyzed amination reaction since it was reported by Buchwald and Hartwig.[14b,54] The use of sodium *tert*–butoxide as the base has limitations with a number of common functional groups such as esters, enolizable ketones, aldehydes, nitriles and nitro groups, and efforts

have been made to replace it with a milder base. In presence of other base such as KOH or Cs_2CO_3, the double amination proceeds slowly and leads to an increased amount of the reductive product.[13b,21b,55] Furthermore, several groups employed this protocol to synthesize polyanilines[52k-l,56] and polyaminosubstituted benzenes.[55,57] Although anilines gave high yields of double amination products, primary amines did not afford the desired *bis*–amination due to competing reductive debromination. While studying double amination of *o*–dibromobenzene with primary amines, Diver *et al.* reported formation of imine besides concomitant reductive debromination as the byproducts.[55] From our laboratory, it was previously reported that KF–alumina could serve as a potential basic surface for palladium–catalyzed amination of halopyridines.[58] The solvent free dry media reaction has been found to have advantages in the case of halopyridines. While extending the preparative advantages for amination of haloaromatics, we conducted KF–alumina mediate palladium–catalyzed C–N cross–coupling should be studied with polyhalobenzenes to extend the scope and the amelioration of the various parameters of this amination process.

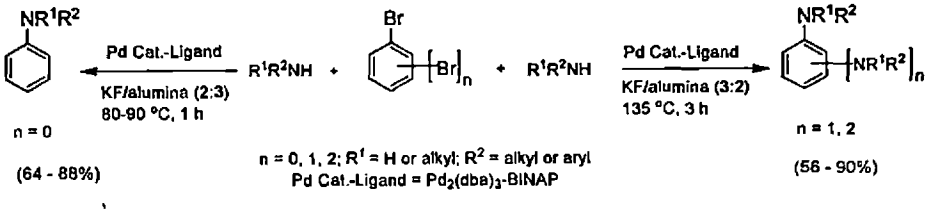
II.3: Present Work: Results and Discussion

The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C–N bond formation and has many potential applications for the synthesis of aniline derivatives, which are inaccessible through other routes.[10,12,13b] The most commonly used catalysts for this transformations are based on chelating phosphine such as BINAP and DPPF,[13b] aryl bromide are the most frequently employed substrates[10,12,13b] Recent reports have described the use of other catalyst system based on bulky, electron–rich, phosphine ligands.[16,17b,18,33,53,59] However, the BINAP catalyst system remains the most active and general catalyst for the coupling of aryl bromide with primary and secondary amines. Additionally, the BINAP catalyst system functions well in the presence of the weak base KF/Al_2O_3, allowing for a high level of functional group tolerance. In this part, we have described our studies on the scope and limitations of the Pd/BINAP–catalyzed amination of aryl bromides. Certain types of secondary amines were also efficiently arylated using the Pd/BINAP catalyst system. These reactions provided the best results when conducted without solvent. Considerably improved results were obtained for several substrate combinations that gave low yields with catalysts supported by P(*o*–tol)$_3$ and 1,2–*bis* (diphenylphosphino)ethane ligands. For example, the reaction of Piperidine with 1,3–dibromobenzene (entry 15 table 1) afforded the desired *bis*–aminated

product in 78% and mono–aminated product 12% isolated yield using 2 mol% of the $Pd_2(dba)_3$/BINAP catalyst. In comparison, the $Pd_2(dba)_3$/P(*o*–tol)$_3$ and $Pd_2(dba)_3$/1,2–*bis* (diphenylphosphino)ethane catalyst did not produce the desired product even when other conditions remain same. In above similar case $Pd(OAc)_2$/BINAP combination gives major mono–aminated product in 71% and *bis*–aminated product in 12% isolated yield.

In the course of developing synthetic protocol towards amination of polyhaloaromatics on KF–alumina surface, we first employed similar conditions that we had developed for mono–amination of bromopyridines [amine (2 mmol), KF–alumina (1:4; 1 g/mmol), palladium–phosphine catalyst (2 mol%) for bromopyridines (1 mmol)]. Although amination of bromobenzene with *sec.* amines did work well under the conditions, the primary amines showed sluggish reactions and poor yields. The conditions were optimized and the best results are achieved when KF impregnated on alumina was used in the ratio of (2:3). In presence of $Pd_2(dba)_3$–BINAP as the catalytic system, bromobenzene underwent amination with both primary (entries 3 and 4) and secondary amines (entries 1 and 2) quite rapidly at moderate temperatures (80–90 °C/1 hour) yielding the corresponding anilines in 73–88% yields (Table 1). Since the use of other bases can affect groups like enolizable ketones, we tested amination of *p*–bromoacetophenone using the solvent–free KF–alumina surface. Gratifyingly, amination occurred effectively without any changes to the base–sensitive functionality (entry 5). In a typical experiment, the catalyst $Pd_2(dba)_3$–BINAP (2 mol%) was admixed intimately with KF–alumina (2:3; 2g), heated at 80–90 °C for 15 min. and then treated with the mixture (2 mmol aryl bromide and 5mmol amine) was stirred at 80–90 °C for 1 hour (Scheme 19). The desired product was then isolated by column chromatography over silica gel.

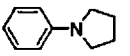
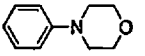
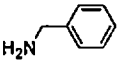
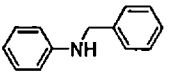
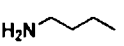
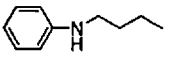
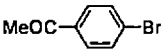
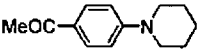
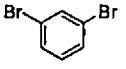
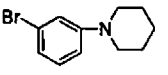
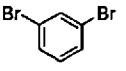
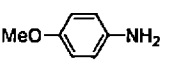
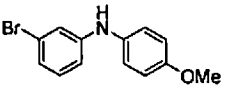
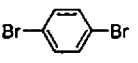
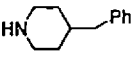
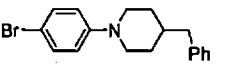
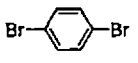
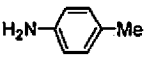
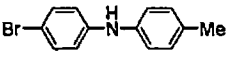
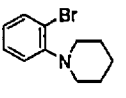
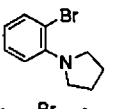
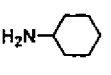
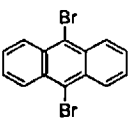
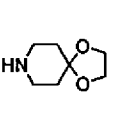
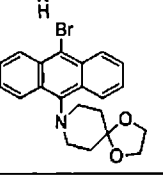
Scheme 19



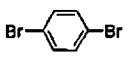
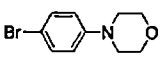
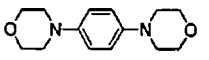
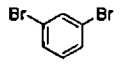
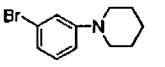
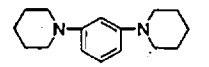
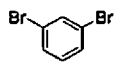
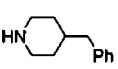
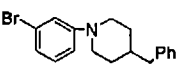
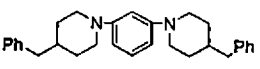
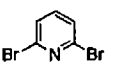
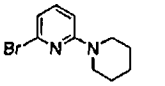
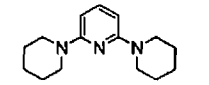
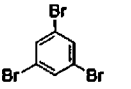
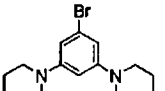
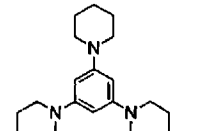
Since poiyaminobenzenes are important compounds for various industries, we wanted to employ the reaction conditions to effect polyamination of polyhaloaromatics. While applying similar conditions to dibromobenzenes, we ended up with mono–aminated products only (entries 6-9, and 13). Earlier we observed

similar results in case of dibromopyridines. In order to obtain the *bis*–aminated products, we examined various proportions of KF–alumina and different catalytic systems. The combination of KF–alumina in the ratio of (3:2) and $Pd_2(dba)_3$–BINAP as the catalyst was found to be suitable for *bis*–, or *tris*–amInations in one–pot reactions (entries 14, 15 and 16). Using the similar conditions, 2,6–dibromopyridine and 1,3,5–tribromobenzene yielded the corresponding *bis*– and *tris*–aminated products (entry 17 and 18) in 90% and 67% yields respectively. Neither reductive debrominatIon nor the formation of imine was observed under this condition, indicating that the possible β–elimination might not be favourable, and thus avoids contamination with any other byproducts. The amination occurs quite rapidly for mono–amination (1 hour) while polyamination requires longer times (3 hour) and higher temperatures (135 °C). In the case of polyaminations, partial mono–aminated products remained in the reaction mixtures, which were easily isolated by column chromatography (Table 1). Interestingly, 1,2–dibromobenzene did not produce the 1,2–*bis*–amines in either condition, possibly due to steric crowding (entries 10–12). Several variations in terms of the catalytic system, the surface (KF–alumina) and temperatures did not change the course of the reactions.

Table: 1 Palladium-catalyzed selective amination of haloaromatics on KF-alumina surface

Entry	Aryl bromide	Amine	Conditions	Product (s)[a]	Yield [%]
1			A		83
2			A		88
3			A		78
4			A		73
5			A		80
6			A		86
7			A		75
8			A		90
9			A		80
10			A or B		90
11			A or B		80
12			A or B		65
13			A		64

Continued from previous page: Table 1

Entry	Aryl bromide	Amine	Conditions	Products		Yield (%)
14			B		17		72
15			B		12		78
16			B		14		73
17			B		5		80
18			B		18		67

II.4: Conclusion

In summary, we have demonstrated that it is possible to effect palladium–catalyzed amination of halobenzenes on a solvent–free surface of KF–alumina without using any strong bases such as sodium *tert*–butoxide. The base–sensitive functional groups remained unaffected under this condition. The procedure is also effective for one–pot mono– or poly–aminations selectively, depending on the conditions used, and thus constitutes a mild and benign method for the synthesis of polyaminobenzenes. No reductive bromination leading to other by products has been observed in this procedure.

II.5: Experimental

II.5.A: Preparation of Activated KF–Al_2O_3 (2:3)

A mixture of basic alumina (Activity I according to Brockmann) (6 g) and KF (4 g) was mixed intimately with a grinder and then activated at 250°C under reduced pressure (0.5 mm of Hg) for 30 min. Then cooled under reduced pressure and opened under a weak flow of N_2 and was used for performing the reactions. The activated KF–alumina may be kept in a glass–stopper flask flashed with N_2 for 2–3 weeks, without any loss of activity.

Activated KF–Al_2O_3 (3:2) was prepared according to the above procedure and changing the proportions only.

II.5.B: General Procedure for the Amination Reactions

Conditions [A]: A mixture of $Pd_2(dba)_3$ (2 mol%) and BINAP (4 moi%) was admixed intimately with KF–alumina (2:3; 2 g) and heated at 80–90 °C for 15 min. Aryl bromide (2 mmol) and an amine (5mmol) were added to the solid surface and the mixture was stirred at 80–90 °C for 1 h. An orange color was developed while mixing and gradually disappeared during one hour. The solid mass was then cooled, packed on a column of silica gel and eluted with EtOAc: light petroleum (1:9) to afford the mono aryl amines. All the products were identified by IR, ^1H and ^{13}C NMR spectral data.

Conditions [B]: The reaction conditions were identical except the amine was taken in 7–8 equivalent; KF–alumina was used in the ratios of (3:2) and the solid mixture was heated at 135 °C for 3 hours. Pure *bis*–amines were obtained by chromatography over silica gel and elution with EtOAc: light petroleum (1:9). The spectral data were consistent with the assigned structures.

II.5.C: A Representative procedure for Mono-amination using KF- Al_2O_3 (2:3)

A mixture of (*rac*)–BINAP (25 mg, 0.04 mmol) and $Pd_2(dba)_3$ (18 mg 0.02 mmol) was mixed intimately with KF–Al_2O_3 (2:3) (2 g) under nitrogen and then heated at 80 °C for 15 min. It was cooled under nitrogen and treated with a mixture of piperidine (680 mg, 8 mmol) and 4–bromo acetophenone (398 mg, 2 mmol). The solid mixture was heated under nitrogen at 80 °C for 1 h. An orange colour, immediately developed on mixing, was gradually disappeared indicating completion of the reaction. After cooling to room temperature, the solid reaction mixture was stacked on a column of silica gel (60–120 mesh) and the desired product was isolated by eluting with petroleum ether: ethyl acetate (19:1) to give 325 mg 1–(4–piperidin–1–yl–phenyl)ethanone (entry 5) with 80% yield.

II.5.D: Spectral Analysis

Entry 1: 1–Phenyl–pyrrolidine
Temp: 90 °C; Time: 1 h,
Yield: 83%; (obtained as lquid); UV (MeOH): λ_{max} 203.6, 254.6 nm; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.2–7.17 (m, 5H), 3.4–3.35 (m, 4H), 1.98–1.93 (m, 4H).

Entry 2: 4–Phenyl–morpholine
Reaction temp: 90 °C; Time: 1 h,

Yield: 88%; (solid) mp 54–58 °C (lit.[60] mp 57 °C); UV (MeOH): λ_{max} 248.0, 283.6 nm; IR (Nujol): ν_{max} 2962.5, 2744.5, 1600.8, 1498.6, 1232.4, 1122.5, 927.7, 759.9 cm^{-1}; ^1H–NMR ($CDCl_3$, 300 MHz) δ = 7.21 (t, 2H, *J* = 7.2 Hz), 6.89–6.80 (m, 3H), 3.8 (t, 4H, *J* = 4.8 Hz), 3.1 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.1, 120.3, 115.8, 66.7, 49.5.

Entry 3: Benzyl–phenyl–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 78%, (solid) m.p. 36–40 °C (lit.[61] mp 36 °C); UV (MeOH): λ_{max} 206.8, 246.8, 295.4 nm; IR (Nujol): ν_{max} 3419.6, 3053.1, 1600.8, 1506.3, 1452.3, 983.6, 748.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.33–7.12 (m, 7H), 6.70–6.59 (m, 3H), 4.3 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.2, 112.9, 48.3.

Entry 4: Butyl–phenyl–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 73%; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.17 (d, 2H, *J* = 6.6 Hz), 6.43 (d, 2H, *J* = 6.9 Hz), 3.0 (t, 2H, *J* = 7.1 Hz), 1.57–1.48 (m, 2H) 1.40–1.28 (m, 2H), 0.874 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 132.0, 115.1, 44.4, 31.2, 20.2, 13.9.

Entry 5: 1–(4–piperidin–1–yl–phenyl)ethanone
Reaction temp: 80 °C, Time: 1 h;
Yield: 80%, (solid) mp 87–89 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ=7.85 (d, 2H, *J* = 8.7 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 3.4 (m, 4H), 2.7–2.5 (s, 3H), 1.8–1.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=196.4, 154.4, 130.5, 126.7, 113.3, 48.7, 26.0, 25.3, 24.4.

Entry 7: (3–Bromo–phenyl)–(4–methoxy–phenyl)–amine
Reaction temp: 90 °C, Time: 1 h;
Yield: 75%, m.p. 139–143 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.22–6.87 (m, 8H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 131.0, 123.9, 122.4, 118.0, 115.2, 114.1, 96.0, 55.0.

Entry 8: 4-benzyl-1-(4-bromophenyl)piperidine
Reaction temp: 90 °C, Time: 1h;
Yield: 90%; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.22–7.07 (m, 7H), 6.69 (dd, 2H, *J* = 6.9 & 2.1 Hz), 3.50 (d, 2H, *J* = 12.3 Hz), 2.58–2.47 (m, 4H), 1.67–1.52 (m, 3H), 1.37-1.32

(m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.7, 140.4, 131.8, 129.2, 128.3, 126.0, 118.1, 111.3, 49.7, 43.1, 37.8, 31.8.

Entry 9: 8–(10–Bromo–anthracene–9–yl)–1,4–dioxa–8–aza–spiro [4,5] decane

Reaction temp: 90 °C, Time: 1 h;

Yield: 64%, mp 136–138°C; UV (MeOH): λ_{max} 220.0, 257.8 nm; IR (Nujol): ν_{max} 1122.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.56 (d, 2H, *J* = 8.7 Hz), 8.48 (d, 2H, *J* = 8.5 Hz), 7.60–7.48 (m, 4H), 4.10 (s, 4H), 3.57 (t, 4H, *J* = 5.3 Hz), 2.05 (t, 4H, *J* = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=131.4, 131.2, 128.3, 126.9, 125.3, 125.2, 107.6, 64.4, 49.9, 36.4.

Entry 10: 1–(2–Bromo–phenyl)–piperidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 82%, (liquid); UV (MeOH): λ_{max} 211.4, 256.2 nm; IR (Nujol): ν_{max} 2935.5, 2850.6, 2804.3, 1473.5, 1232.4, 1022.2, 756.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.54 (d, 1H, *J* = 7.9 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 6.86 (t, 1H, *J* = 7.5 Hz), 2.95 (t, 4H, *J* = 4.6 Hz), 1.57–1.61 (m, 2H), 1.71–1.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 133.7, 128.1, 123.8, 121.0, 120.1, 53.3, 26.2, 24.2.

Entry 11: 1–(2–Bromo–phenyl)–pyrrolidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 80%, (obtained as liquid); UV (MeOH): λ_{max} 209.6, 255.0 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.51 (d, 1H *J* = 9.2 Hz), 7.2 (t, 1H, *J* = 8.3 Hz), 6.98 (m, 1H), 6.76 (t, 1H, *J* = 7.4 Hz), 3.37 (t, 4H, *J* = 6 Hz), 1.95 (t, 4H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.5, 129.6, 123.3, 120.1, 120.0, 115.7, 53.2, 26.9.

Entry 12: (2–Bromo–phenyl)–cyclohexyl–amine

Reaction temp: 135 °C, Time: 3 h;

Yield: 65%, (obtained as liquid); UV (MeOH): λ_{max} 208.6, 246.2, 308.0 nm; IR (Nujol): ν_{max} 3404.1, 2931.6, 2852.5, 1593.1, 1508.2, 1321.1, 1016.4, 738.7 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.40 (d ,1H , *J* = 8.8 Hz), 7.14(t,1H, *J* = 7.1 Hz), 6.6 (d, 1H, *J* = 8.1 Hz), 6.5 (t, 1H, *J* = 7.0 Hz), 1.79–2.1 (m, 2H), 4.26 (s, 1H), 1.79–2.1 (m, 2H), 1.75–1.79 (m, 2H), 1.67–1.63 (m, 1H), 1.44–1.20 (m, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.0, 132.5, 128.3, 117.1, 111.8, 109.8, 51.6, 33.0, 25.8, 24.8.

Entry 13: (4–Bromo–phenyl)–*p*–tolyl–amine

Reaction temp: 135 °C, Time: 3 h;

Yield: 80 %; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.3 (d, 2H, *J* = 8.7 Hz), 7.1 (d, 2H *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 7.9 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 2.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 132.0, 131.0, 120.2, 119.4, 118.9, 20.6.

Entry 14: 1,4–dimorpholino benzene

Reaction temp: 135 °C, Time: 3 h;

Yield: 72%, mp 186–190 °C; UV (MeOH): λ_{max} 204.0, 259.0 nm; IR (Nujol): ν_{max} 2829.4, 1515.9, 1234.4, 1120.6, 923.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.85 (s, 4H), 3.8 (t, 8H, *J* = 4.8 Hz), 3.01 (t, 8H, *J* = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.2, 117.3, 66.8, 50.4.

4–(4-bromophenyl)morpholine

Reaction temp: 135 °C; Time: 3 h,

Yield: 17%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.28 (d, 2H, *J* = 9 Hz), 6.7 (d, 2H, *J* = 9 Hz), 3.77 (t, 4H, *J* = 4.8 Hz), 3.04 (t, 4H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.8, 129.1, 117.2, 115.8, 66.7, 49.5.

Entry 15: 1,3–dipiperidino benzene

Reaction temp: 80 °C, Time: 1 h;

Yield: 78%, (obtained as liquid); UV (MeOH): λ_{max} 233.2 nm; IR (Nujoi): ν_{max} 2931.6, 2850.6, 2790.8, 1595.0, 1498.6, 1201.6, 1124.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.15 (t, 1H, *J* = 8.1 Hz), 6.61 (s, 1H), 6.49 (d, 1H, *J* = 2.25 Hz), 3.16 (t, 8H, *J* = 5.4 Hz), 1.78–1.70 (m, 8H0, 1.62–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=155.9, 132.0, 11.4, 108.8, 53.9, 28.7, 27.1.

Entry 16: 1-(3-bromo-5-(piperidin-1-yl)phenyl)piperidine

Reaction temp: 135 °C, Time: 3 h;

Yield: 14%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.57 (s, 2H), 6.50 (s, 1H), 3.13 (t, 8H, *J* = 5.4 Hz), 1.70-1.63 (m, 8H), 1.60-1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 123.5, 111.0, 103.9, 50.7, 25.6, 24.1.

1,3–Di (4–Benzyl piperidin–1–yl)–benzene

Reaction temp: 135 °C, Time: 3 h;

Yield: 73%, (solid) mp 80–83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.31–7.11 (m, 11H), 6.60–6.46 (m, 3H), 3.62 (d, 4H, *J* = 12 Hz), 2.70–2.57 (m, 8H), 1.76–1.43 (m, 10H),

Entry 17: 3,4,5,6,3",4",5",6"–Octahydro–2H,2"H–[1,2',6',1"]terpyridine
Reaction temp: 135 °C, Time: 3 h;
Yield: 90%, (solid) mp 35–38 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.21 (t, 1H, *J* = 8.0 Hz), 5.9 (d, 2H, *J* = 8.01 Hz), 3.38–3.40 (m, 8H), 1.61–1.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.5, 138.8, 95.3, 46.3, 25.5, 24.8.
2-Bromo-6-(piperidIn-1-yl)pyridine
Reaction temp: 135 °C; Time: 3 h,
Yield: 5%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.22 (dd, 1H, *J* = 8.1 & 7.2 Hz), 6.65 (d, 1H, *J* = 7.5 Hz), 6.48 (d, 1H, *J* = 8.4 Hz), 3.50 (t, 4H, *J* = 6.0 Hz), 1.66-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.2, 140.1, 139.2, 114.8, 104.6, 45.9, 25.1, 24.5.
Entry 18: 1,3,5–Tripiperidino benzene
Reaction temp: 135 °C, Time: 3 h;
Yield: 55%, (solid) mp 178–180°C; UV (MeOH): λ_{max} 240.8 nm; IR (Nujol): ν_{max} 2935.5, 2790.8, 1541.0, 1448.4, 1199.6, 1122.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.14 (s, 3H), 3.10 (t, 12H, *J* = 5.3 Hz), 1.78–1.66 (m, 12H), 1.58–1.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.7, 99.2, 51.5, 26.0, 24.3.

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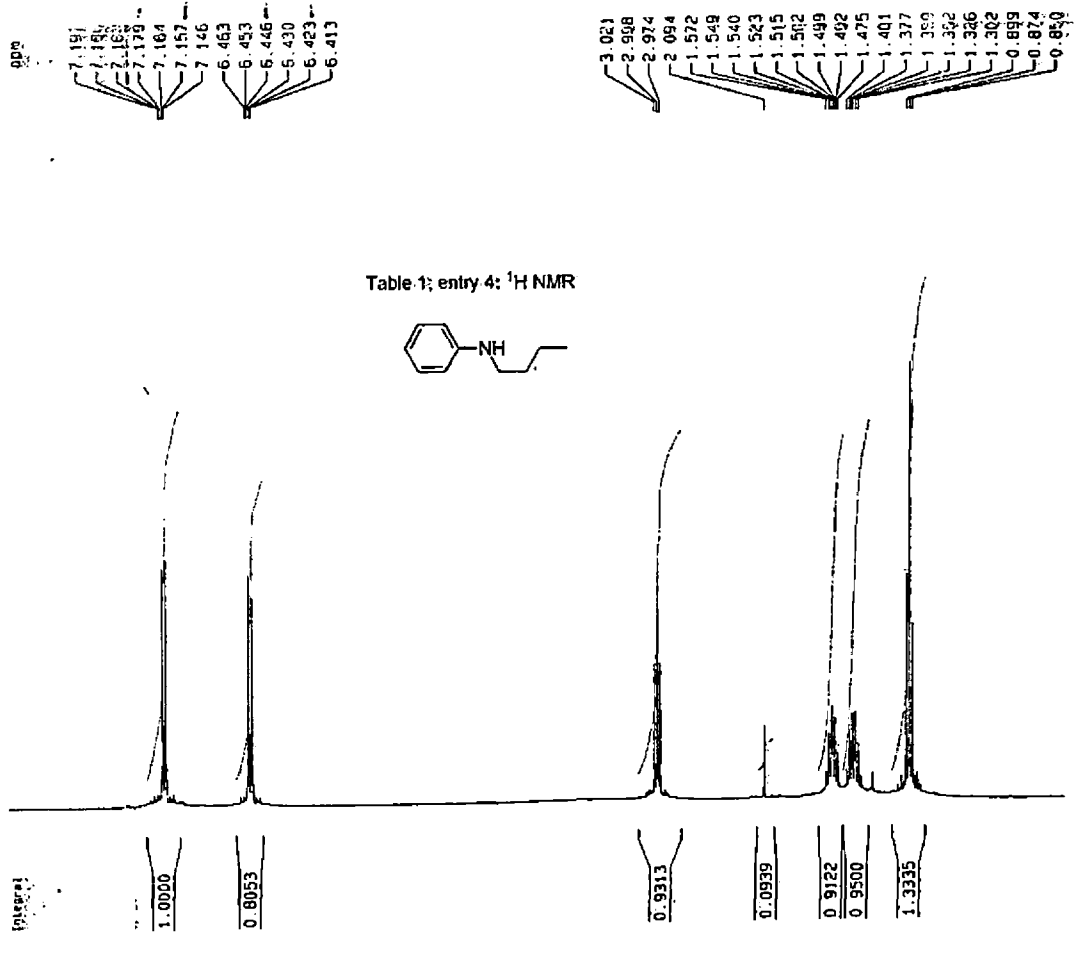

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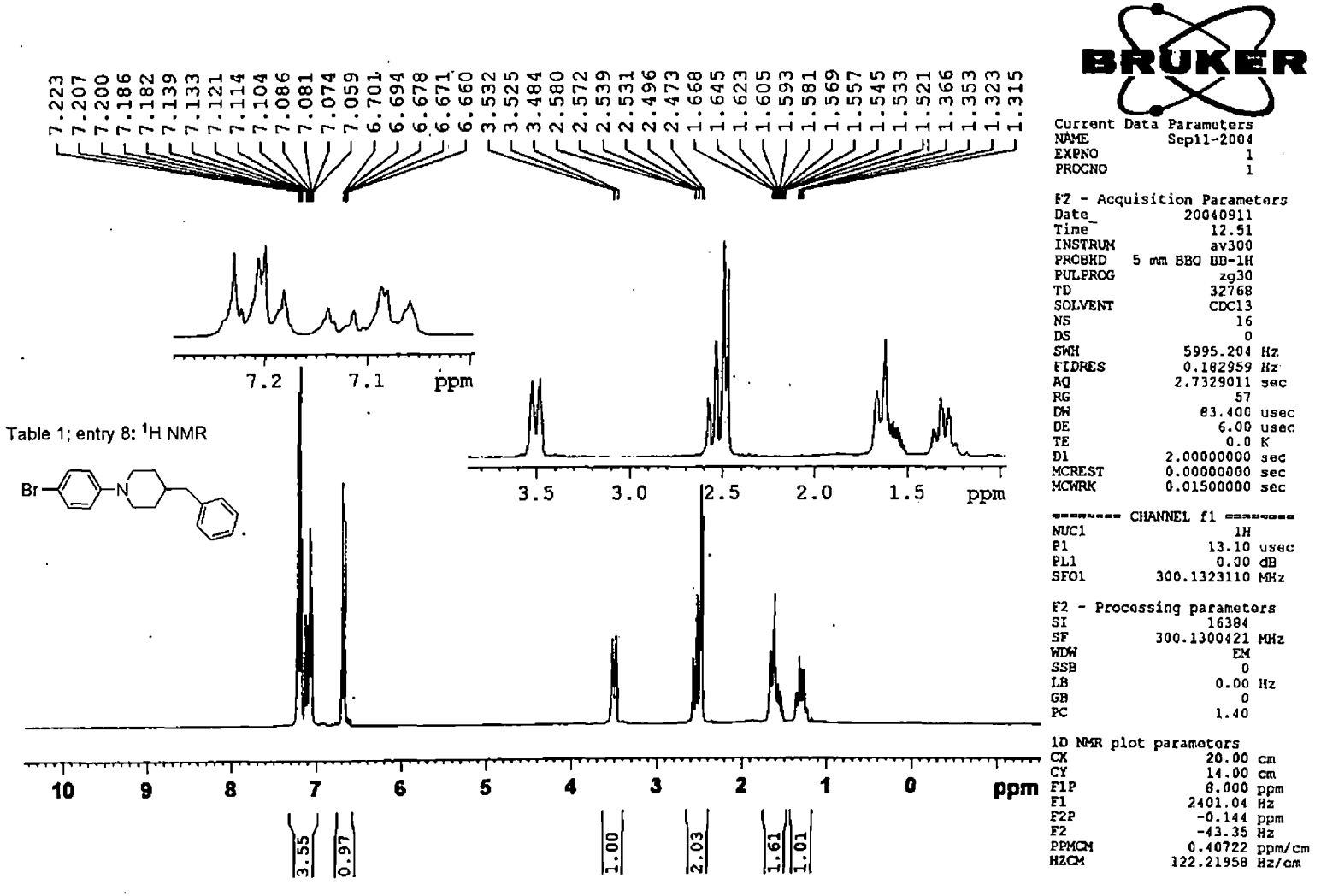
F1 2551.18 Hz
F2P -0.438 ppm
F2 -131.55 Hz
PPMCM 0.44691 ppm/cm
HZCM 134.13254 Hz/cm



BRUKER

Current Data Parameters

NAME	Sep11-2004
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	12.51
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PULPROG	zg30
TD	32768
SOLVENT	CDCl3
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DS	0
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	57
DW	83.400 usec
DE	6.00 usec
TE	0.0 K
D1	2.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

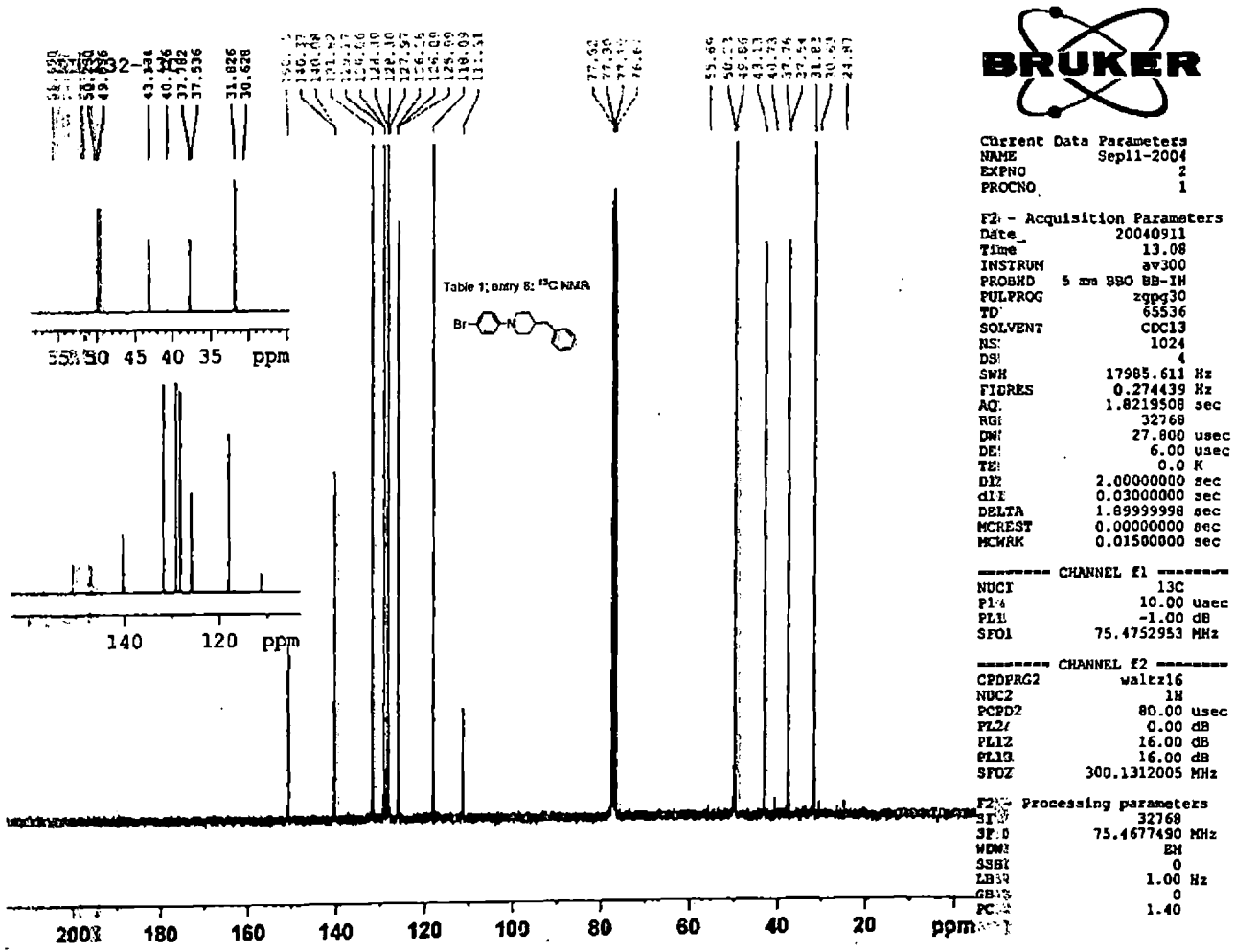
NUC1	1H
P1	13.10 usec
PL1	0.00 dB
SFO1	300.1323110 MHz

F2 - Processing parameters

SI	16384
SF	300.1300421 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	14.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	-0.144 ppm
F2	-43.35 Hz
PPMCM	0.40722 ppm/cm
HZCM	122.21958 Hz/cm



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Current Data Parameters

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PROCNO	1

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PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	17985.611 Hz
FIDRES	0.274439 Hz
AQ	1.8219508 sec
RG	32768
DW	27.800 usec
DE	6.00 usec
TE	0.0 K
D12	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	10.00 usec
PL1	-1.00 dB
SFO1	75.4752953 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	16.00 dB
PL13	16.00 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

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SSB	0
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GB	0
PC	1.40

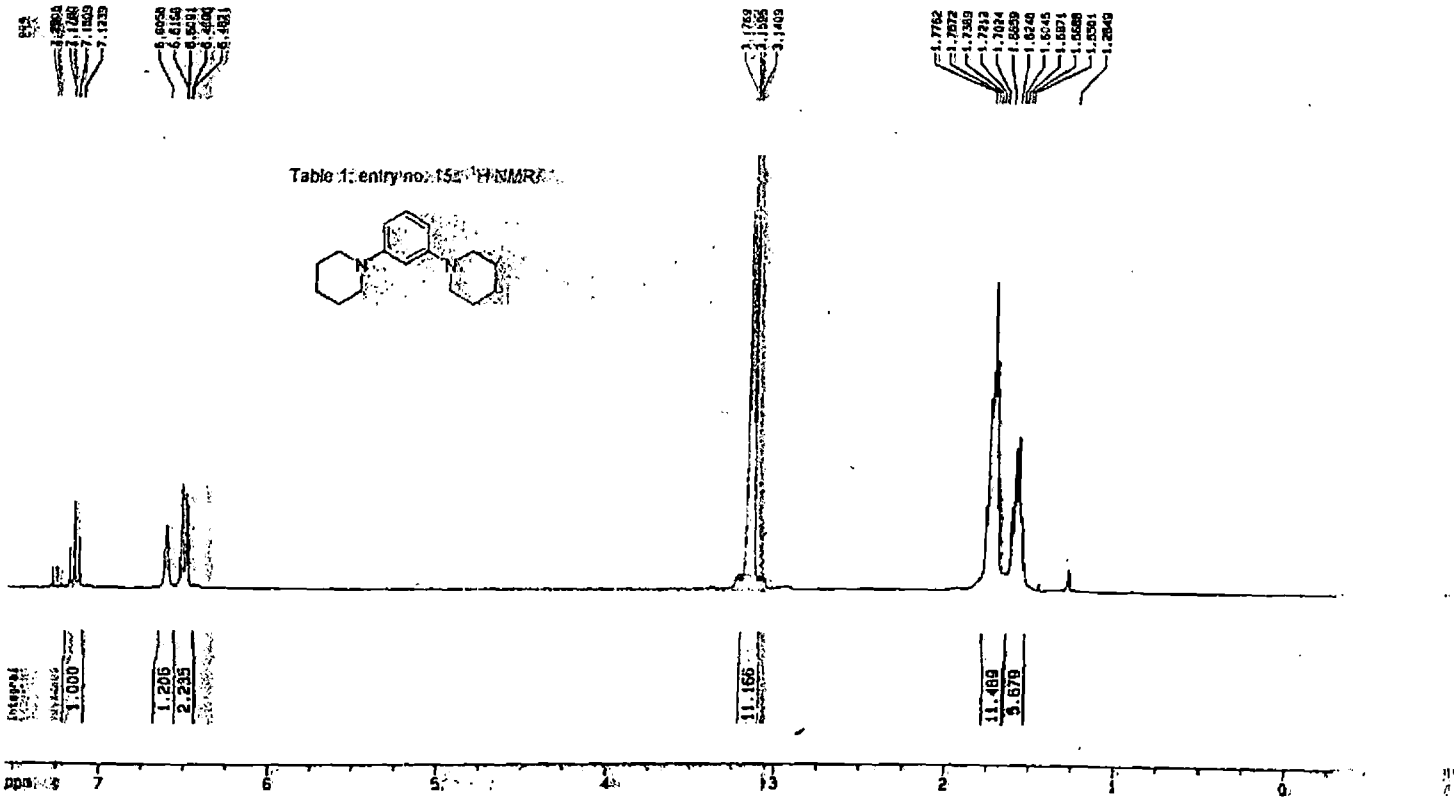


Table 1: entry no. 15 ^{1}H NMR
1.000
1.206
2.235
11.166
11.469
5.679
ppm
7
6
5
4
3
2
1
0

Table 1; entry no. 15; ^{13}C NMR

Table 1; entry no. 17: ^{1}H NMR

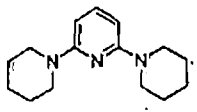
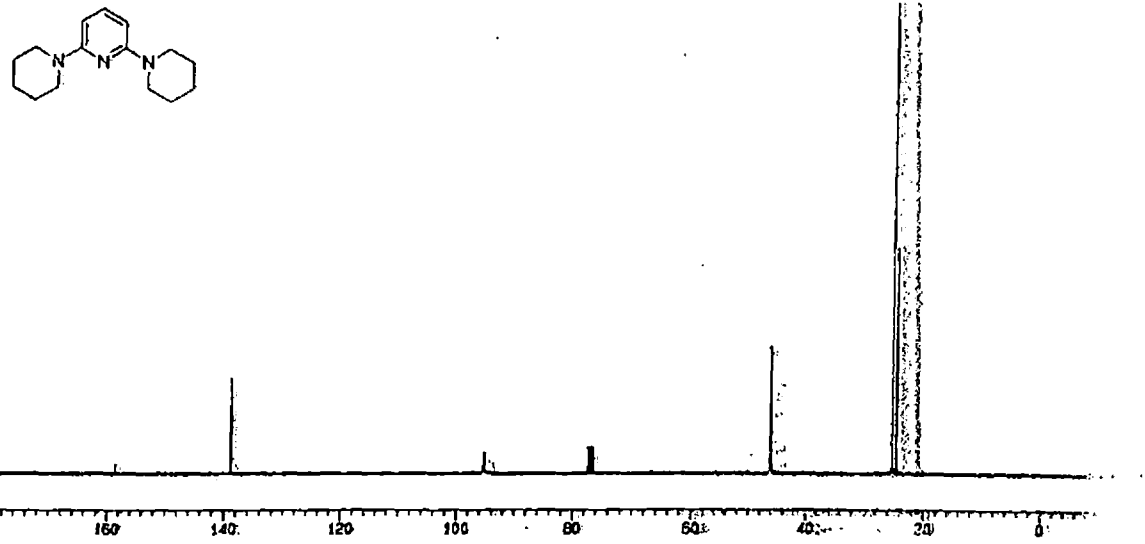


Table 1: entry no. 17: ^{13}C NMR



ppm
153.673
99.215
77.347
76.923
76.501
51.490
25.943
24.298
Table 1; entry 18; ^{13}C NMR
ppm
160
140
120
100
80
60
40
20
0

Molecular Diversity (2005) 9: 259–262
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Short communication

Transfer hydrogenation using recyclable polymer-supported formate (PSF): Efficient and chemoselective reduction of nitroarenes

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Key words: aniline, ion-exchange resin, nitroarene, palladium acetate, polymer-supported formate, transfer hydrogenation

Summary

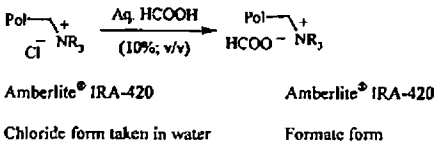
Nitroarenes can be reduced in high yields to the corresponding anilines by transfer hydrogenation using a stable H-donor, polymer-supported formate (PSF) in combination with palladium acetate (catalytic). The reactions occur at 100–120 °C in dimethyl-formamide and the PSF can be recycled for at least three runs. The procedure is chemoselective for nitro group; ester, ketone, aldehyde, and halide substituents on aromatic ring remain unaffected.

Introduction

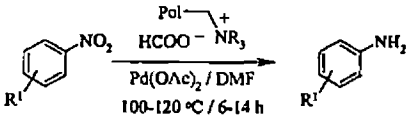
Reduction of nitroarenes to anilines is a synthetically important transformation, both in the laboratory and in industry [1–4]. The resulting aromatic amines are widely used as dyes, medicinal supplies, agrochemicals and electronic materials [5–8]. Furthermore, anilines are often converted into diazonium salts, which can be substituted for many other functional groups [9]. A large number of methods have therefore been developed for the reduction of nitro groups [1–4]. The reagents that are generally employed for the reduction include catalytic hydrogenation [10–11] with Pd/C, Raney Ni and PtO_2 or dissolving metal reduction, for example, with Sn/HCl [12], Fe/HCl [13] and Fe/AcOH [14]. Reduction of aromatic nitro compounds with indium powder in ethanolic ammonium chloride [15] or SmI_2 [16–17] results in selective reduction. Most of these methods require high pressure, specific hydrogenation apparatus, harsh reaction conditions or use of expensive metals and therefore lack the desired generality for true synthetic utility. Moreover, poor selectivity was reported in the reduction of aromatic nitro compounds bearing other potentially reducible groups such as carbonyl and halogen substituents.

Catalytic transfer hydrogenation (CTH) with the aid of a stable H-donor is a useful alternative method to catalytic hydrogenation by molecular hydrogen [18–20]. In transfer hydrogenation, several organic molecules such as hydrocarbons, primary and secondary alcohols, and formic acid and its salts have been employed as the hydrogen source. The use of a H-donor has some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with hydrogen gas as well as the necessity for pressure vessels and other equipment. Formic acids and its salts are frequently employed as hydrogen donor in CTH reactions and nitroarenes can be reduced to anilines using ammonium formate and Pd-C or Raney nickel [21–23]. However, reductive elimination of halogen substituents on the aromatic nucleus and formation of *N*-formyl derivatives instead of arylamines are the major drawbacks on using ammonium formate/Pd-C [24]. On the other hand, combination of $NaBH_4$ with Cu(II), Co(II) or Rh(III) halides has been used to reduce the nitro group, which is inert to $NaBH_4$ itself [11]. Metal hydrides are, however, water-sensitive as well as expensive chemicals.

Synthetic applications of solid phase organic chemistry have received, in recent years, an enormous boost from the expeditious development of the combinatorial approach [25–27]. The use of solid phase-bound reagents and catalysts allows much simpler work-up procedures and, in many cases, eliminates the need for strict control of reagent ratios [28–29]. In addition, reagents immobilized on insoluble matrices offer advantages for recycling thus becoming cost effective. Borohydride exchange resin (BER), an immobilized hydride reagent, in combination with transition metal salts has been shown to reduce the nitro group selectively [30]. In connection with our interest in CTH reactions [31–32], we have recently demonstrated that resin-bound formate (PSF) can function as stable H-donor and be utilized in palladium-catalyzed transfer hydrogenation of functionalized alkenes [33]. We have also shown that several other reducible groups such as cyano, carbonyl, ester can be tolerated the process. In continuation of our interest, we wish to report herein that



Scheme 1.



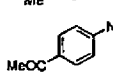
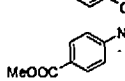
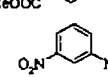
Scheme 2.

the PSF can also serve as a stable H-donor in reducing the nitroarenes to anilines. The reaction conditions have been optimized so that the aromatic nitro group can be reduced in a chemoselective manner where the other groups such as ketone, aldehyde and halide substituents on aromatic ring remain unaffected.

The PSF was prepared using Amberlyst resin (IRA® 420), the chloride form being exchanged with formic acid, according to our procedure reported previously [33] (Scheme 1). When the PSF was treated with catalytic amount of palladium acetate (2 mol% with respect to the substrate) in DMF, an efficient reductant is generated that can be used for efficient reduction of nitroarenes (Scheme 2).

The reduction of nitro group was carried out using 2 mol% $Pd(OAc)_2$ and formylated (aminomethyl)polystyrene (PSF) in a minimum quantity of DMF at 100–120 °C for 6–14 h (Table 1). After filtration, extraction with ether followed by

Table 1. Reduction of nitroarenes to anilines using PSF and Pd-catalyst[a]

Entry	Nitroarene	Temp (°C) / Time (h)	Anilines	Yield[b], (%)
1		100 / 8		82
2		110 / 8		77
3		120 / 12		71
4		100 / 10		76
5		100 / 8		70
6		110 / 8		85
7		120 / 14		68
8		100 / 8		90
9		110 / 10		92
10		120 / 12		No reaction
11		110 / 10		77
12		100 / 12		66

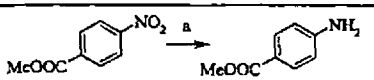
[a]Reaction conditions: Nitroarene (2 mmol), $Pd(OAc)_2$ (0.04 mmol), PSF (1 g) in DMF (2 mL).
[b]Yield refers to isolated product by column chromatography and average of 2–3 runs.

chromatographic purification afforded the desired anilines in good yields. The anilines in most cases were identified by comparison of spectroscopic data and/or melting points with literature values. Initially, reduction of nitrobenzene leading to aniline was performed in 82% yield. Concomitant reductive elimination of halogen on aromatic nucleus is often associated with transfer hydrogenation [34] and therefore poor selectivity was observed in the reduction of aromatic nitro compounds bearing halogen substituent. In our conditions, however, *o*- and *p*-chloronitrobenzene underwent reduction of the nitro group chemoselectively leading to corresponding chloroanilines in 71 and 77% yield, respectively. *p*-Nitrophenol and *p*-nitrotoluene also underwent smooth reduction of the nitro group leading to the desired anilines. The selective and rapid reduction of nitro groups in the presence of carbonyl functionalities is also a highly valuable transformation in organic synthesis. The development of an efficient solid phase-bound reagent to achieve this goal has attracted considerable effort recently. We therefore investigated reduction of *m*-nitroacetophenone, *o*-nitrobenzaldehyde and methyl *p*-nitrobenzoate. The results showed that the formylated (aminomethyl)polystyrene (PSF) can effect highly efficient reduction of nitro groups in the presence of carbonyl functionalities. In transfer reduction of polynitrobenzenes, it was reported that use of much greater proportions of catalyst to substrates afforded only aminonitroarenes [20]. In a typical case, dinitroarenes (*o*-, *m*-, *p*-) are reported to yield corresponding nitroanilines in 90% yields. At our hand, reduction of *p*-dinitrobenzene gave *p*-nitroaniline in 92% yield and further reduction to *p*-diaminobenzene was not possible. Previously, we observed reduction of the C=N bond of imine using PSF and catalytic $Pd(OAc)_2$ [33]. The imine bearing a nitro group was examined under this condition and we obtained reduction of nitro group in addition to the imino group.

To explore the efficiency and stability of the H-donor (PSF), recycling was examined with methyl *p*-nitrobenzoate as a substrate. Reduction proceeds to completion giving excellent yields through three successive recycle runs (Table 2). It should be noted that after separation of the Amberlite resin at the end of the three successive runs, the PSF can be easily generated and could be reused in further reductions.

In summary, we have demonstrated that polymer-supported formate (PSF) can efficiently perform reduction of nitroarenes leading to anilines under palladium-catalyzed transfer hydrogenation conditions in small-scale. The procedure is chemoselective for nitro group; and several other potentially reducible functionalities such as ketone, aldehyde, ester, and halide substituents on aromatic ring remain unaffected. Other advantages are clean work-up, high yields, and reusability of the PSF for at least three times and regeneration of PSF by reusing the recovered resin. Further applications of PSF in reduction of other organic functional groups are under active pursuit.

Table 2. Recycling experiments



Run	1	2	3
Yield (%)	90	90	84
Time/h	6	7	8

[a]Reagents and conditions: 2 mol% $Pd(OAc)_2$/PSF (0.5 g/1 mmol nitro compound)/DMF (1 mL)/100 °C.

Experimental section: General

All reactions were performed in screw cap sealed tubes flashed with nitrogen. The minimal reaction times were determined by monitoring TLC of the reaction mixture. Silica gel (60–120 mesh) was used for chromatographic purifications. DMF was dried by distillation over P_2O_5. ^{1}H-NMR and ^{13}C-NMR were recorded at 300 MHz and 75 MHz respectively using Bruker AV-300 spectrometer. Amberlite® IRA-420 (Cl) standard grade (14–52 mesh) and palladium acetate were purchased from commercial suppliers and were used directly.

General procedure for reduction of nitroarene to aniline

To a mixture of nitroarene (2 mmol) and palladium acetate (0.04 mmol, 2 mol%) in freshly distilled DMF (2 mL) was added PSF (1 g) and the reaction mixture was purged with N_2 for 2–3 min. The screw-cap tube was tightened and placed in a pre-heated oil bath for several hours (Table 1). After completion of the starting material as analyzed by TLC, the reaction mixture was taken in water, filtered through a cotton-bed and washed with ether. The ethereal layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified either by column chromatography over silica gel or by crystallization to afford the desired aniline.

Acknowledgements

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Co-immobilized formate anion and palladium on a polymer surface: a novel heterogeneous combination for transfer hydrogenation

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Received 15 July 2005; revised 20 September 2005; accepted 29 September 2005
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Dedicated to Professor Debabrata Mukherjee on the occasion of his 65th birthday

Abstract—A novel heterogeneous combination of a formate reagent and palladium catalyst co-immobilized on a resin support has been developed and shown to be highly efficient and recyclable for transfer hydrogenation of alkenes, imines, nitroarenes and 1,2-dicarbonyl compounds.

Catalytic transfer hydrogenation (CTH) with the aid of a stable hydrogen donor is a useful alternative method for catalytic hydrogenation by molecular hydrogen.[1] In transfer hydrogenation, organic molecules such as hydrocarbons,[2] primary and secondary alcohols[3] and formic acid and its salts[4] have been employed as the hydrogen source. The use of a hydrogen donor has some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with hydrogen gas as well as the necessity for pressure vessels and other equipment. Although metal-catalyzed transfer hydrogenation using a stable H-donor has been found to be reliable, the current emphasis on cleaner methods for chemical transformations requires high selectivity, low cost, easy separation and the production of minimum waste. From a practical point of view, a more attractive approach is to develop a heterogeneous catalyst that is efficient for this transformation. Immobilized reagents and immobilized catalysts can afford clean transformations for laboratory to large-scale operations. While several immobilized reagents or immobilized catalysts have been demonstrated for numerous organic transformations,[5] we envisaged that both the reagent and the catalyst could be bound on the same polymer surface and employed for suitable transformations. Such an approach would provide further operational simplicity and economic control.

As a part of a continuous effort to develop solid phase organic reactions, we recently reported that polymer-supported formate (PSF) could be used as a potential H-donor in palladium-catalyzed transfer hydrogenation of alkenes, imines and aromatic nitro compounds.[6] The conditions appeared to be mild and selective for many functional groups such as ketones, esters, halogens and nitriles. The reactions were performed using catalytic palladium acetate (2 mol %) in DMF and it was assumed that the palladium catalyst worked as a homogeneous catalyst. The high degree of chemoselectivity in palladium-catalyzed transfer hydrogenation using HCOOH or its salts has been explained on the basis that the hydrogen is delivered directly from a Pd formate species which has much stronger hydridic nature compared to that of a Pd hydride species.[7] The combination of formic acid and palladium acetate is known to undergo anionic ligand exchange to form a palladium diformate complex, eventually producing Pd(0) through decarboxylation and loss of molecular hydrogen.[8] In CTH, either a source of palladium is required for each operation or it may be supported by a polymer framework and reused several times. We reasoned that the palladium catalyst might be anchored to the PSF so that it could be used and recycled. Palladium is usually attached to a solid surface either by adsorption on the polymeric surface, by

Keywords: Transfer hydrogenation; Polymer-supported formate; Supported palladium catalyst; Alkenes; Imine; Nitroarenes; 1,2-Diketones.
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coordination through the ligand or by the relatively new technique of microencapsulation.[9] In this latter,[4] we report that palladium can be immobilized on the PSF and used effectively in the CTH of a variety of functional groups. Furthermore, the formate (the H-donor) and palladium (the catalyst) supported on a polymeric surface (PSF-Pd) can be recycled at least four-times without any appreciable loss of activity. To the best of our knowledge, this approach, where both the reagent and the catalyst are co-immobilized on same polymeric backbone, has not previously been reported.

The overall procedure is simple and straightforward. The polymer-supported formate (PSF) was prepared using Amberlyst resin (IRA® 420), the chloride form being exchanged with formic acid, according to our previously reported procedure.[6] To a suspension of PSF (1 g) in DMF (5 ml) was added palladium acetate (10 mg) and the mixture magnetically stirred under nitrogen at room temperature for 2 h. The PSF beads turned black indicating that the Pd(II) species may have been reduced to Pd(0), and the solvent became colourless. The resulting mixture was filtered, washed with DMF and dried under vacuum overnight. The resulting black PSF beads of the resin supporting both the reagent and palladium catalyst (PSF-Pd) were used for the reduction.[10]

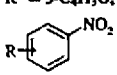
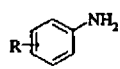
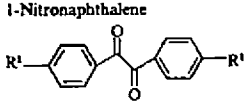
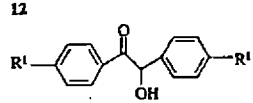
Table 1. FT-IR data (KBr) for the carboxylate anion

Formate	Stretching vibration (ν_{max}) cm^{-1}	Anti-symmetrical/symmetrical vibration (ν_{max}) cm^{-1}
$HCOONH_4$	1354	1595
HCOOK	1348	1593
PSF	1344	1593
PSF-Pd	1404	1653

The PSF-Pd was characterized by IR spectroscopy. The FT-IR spectral data for the carboxylate anion of different formate salts, PSF and PSF-Pd are given in Table 1. The FT-IR spectrum of PSF-Pd was compared with those of ammonium formate, potassium formate and the PSF. The absorptions of the carboxylate anions of $HCOONH_4$, HCOOK and PSF were observed at 1595, 1593 and 1593 cm^{-1}, respectively, while that of PSF-Pd occurred at 1653 cm^{-1}. The significant increase of ν_{max} for PSF-Pd clearly indicated binding of the palladium metal through complexation with PSF.[11]

The efficiency and stability of this newly developed PSF-Pd was first examined in the reduction of electron-deficient alkenes conjugated with ketones, nitriles and carboxylate esters (entries 1–5 in Table 2). An excess of the polymer-supported formate/palladium catalyst (0.5 g of PSF-Pd per mmol of the substrate) was em-

Table 2. Catalytic transfer reduction using PSF-Pd

Entry	Substrate	Conditions[a] temperature (°C)/time (h)	Product	Yield (%)[b]
				
1.	R^1 = Ph; R^2 = H; R^3 = CN; R^4 = COOEt	65/8	1	82
2.	R^1 = 4-MeOC$_6$H$_4$; R^2 = H; R^3 = CN; R^4 = COOEt	70/8	2	80
3.	R^1 = 4-MeOC$_6$H$_4$; R^2 = H; R^3 = R^4 = CN	50/6	3	86
4.	R^1 = Ph; R^2 = Me; R^3 = CN; R^4 = COOEt	70/7	4	78
5.	R^1 = 4-ClC$_6$H$_4$; R^2 = H; R^3 = H; R^4 = CO(3-C$_4$H$_3$O)	80/12	5	75
				
6.	R^1 = 3-NO$_2$; R^2 = H; R^3 = Ph	70/7	6	80
7.	R^1 = 4-C$_5$H$_4$N; R^2 = H; R^3 = Ph	50/6	7	87
8.	R^1 = 3-C$_4$H$_3$O; R^2 = H; R^3 = Ph	60/6	8	78
				
9.	R = 4-Cl	110/11	9	76
10.	R = 4-COOMe	100/10	10	85
11.	R = 3-COMe	100/10	11	81
12.	1-Nitronaphthalene	100/10	12	75
				
13.	R^1 = H	100/10	13	85
14.	R^1 = Me	110/12	14	77
15.	R^1 = OMe	110/10	15	88

[a] 0.5 g of PSF-Pd per 1 mmol of the substrate in DMF (1 cm^3).

[b] Yields are based on at least two runs and the products were isolated as pure compounds after column chromatography. All products showed satisfactory IR, ^{1}H NMR and ^{13}C NMR spectral data.

ployed, with the expectation that other functional groups would not react, to force the reaction to completion. The reduction of the C–C double bond proceeded smoothly at 50–80 °C requiring only gentle agitation; work-up was then achieved by simple filtration, extraction with diethyl ether and evaporation. The reduced product was purified by column chromatography over silica gel and isolated in 75–86% yield. Other reducible groups such as the ketone, nitrile or halogen and ester groups remained unaffected under the reaction conditions.

To extend the scope and generality of the PSF-Pd in CTH, we explored reduction of the C–N double bonds of imines. Since imines are generally derived from the corresponding aldehydes or ketones, the overall reaction in one-pot constitutes a method for 'direct reductive amination' and is an attractive synthetic route to secondary and tertiary amines. Using the PSF-Pd, the imines could be reduced efficiently at 50–70 °C (entries 6–8 in Table 2). A nitro group and heteroaromatic moiety remained unaffected under the reaction conditions.

The reduction of nitroarenes to anilines is a synthetically important transformation both in the laboratory and in industry. To broaden the scope of PSF-Pd, reduction of the nitro group was investigated with nitroarenes as the substrates. While the nitro group was not reducible at a lower temperature (70 °C) it could be reduced at 100–110 °C to yield the corresponding anilines (entries 9–12 in Table 2). Several other reducible groups such as a halogen, ester or ketone were inert to these conditions illustrating a clear advantage in terms of chemoselectivity.

Further applications of this new heterogeneous reductive system were tested with 1,2-dicarbonyl compounds. When benzil or substituted benzils were used as the substrate, the reduction of one of the carbonyl groups with PSF-Pd in DMF at 100 °C reached completion after 10–12 h to give the corresponding α-hydroxyketone (benzoin) in a 77–88% isolated yield (entries 13–15 in Table 2).

The novel combination PSF-Pd was easily used for four successive recycling runs without any significant drop of reactivity. With methyl 4-nitrobenzoate as the substrate, the reduction proceeded to completion giving excellent yields for up to four runs.

In summary, formic acid as its formate anion and a palladium catalyst from palladium acetate have been co-immobilized effectively on an inexpensive Amberlyst ion-exchange resin. This resin (PSF-Pd) proved to be a versatile and heterogeneous reductive combination for transfer hydrogenation of functionalized alkenes, imines, nitroarenes and 1,2-diketones. This new technique also demonstrates high chemoselectivity in the reduction of alkenes, imines and nitro groups, thus establishing an efficient, environmentally benign, economically friendly and sustainable process. Further studies on structural aspects and the reaction behaviour (leaching of the palladium) of PSF-Pd along with newer applications for other transformations are currently underway.

Acknowledgements

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10. *A representative procedure for the CTH of 1,2-diketones using PSF-Pd*: To a solution of 4,4′-dimethoxybenzil (2 mmol) in freshly distilled DMF (2 cm^3) was added PSF-Pd (1 g) and the reaction mixture was stirred at 110 °C for 10 h. The reaction mixture was diluted with ether (15 cm^3) and filtered through a bed of cotton. The filtrate was extracted with ether (2 × 15 cm^3) and the combined organic layers were washed brine (2 × 10 cm^3) and dried (Na_2SO_4). Evaporation under reduced pressure and purification by column chromatography afforded 4,4′-dimethoxybenzoin as a pale yellow solid (88% yield); mp 111–112 °C; FT IR (Nujol): ν_{max} 3466, 1666, 1597, 1512, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 9$ Hz, 2H), 7.26 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 9$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.87 (s, 1H), 4.85–4.3 (br s, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.3$, 163.9, 159.6, 131.8, 131.5, 129.0, 126.2, 114.5, 113.9, 75.2, 55.4, 55.2.
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Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

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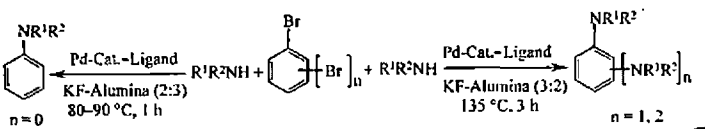
Abstract: An effieient palladium-catalyzed amination, including polyaminations of aromatic bromides mediated on a surface of KF-alumina, is reported. The solvent-free one-pot protocol avoids the use of a strong base (sodium *tert*-butoxide) making it applicable to substrates containing a base-sensitive functional group. It proceeds without concomitant reductive bromination and provides access to selective amination of polyhaloaromatics.

Key words: aryl halides, aryl amines, amination, palladium, KF-alumina

Aromatic amines are an integral part of pharmaceuticals, dyes, polymers, organic materials with important electronic properties, and ligands for transition metals.[1] The preparation of aryl amines is therefore important to synthetic organic chemists. The palladium-catalyzed cross-coupling of aryl halides with amines, developed independently by Buchwald[2] and Hartwig,[3] represents a mild alternative to the classical construction[4] of aryl amines. The Buchwald–Hartwig reaction has emerged during the last decade as a very powerful tool for the synthesis of aryl amines. The hetero cross-coupling reaction is normally carried out in the presence of a palladium catalyst, most commonly a bis-phosphine ligand and a base (3–5 equiv), preferably sodium *tert*-butoxide.[2d] Many advances have been made in this palladium-catalyzed amination reaction since it was reported by Buchwald and Hartwig.[5] The use of sodium *tert*-butoxide as the base eliminates a number of common functional groups such as esters, enolizable ketones, aldehydes, nitriles and nitro groups, and efforts have been made to replace it with a milder base. In the presence of other bases such as KOH or Cs_2CO_3, the double amination proceeds slowly and leads to an increased amount of the reductive product.[6,8a] Furthermore, several groups have employed this protocol to synthesize polyanilines[1d,7] and polyamino-substituted benzenes.[8] Although anilines gave high yields of double amination products, primary amines did not afford the desired *bis*-amination due to competing reductive debromination. While studying double amination of *o*-dibromobenzene with primary amines, Diver et al. reported formation of imine as the byproduct besides concomitant reductive debromination.[8a] Recently, we reported a procedure for palladium-catalyzed amination of heteroaryl halides using KF-alumina as the base.[9] The solvent-free dry reaction has been found to have advantages in the case of halopyridines. While extending the preparative advantages for amination of haloaromatics, we conducted KF-alumina mediated palladium-catalyzed C–N cross couplings between the aryl bromides and amines. We envisaged that the Buchwald–Hartwig C–N couplings should be studied with polyhalobenzenes to extend the scope and the amelioration of the various parameters of this amination process. We report herein our observations, which finally constitute not only a mild and efficient procedure for amination of aromatic bromides on a solvent-free surface of KF-alumina but also provide an expedient route for selective amination of polyhaloaromatics.

In the course of developing synthetic protocol toward amination of polyhaloaromatics on a KF-alumina surface, we first employed similar conditions to those developed for mono-amination of bromopyridines [amine (2 mmol), KF-alumina (1:4; 1 g/mmol), palladium-phosphine catalyst (2 mol%) for bromopyridines (1 mmol)]. Although amination of bromobenzene with secondary amines worked well under the conditions, the reaction with



n = 0, 1, 2; R^1 = H or alkyl; R^2 = alkyl or aryl
Pd-Cat.-Ligand = $Pd_2(dba)_3$–BINAP

Scheme 1

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primary amines was sluggish and poor yields were obtained. The conditions were optimized and the best results were achieved with KF impregnated on alumina was used in a ratio of 2:3. In the presence of $Pd_2(dba)_3$/BINAP as the catalytic system, bromobenzene underwent amination with both primary (Table 1, entries 3 and 4) and secondary amines (Table 1, entries 1 and 2) quite rapidly at moderate temperatures (80–90 °C/1 h) yielding the corresponding anilines in 73–88% yields (Table 1). Since the use of other bases can affect groups like enolizable ketones, we tested the amination of *p*-bromoacetophenone using the solvent-free KF-alumina surface. Gratifyingly, amination occurred effectively without any changes to the base-sensitive functionality (Table 1, entry 5). In a typical experiment,[10] the catalyst $Pd_2(dba)_3$/BINAP (2 mol%) was admixed intimately with KF-alumina (2:3; 2 g), heated at 80–90 °C for 15 minutes, and then treated with a mixture of aryl bromide (2 mmol) and amine (5 mmol). The solid mixture was stirred at 80–90 °C for 1 hour. The desired product was then isolated by column chromatography over silica gel.

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

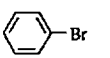
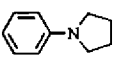
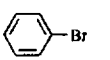
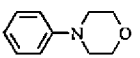
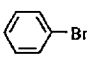
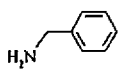
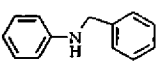
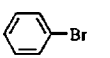
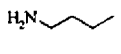
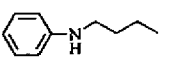
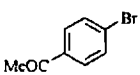
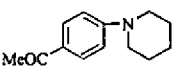
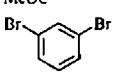
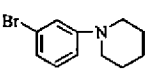
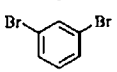
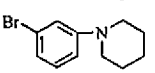
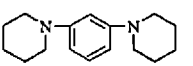
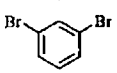
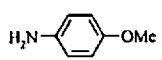
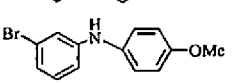
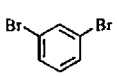
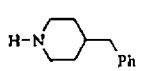
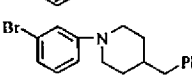
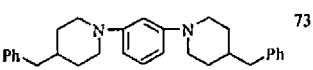
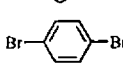
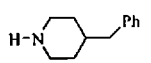
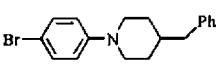
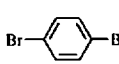
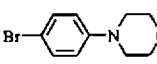
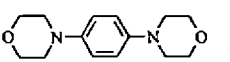
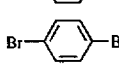
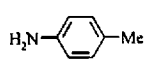
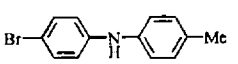
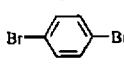
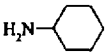
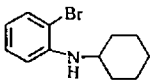
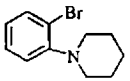
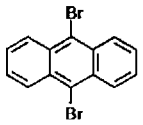
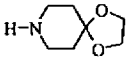
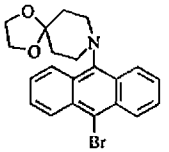
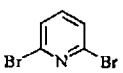
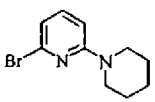
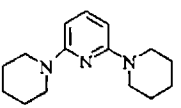
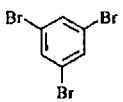
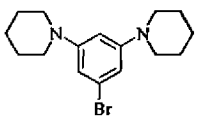
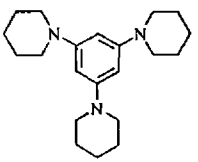
Entry	Aryl bromide	Amine	Conditions[a]	Products[b]			
				Monoamine	Yield (%)	Bisamine	Yield (%)
1			A		83		
2			A		88		
3			A		78		
4			A		73		
5			A		80		
6			A		86		
7			B		12		78
8			A		75		
9			B		14		73
10			A		90		
11			B		17		72
12			A		80		
13			B		23		56
14			A or B		80		

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface (continued)

Entry	Aryl bromide	Amine	Conditions[a]	Products[b]			
				Monoamine	Yield (%)	Bisamine	Yield (%)
15			A or B		65		
16			A or B		90		
17			A		64		
18			B		5		90
19			B		18		67

[a] A: KF-Al_2O_3 (1:4 or 2:3), Pd_2dba_3/BINAP, 80–90 °C, 1 h; B: KF-Al_2O_3 (3:2), Pd_2dba_3/BINAP, 135 °C, 3 h.
[b] Isolated products; structure determined by IR, ^1H NMR, and ^{13}C NMR spectra.[11]

Since polyaminobenzenes are important compounds for various industries, we wanted to employ the reaction conditions to effect polyamination of polyhaloaromatics. While applying similar conditions to dibromobenzenes, mono-aminated products only resulted (Table 1, entries 6, 8, 10, 12, and 17). Earlier we observed similar results in the case of dibromopyridines.[8] In order to obtain the bis-aminated products we examined various proportions of KF-alumina and different catalytic systems. The combination of KF-alumina in the ratio of 3:2 and $Pd_2(dba)_3$/BINAP as the catalyst was found to be suitable for bis-, or tris-aminations in a one-pot reaction (Table 1, entries 7, 9, 11, and 13). Under similar conditions, 2,6-dibromopyridine and 1,3,5-tribromobenzene yielded the corresponding bis- and tris-aminated products (Table 1, entry 18 and 19) in 90% and 67% yields, respectively. Neither reductive debromination nor the formation of imine was observed under these conditions, indicating that the possible β-elimination might not be favorable, and thus contamination with any other byproducts is avoided. The amination occurs quite rapidly for mono-amination (1 h) while polyamination requires a longer time (3 h) and higher temperatures (135 °C). In the case of polyaminations, partial mono-aminated products remained in the reaction mixtures, which were easily isolated by column chromatography (Table 1). Interestingly, 1,2-dibromobenzene did not produce the 1,2-bis-amines in either condition, possibly due to steric crowding (Table 1, entries 14–16). Several variations in terms of the catalytic system, the surface (KF-alumina), and temperatures did not change the course of the reactions.

In conclusion, we have demonstrated that it is possible to effect palladium-catalyzed amination of halobenzenes on a solvent-free surface of KF-alumina without using any strong bases such as sodium *tert*-butoxide. The base-sensitive functional groups remained unaffected under this condition. The procedure is also effective for one-pot mono- or poly-aminations selectively, depending on the conditions used, and thus constitutes a mild and benign method for the synthesis of polyaminobenzenes. No reductive bromination leading to other byproducts has been observed in this procedure.

Acknowledgment

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(10) **General Procedure for the Amination Reactions:**
A: A mixture of $Pd_2(dba)_3$ (2 mol%) and BINAP (4 mol%) was admixed intimately with KF-Alumina (2:3; 2 g) and heated at 80–90 °C for 15 min. Aryl bromide (2 mmol) and amine (5 mmol) were added to the solid surface and the mixture was stirred at 80–90 °C for 1 h. An orange color developed while mixing and gradually disappeared over 1 h. The solid mass was then cooled, packed on a column of silica gel and eluted with EtOAc–light petroleum (1:19) to afford the mono-aryl amines. All the products were identified by IR, ^1H and ^{13}C NMR spectral data.
Condition B: The reaction conditions were identical except the quantity of amine was increased to 7–8 equiv, KF-alumina was used in the ratio of 3:2, and the solid mixture was heated at 135 °C for 3 h. Pure bis-amines were obtained by chromatography over silica gel and elution with EtOAc–light petroleum (1:9). The spectral data were consistent with the assigned structures.

(11) **Selected Spectral Data for Mono- and Bis-Coupled Products**
Table 1, Entry 5: 1-(4-Piperidin-1-yl-phenyl)ethanone: IR (Nujol): 1675, 1206.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.65 (m, 6 H), 2.50 (s, 3 H), 3.34 (m, 4 H), 6.84 (d, 2 H, J = 9.0 Hz), 7.85 (d, 2 H, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 25.3, 26.0, 48.6, 113.3, 126.7, 130.5, 154.4, 196.4.
Table 1, Entry 7: 1, 3-Dipiperidino Benzene: IR (Nujol): 1201.6, 1124.4 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.55–1.62 (m, 4 H), 1.70–1.78 (m, 8 H), 3.16 (t, 8 H, J = 5.4 Hz), 6.49 (dd, 2 H, J = 8.1, 2.2 Hz), 6.61 (s, 1 H), 7.15 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.4, 26.0, 51.2, 106.1, 108.7, 129.3, 153.2.
Table 1, Entry 11: 1,4-Dimorpholino Benzene: IR (Nujol): 1234.4, 1120.6 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.01 (t, 8 H, J = 4.7 Hz), 3.80 (t, 8 H, J = 4.7 Hz), 6.85 (s, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.5, 66.9, 117.4, 145.8.
Table 1, Entry 13: 1,4-Di-[8-(1,4-dioxa-8-aza-spiro[4,5]decane)]benzene: IR (Nujol): 1125 cm^{-1}. ^1H NMR (acetone-d_6, 300 MHz): δ = 1.76 (t, 8 H, J = 5.7 Hz), 3.16 (t, 8 H, J = 5.7 Hz), 3.94 (s, 8 H), 6.88 (s, 4 H). ^{13}C NMR (acetone-d_6, 75MHz): δ = 34.7, 48.6, 63.9, 107.5, 117.9.
Table 1, Entry 15: (2-Bromophenyl)cyclohexylamine: IR (Nujol): 1321.1, 1016.4 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.20–1.44 (m, 6 H), 1.75–1.79 (m, 2 H), 2.02–2.1 (m, 2 H), 3.30 (m, 1 H), 4.26 (br s, 1 H), 6.5 (m, 1 H), 6.6 (d, 1 H, J = 8.1 Hz), 7.14 (m, 1 H), 7.40 (d, 1 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.8, 25.8, 33.0, 51.6, 109.8, 111.8, 117.1, 128.3, 132.5, 144.
Table 1, Entry 17: 8-(10-Bromoanthracene-9-yl)-1,4-dioxa-8-aza-spiro[4,5]decane: IR (Nujol): 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.05 (t, 4 H, J = 5.3 Hz), 3.57 (t, 4 H, J = 5.3 Hz), 4.10 (s, 4 H), 7.48–7.60 (m, 4 H), 8.48 (d, 2 H, J = 8.7 Hz), 8.56 (d, 2 H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.4, 49.9, 64.4, 107.6, 125.2, 125.3, 126.9, 128.3, 131.2, 131.4, 134.1, 145.3.
Table 1, Entry 19: 1,3,5-Tripiperidino Benzene: IR (Nujol): 1199.6, 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.51–1.58 (m, 6 H), 1.66–1.73 (m, 12 H), 3.10 (t, 12 H, J = 5.3 Hz), 6.14 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 26.0, 51.5, 99.2, 153.7.