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# Recent Synthetic Advances in the Nucleophilic Amination of Benzenes

Andrew J Belfield, George R Brown* and Alan J Foubister

AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG

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* Address correspondence to: George R. Brown, at AstraZeneca. Phone: 01625-515918. FAX: 01625 516667. E-mail: George.Brown@alderley.zeneca.com

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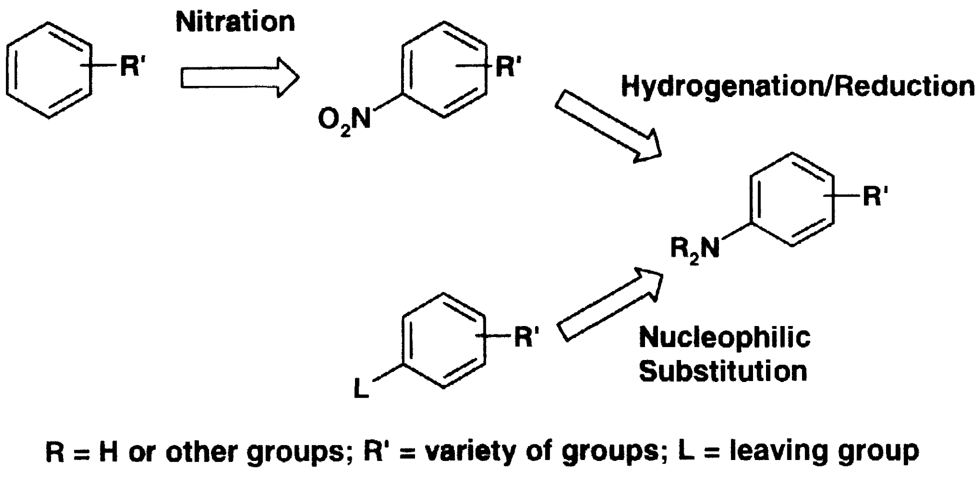
# 1. Introduction

## 1.1 Scope

Arylamines are a very common and important feature in many organic molecules. They are found in biologically active natural products and medicinally important compounds as well as in materials with useful electrical and mechanical properties. Their use in the synthesis of pharmaceuticals, dyes, pesticides and heterocyclic compounds is widespread. It is therefore important that methods exist for the synthesis of novel arylamines on laboratory to manufacturing scales, and that new methods are developed for the synthesis of less accessible derivatives.

Historically[1] arylamine synthesis was carried out mainly by electrophilic aromatic substitution in two steps (Scheme 1): nitration or nitrosation followed by catalytic hydrogenation or reduction with a metal salt. These procedures have found large scale use, but have some limitations. For example, nitration may require strong acidic and oxidizing reaction conditions, and may be incompatible with certain functional groups causing the multi-step use of protective groups. Regioselectivity may also be a significant issue in synthesis, with the production of *ortho/para* mixtures. Aromatic nucleophilic substitution has the advantage of being a single reaction step, but was restricted[2] in synthetic use to substrates containing an electron withdrawing group (EWG). In recent years however, the nucleophilic substitution approach has been much developed by the discovery of metal-catalyzed carbon-nitrogen bond forming reactions. This new field has been rapidly developing since 1994, and has been reviewed from the organometallic viewpoint. Thus Buchwald[3] and Hartwig[4] the pioneers of the palladium catalyzed aminations have each summarized progress describing catalyst design and the choice of appropriate ligands. A review[5] of developments from mid-1996 to December 1997 also covers

**Scheme 1**

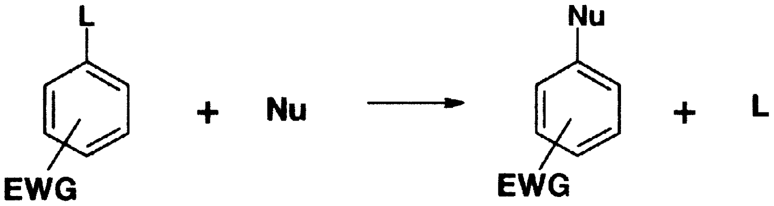


R = H or other groups; R' = variety of groups; L = leaving group reactions with the more reactive oxygen and sulphur nucleophiles, as well as the amination chemistry. This new review covers important developments from 1990 to March 1999, and embraces advances in non-catalyzed reactions as well as the metal catalyzed processes. The main aim of this report is to give a broader perspective of nucleophilic amination of aromatic systems, particularly with the synthetic options in mind.

## 1.2 Synthetic Limitations of Nucleophilic Substitution Mechanisms

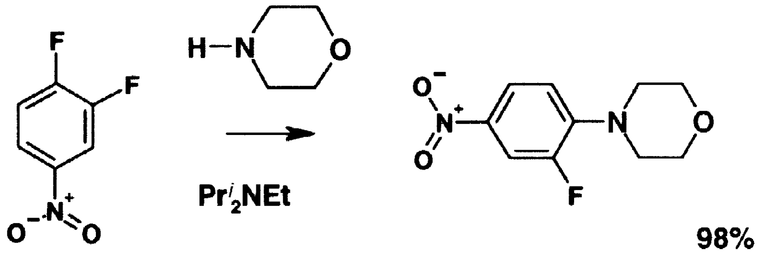
Nucleophilic aromatic substitution is a long established reaction in organic synthesis,[6] and substitution can proceed by several mechanisms:[7] namely $S_N1$, $S_N2$ ($S_NAr$), *via* benzynes, free-radicals or by photo-substitution. These mechanisms each place restrictions on the synthetic utility of the reaction, especially for amination. In the general reaction pathway (Scheme 2), L represents a suitable leaving group which either has no charge (such as H, F, Br or triflate) or is positively charged ($N_2^+$). In some substrates certain nucleophiles (e.g. hydroxylamine) may react[2] with hydrogen as the leaving group, with concomitant departure of part of the nucleophile; this is termed vicarious nucleophilic substitution.

**Scheme 2**



The most common example of an $S_N1$ mechanism is the decomposition of diazonium salts in solution.[3] In this process there is already nitrogen substitution in the substrate at the reaction site, and it has found only very limited use in amination chemistry. The $S_NAr$ mechanism (Scheme 3) occurs by an addition-elimination mechanism involving a resonance stabilized intermediate,[1] and is restricted in synthetic use to

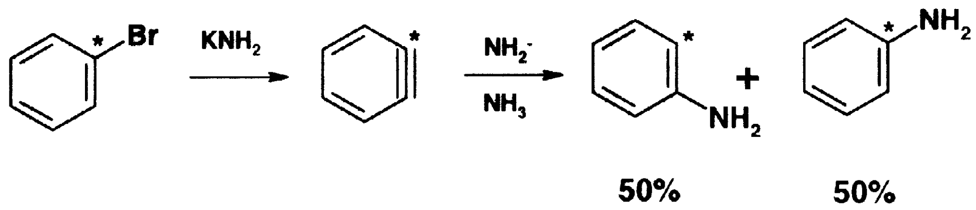
**Scheme 3**



substrates with an EWG at the *ortho* and/or *para* position, which helps stabilize the intermediate cyclohexadienyl anion. This process has been the most widely used direct synthetic amination procedure, before the advent of catalytic methods, and continues to be used frequently.[8]

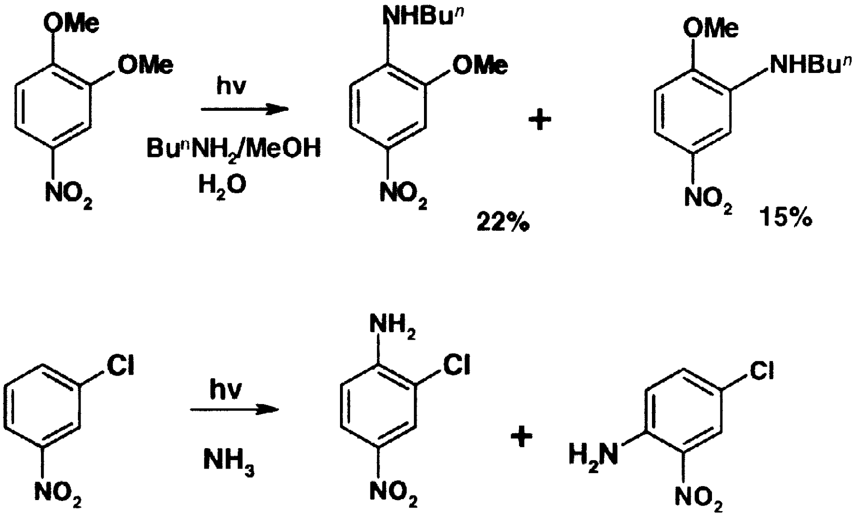
The benzyne mechanism involves the generation of a highly reactive intermediate produced by the elimination of the leaving group.[2] The intermediate can then react with the nucleophile in two possible positions giving two regioisomers, if ring substituents are present (Scheme 4). The ratios in which the isomers are produced is dependent on the relative stabilities of the intermediates and steric effects, thereby limiting synthetic feasibility.

**Scheme 4**



Nucleophilic aromatic substitution may proceed *via* a radical mechanism,[2] but this has not found use in benzene amination. Photosubstitution leads to mixtures[9] of anilines, and in some cases *cine*-substituted products[10] (Scheme 5).

**Scheme 5**



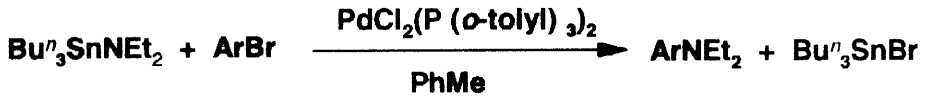
These well established uncatalyzed mechanisms thus have limitations in synthetic use. For example *meta* substitutions are unfavoured, reactions may be relatively slow and some mechanisms afford regioisomers. It is for these reasons that catalyzed aminations have been rapidly developed, and work has continued to improve the more traditional synthetic methodology.

## 2 Transition Metal Catalyzed Methods

### 2.1 Palladium Catalysis

Palladium catalyzed nucleophilic aromatic substitution has become a very useful and diverse synthetic method for introducing an amine functionality onto a benzene ring.[3, 4, 5] It was first reported by Kosugi[11] in 1983; he reported the reaction of *N,N*-diethylamino-tributyltin with bromobenzene (Scheme 6), resulting in

**Scheme 6**



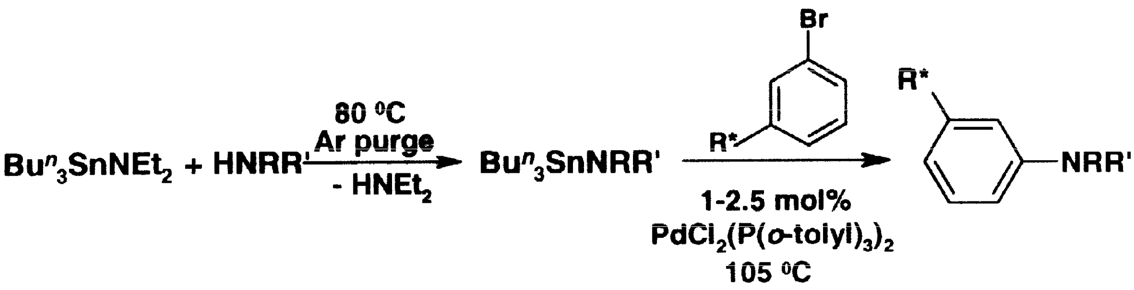
$$Bu^n_3SnNEt_2 + ArBr \xrightarrow[PhMe]{PdCl_2(P(o\text{-tolyl})_3)_2} ArNEt_2 + Bu^n_3SnBr$$

**10 examples** **16-81%**

the formation of *N,N*-diethylaminobenzene. Iodide and chloride were both tried as alternative leaving groups to bromide, but in each case no product was obtained. A benzyne $S_{NAr}1$ mechanism was dismissed as an explanation for product formation, as no regioisomers were observed. An $S_{NAr}1$ mechanism was also dismissed as reaction did not take place with iodobenzene (a good substrate for the $S_{NAr}1$ process), and reaction with *para*-chlorobromobenzene did not give a *di*-substituted product (as expected in the $S_{NAr}1$ process). A probable mechanism of oxidative-addition and trans-metalation followed by reductive elimination was proposed,[8] but not proven.

In 1994, Buchwald[12] reported an extension of this work involving a procedure for the general synthesis of arylamines (as opposed to only diethylamino derivatives) *via in situ* generation of aminostannanes using a transamination reaction with $Bu_3SnNEt_2$ (Scheme 7). However, good yields were obtained only when using

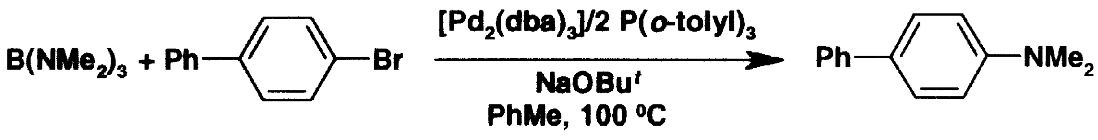
**Scheme 7**



55-88%

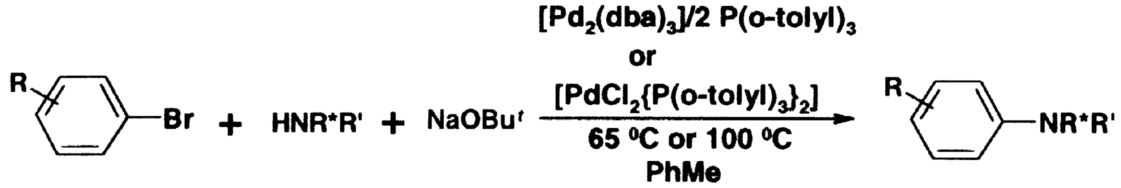
freshly distilled aminostannane under anhydrous reaction conditions. This provided a route to a variety of useful arylamines, but it has a drawback in that the use of tin reagents leads to isolation, disposal and potential toxicity problems. In addition, reactions using primary aliphatic amines were not possible. Concurrently, Hartwig[13] reported an independent investigation of this amination reaction, which focused on identifying the reaction intermediates and making catalyst improvements. A year later Buchwald devised an alternative to the tin reagents by extending Suzuki's use of borane reagents in C-C bond forming reactions to the formation of C-N bonds.[14] Palladium-catalyzed reactions of aryl halides and aminoboranes were investigated, and the commercially available tris(dimethylamino)borane was reacted with 4-bromobiphenyl, (Scheme 8), to give product in an 85% isolated yield. In a similar reaction to the transamination of the tributyltin amide mentioned earlier, the tris(dimethylamino)borane species can undergo trans-amination reactions, which in turn can lead to a more diverse range of arylamines. Further investigation led to the discovery that aminoboranes were not an essential requirement, and that aryl bromides could react efficiently with amines in the presence of $NaOBu^t$ and a catalytic amount of [$PdCl_2$(P(*o*-tolyl)$_3$)$_2$] or [$Pd_2$(dba)$_3$]-2eq. P(*o*-tolyl)$_3$ in toluene (dba = dibenzylideneacetone) to form arylamines (Scheme 9). This reaction is viable for the reaction of aryl bromides containing electron withdrawing and/or electron donating groups with secondary and primary amines (although poor yields and

**Scheme 8**



55-88%

**Scheme 9**



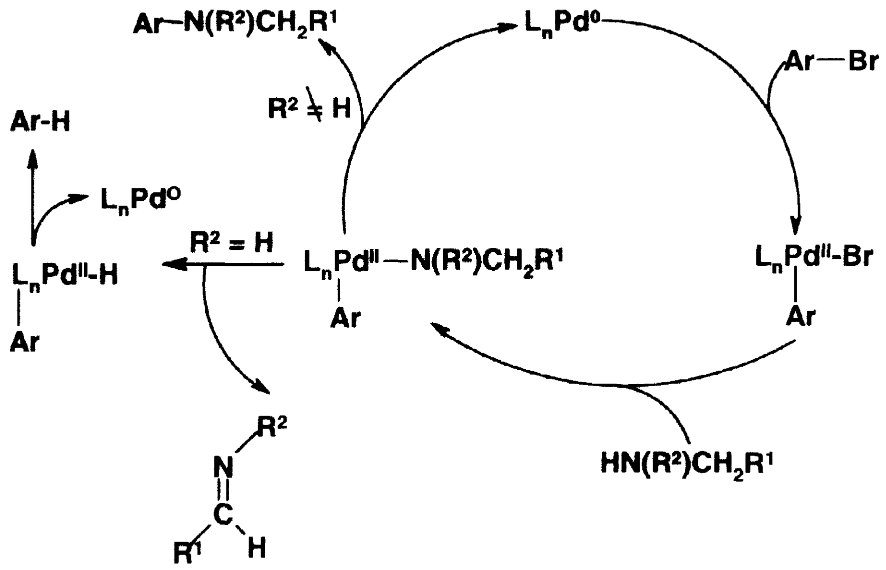
67-88%

| R | R* | R' | Yield % |
|---|---|---|---|
| 3,5-di-Me | *n*-hexyl | H | 88 |
| 4-CN | *n*-hexyl | H | 97 |
| 2-OMe | Ph | Me | 66 |
| 3-$CO_2Bu^t$ | $PhCH_2$ | H | 71 |

by-products were commonly observed with many primary amines). It is also suitable for substrates with acid sensitive groups (e.g. hemiacetals), but base sensitive groups are not tolerated. Hartwig[15] also independently developed a method for arylamine synthesis using free secondary amines and without the need for tin or boron reagents. Like Buchwald, he used the ligand P(*o*-tolyl)$_3$, but used the silylamide base $LiN(SiMe_3)_2$ in the place of NaOBu$^t$, which was found to increase reaction rates.

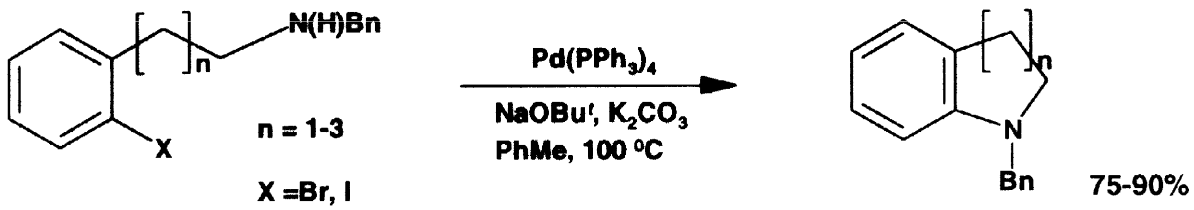
Buchwald proposed a possible mechanism[14] (Scheme 10) for the catalyzed reaction cycle which involves

**Scheme 10**



the oxidative addition of the aryl bromide to the Pd(0) species followed by the formation of a Pd(II) species which undergoes reductive elimination to give the required product and the regenerated Pd(0) catalyst. In the same paper, variation of the ligand ($PPh_3$,1,1'-bis(diphenylphosphino)-ferrocene (DPPF) and 1,3-bis(diphenylphosphino)propane (DPPP)) was carried out. These ligands were found to be unsuitable as either no amine product was formed or the major product was *m*-xylene. This result led Buchwald[14] to the conclusion that the P(*o*-tolyl)$_3$ ligand was crucial to the success of the reaction, although this was later found to be incorrect.[18] Also found to be critical was the choice of base used; NaOMe and $K_2CO_3$ were both tried as alternatives to NaOBu$^t$ , but both were found to be unsuitable. This reaction method was also found to be useful for the synthesis, by intramolecular cyclisation, of nitrogen heterocycles of ring size 5-7,[14] (Scheme 11) and has been investigated in more detail by Buchwald.[16] One problem with the use of P(*o*-tolyl)$_3$ as a ligand is that poor yields are often observed in the cross coupling of primary amines with aryl bromides. Hartwig has shown[17] that when P(*o*-tolyl)$_3$ /Pd is used as the catalyst system, oxidative addition, palladium-nitrogen bond formation and reductive elimination proceed through monophosphine palladium complexes. These intermediate complexes are thought to allow *beta*-hydride elimination in the reaction with primary amines giving the arene by-product in high yields, and restricting formation of the arylamine (Scheme 10). Use of chelating bis-phosphine ligands had

**Scheme 11**



been found to inhibit *beta*-hydride elimination and it was for this reason that Buchwald[18] examined BINAP (2.2'-bis(diphenylphosphino)-1.1'-binaphthyl) as the ligand component. A combination of $Pd_2(dba)_3$ and BINAP in the presence of $NaOBu^t$ was found to be an excellent catalyst system for the coupling of amines to aryl bromides. Importantly, this system was found to work well for the coupling of primary amines to aryl bromides (Scheme 12).

**Scheme 12**

$$\text{ArBr} + \text{RNH}_2 \xrightarrow[\text{NaOBu}^t \text{ PhMe, 80 °C}]{\text{Cat Pd}_2\text{(dba)}_3 \text{ BINAP}} \text{ArNHR}$$

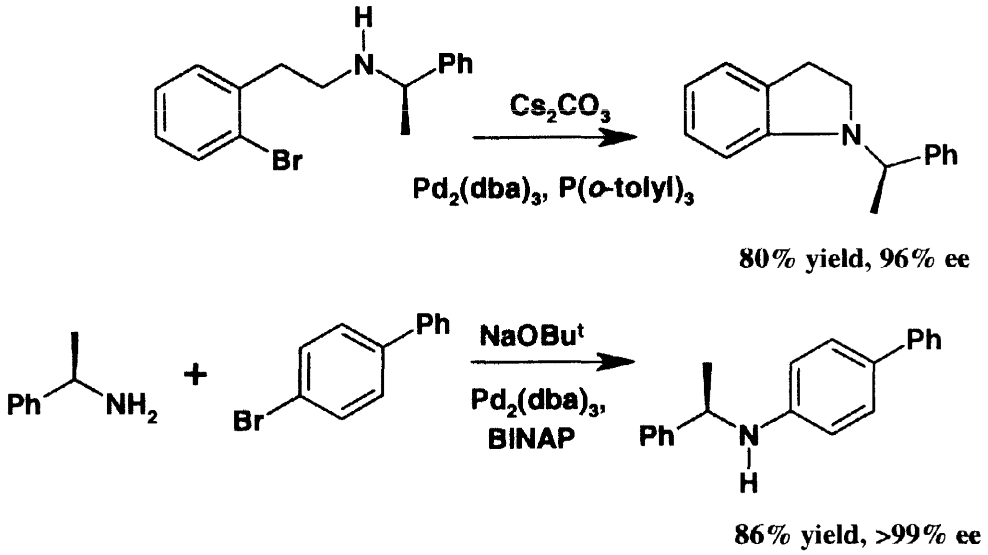
61-97%

| Ar | R | Yield % |
|---|---|---|
| 3,5-di-MePh | $PhCH_2$ | 79 |
| 3,5-di-MePh | cyclohexyl | 83 |
| 2-Me, 4-OMe | *n*-hexyl | 95 |

*Beta*-hydride elimination is inhibited in the (BINAP)Pd species, which is formed during the catalytic cycle, because of the inaccessibility of the three-coordinate monophosphine intermediate. BINAP also has the ability to inhibit formation of catalytically inactive palladium bis(amine) aryl halide complexes and bridging amido complexes which are resistant to reductive elimination. These factors result in BINAP being a very efficient ligand in the Pd-catalyzed cross-coupling of amines, and is especially useful for primary amines. Using BINAP allows catalyst loadings of as low as 0.05% to be used, and good reaction to still be observed. Buchwald later extended the use of BINAP to the catalysis of the coupling of amines to aryl triflates to give arylamines.[19] This is particularly useful in synthesis given the ready availability of aryl triflates from phenols. Buchwald also discovered that the cheaper Tol-BINAP (2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl) could be used as a ligand in place of BINAP, giving just as good yields. In addition, it was also found that the milder $Cs_2CO_3$ could be used as the base,[3] leading to greater functional group compatibility.

Buchwald's group also discovered that (R)- or (S)- BINAP could be used to produce enantiomerically pure products (Scheme 13) from optically pure chiral amines *via* intermolecular cross-couplings.[20] In this process the bulkiness of BINAP was thought to inhibit the *beta*-hydride elimination/facial isomerisation/reinsertion sequence, which is responsible for isomerisation. However, BINAP was found to be unsuitable for intramolecular couplings. Here $P(o\text{-tolyl})_3$ was found to be the ligand of choice, giving good yields of product with no loss of stereochemistry.

**Scheme 13**

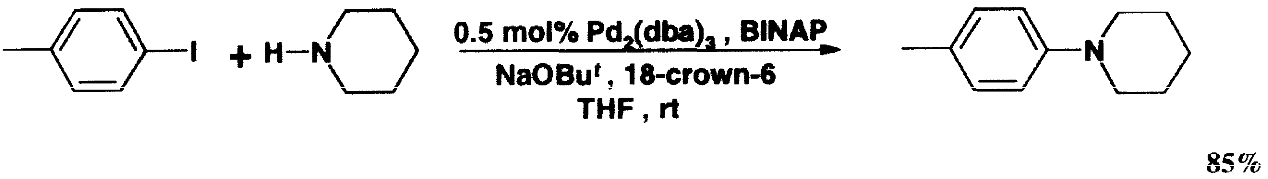


The Pd-catalyzed methods mentioned so far have the drawback that they are conducted at temperatures of 65-110 °C and all involve the use of aryl bromides or triflates. Kang[21] approached this problem by using diphenyliodonium tetrafluoroborate to introduce a phenyl ring onto secondary amines. This process was found to take place at ambient temperature in the presence of $LiN(SiMe_3)_2$ or $NaOBu^t$ using a catalyst of $Pd_2(dba)_3.CHCl_3$ or Pd/C as a Pd(0) source for the binding of $P(o\text{-tolyl})_3$.

In the Ullman ether synthesis, 18-crown-6 had been used to promote the reaction, and this led Buchwald[22] to use it to enable the intermolecular coupling of amines to aryl iodides (previously these couplings had not been as successful as in the intramolecular process). The presence of the crown ether led to the reaction conditions shown (Scheme 14), where amines were coupled to aryl iodides at 20-40 °C in yields of 70-90%.

The scope of palladium catalyzed amination was further increased in 1996 when Ward and Farina[23] showed that this methodology could be used to couple secondary amines to resin-bound aryl bromides. BINAP and DPPF were found to be the most compatible ligands for these Rink resin based reactions. Shortly after, Willoughby and Chapman[24] described the synthesis of arylamines on Rapp Tenta-Gel S RAM resin, and reported that a ligand of $P(o\text{-tolyl})_3$ gave products of a greater purity than if BINAP was used as the ligand. In addition,

**Scheme 14**

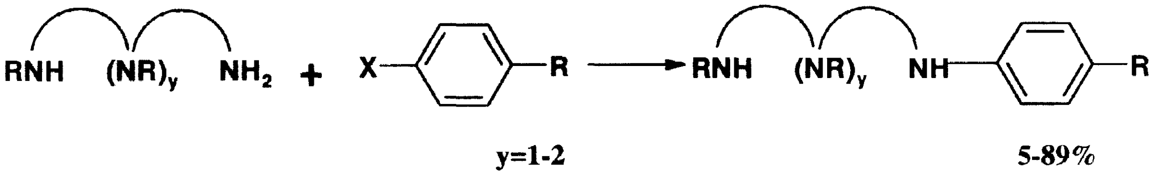


BINAP allowed the coupling of primary amines in a good yield and purity. These examples show the feasibility of producing combinatorial libraries using this Pd-catalyzed amination chemistry.

Zhao[25] demonstrated optimized reaction conditions in which *N*-monoarylpiperazines in preference to N,N'-bisarylpiperazines were synthesized *via* the use of unprotected piperazines. The method is applicable to piperazine itself and C-substituted piperazines. When unsymmetrical piperazines are used, the reaction becomes highly stereo-specific with the *trans*-diastereomeric product being produced preferentially in a 5:1 ratio, enabling the facile synthesis of novel arylpiperazines. The process, however, requires relatively high loadings of catalyst (3 mol%) and product yields were relatively low (13-63%). An improved system for the formation of arylpiperazines was reported by Nishiyama,[26] using the relatively simple $P(t\text{-}Bu)_3$ ligand. Catalyst loadings of 0.5 mol% were used, but results showed good catalytic activity at loadings as low as 0.01-0.02%, demonstrating the high activity of the catalyst. This activity and selectivity were attributed to the strong basicity and steric bulk of the ligand helping reductive elimination from the reaction intermediate. The $P(t\text{-}Bu)_3$ ligand was also found to be suitable for the coupling of aryl chlorides as well as bromides and iodides. The coupling of acyclic secondary amines using the ligands mentioned so far had always been less effective than the coupling of cyclic secondary amines and primary amines. Buchwald[27] has described ligands derived from (rac)-PPFA and (rac)-PPF-OMe which increased the yields of the coupling of acyclic secondary amines to as high as 97%.

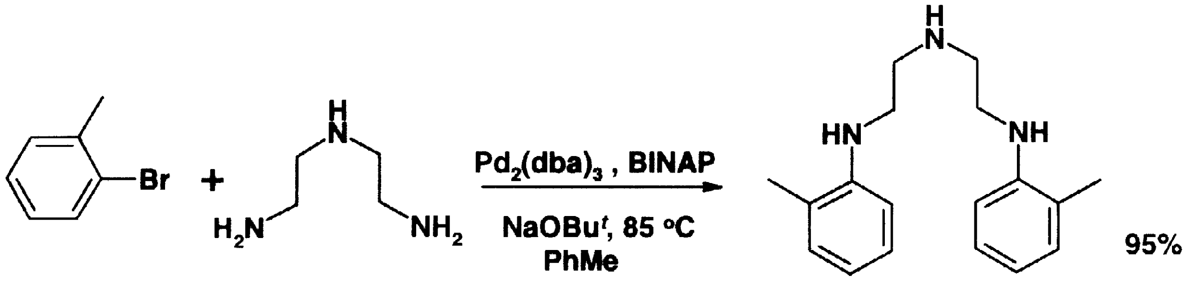
Beletskaya[28] reported a highly selective method for the synthesis of *mono*-aryl substituted polyamines from aryl bromides and iodides *via* palladium catalysis. Polyamines containing up to 4 amino groups linked *via* 1,2-diaminoethyl and/or 1,3-diaminopropyl fragments were coupled with aryl halides using $(DPPF)PdCl_2$ as catalyst and $NaOBu^t$ as base. Reactions, conducted with aryl halides containing electron-withdrawing and electron-donating substituents in the *ortho* or *para* positions, gave almost exclusively the mono-arylated polyamine, (Scheme 15).

**Scheme 15**



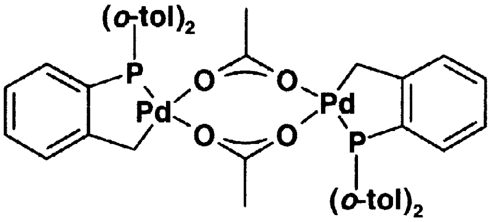
Hong[29] demonstrated another highly selective system using polyamines. Here polyamines containing both primary and secondary amino groups were used in coupling to aryl bromides with BINAP being used as the ligand. Selectivities ranging from 9:1 to 99:1 were observed, with the preferential product being the result of coupling at the primary amine. If compounds containing two primary amines were used then the bis-aryl product was observed (Scheme16).

**Scheme 16**



One drawback with the use of BINAP as a ligand is that it only catalyses the amination of aryl bromides

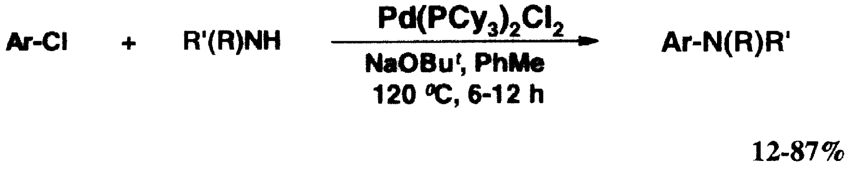
**Figure 1, Ligand 1**



triflates, and to a lesser extent iodides, and is ineffective in the amination of aryl chlorides due to the low reactivity of the aryl C-Cl bond. Beller[30] developed the first palladium catalyzed amination of an aryl chloride using a palladacycle (Figure 1, Ligand 1) catalyst system in similar reaction conditions to that of Buchwald.

Reddy[31] also advanced catalyst design by applying knowledge that a metal centre coordinated by bulky and electron rich phosphine ligands (e.g. $PCy_3$ or $P^iPr_3$) can cleave a C-Cl aryl bond. This resulted in the development of the catalyst $Pd(PCy_3)_2Cl_2$ (Scheme 17), for coupling secondary amines to aryl chlorides. Hartwig[32] also examined amination catalysts for aryl halide substrates and was first to achieve amination of aryl tosylates, whilst further accelerating the reaction of aryl bromides and iodides. These alkyl phosphines were considered as ligands because they would increase reactivity by increasing electron density at the metal centre. Their tight binding properties required bulky groups to be used to promote dissociation, as it had been shown[32] that the oxidative addition involves the complete dissociation of a chelating phosphine ligand (e.g. BINAP ). DB$^t$PF (1,1'-bis(di-*tert*-butylphosphino)ferrocene) was the main ligand examined, and it gave very good yields,

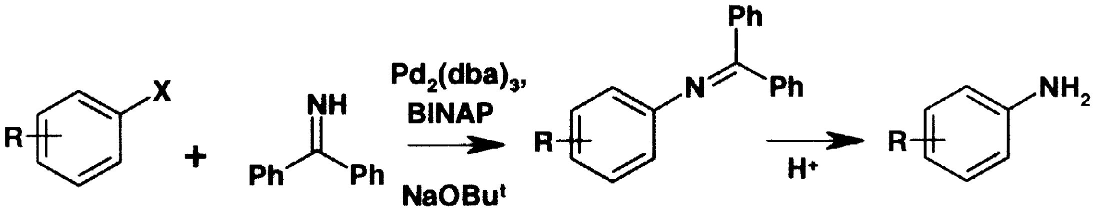
**Scheme 17**



allowing mild conditions (typically 110 °C, 24 h) to be used for the amination of unactivated aryl chlorides. The importance of the steric hindrance from the *tert*-butyl groups was demonstrated by the inactivity of the corresponding methyl substituted catalyst system.

Buchwald developed[33] a useful "ammonia equivalent" palladium catalyzed amination reaction for the production of unsubstituted primary anilines (Scheme 18), since only substituted anilines had previously been

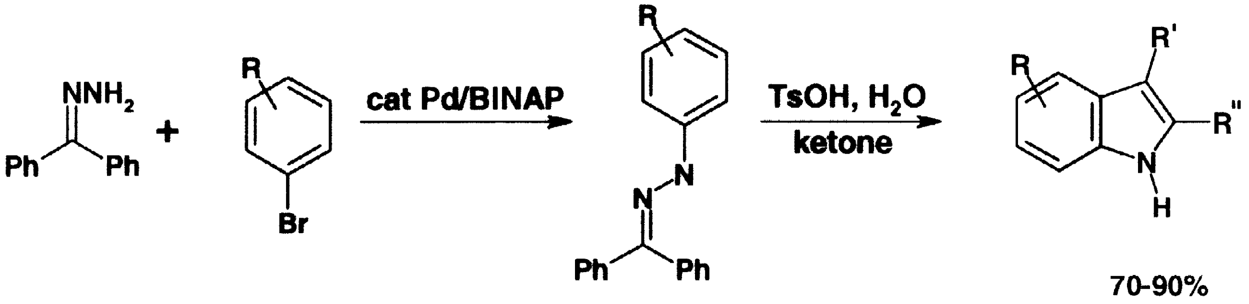
**Scheme 18**



produced. The reaction involves the catalyzed coupling of the available benzophenone imine to an aryl halide or triflate followed by cleavage of the C=N bond to form the unsubstituted aniline. The catalytic system used was $Pd(OAc)_2$ or $Pd_2(dba)_3$ with BINAP in toluene with either $Cs_2CO_3$ (for triflates) or $NaOBu^t$ (for halides) as base. Effective cleavage of the double bond required variation of the reaction conditions based on the nature of the substrate. In general, acidic conditions were used in wet THF or MeOH solvent or a catalytic amount of Pd/C was sometimes used. Hartwig[34] later used a catalytic system of DPPP/$Pd(OAc)_2$ in toluene with $Cs_2CO_3$ or $NaOBu^t$ at 65-120 °C for 3-48 h to couple imines and azoles to aryl bromides. These conditions are suitable for electron-rich, electron-neutral and electron-poor aryl halides and can also be used to couple pyrrole, indole and carbazole substrates. The hydrazone moiety was introduced on an aryl bromide by Hartwig[35] *via* palladium catalysis using diphenylhydrazone with a catalyst system of $PdCl_2(P(o\text{-tolyl})_3)_2$ and either DPPP or BINAP in toluene with $Cs_2CO_3$ as a base. Buchwald used the *N*-arylhydrazones (prepared using the method mentioned earlier[35]) in a novel route for the Fischer indole synthesis.[36] The hydrazones were treated with a ketone in acidic conditions to give the indole *via* an enolizable hydrazone, which undergoes Fischer indolisation (Scheme 19).

Large scale synthesis of arylamines using the majority of the ligands mentioned above is limited, due to their cost. Bis[2-(diphenylphosphino)phenyl]ether (DPEphos) is an inexpensive ligand produced in a one-pot synthesis on a multigram scale, making it the method of choice for larger scale palladium catalyzed amination

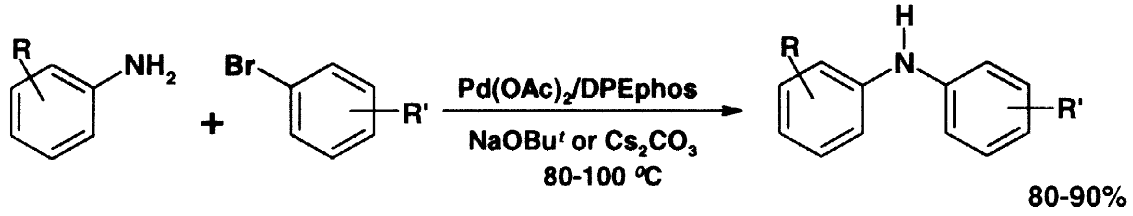
**Scheme 19**



**Ketone = cyclohexanone**
**methylisopropyl ketone**
**acetophenone**

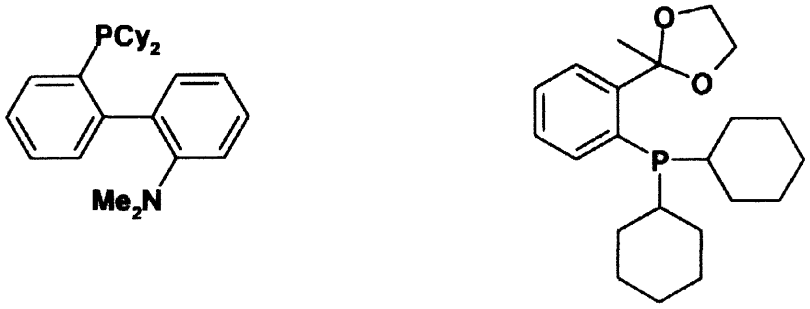
reactions. Buchwald$^{37}$ reported the use of this ligand in combination with $Pd(OAc)_2$, in the coupling of primary anilines to aryl bromides (Scheme 20). The catalyst system was not suitable for the coupling of alkylamines and *N*-alkylamines, but in the coupling of primary anilines was found to be equally as active as $Pd(OAc)_2$/rac-BINAP and more active than $Pd(OAc)_2$/DPPF. Recently, Buchwald has developed$^{38}$ a very active ligand system, which catalyses the amination of unactivated aryl chlorides at 80 °C and can be used in the catalysis of the amination of activated aryl chlorides at room temperature. The system used was a combination of $Pd_2(dba)_3$ and Ligand 2 in toluene or DME with $NaOBu^t$ or $K_3PO_4$ and also catalyses the amination of a range of aryl bromides and iodides at room temperature. Guram$^{39}$ used a ligand of 2-(2'-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane (Figure 2, Ligand 3) in the coupling of aryl chlorides with primary and secondary amines. The ligand is a modification on a novel ligand designed by Guram for use with aryl bromides and iodides, and is designed to increase electron density at the palladium centre to promote oxidative addition of unreactive aryl chlorides. The system was found to be an efficient catalyst in the coupling of the previously problematic acyclic secondary amines. For example, the ligand was used with $Pd_2(dba)_3$ to couple electron-rich and electron-deficient aryl chlorides with amines in yields of up to 97%.

**Scheme 20**



Kocovsky reported$^{40a}$ the synthesis of the novel BINAP analogue 2-amino-2'-diphenylphosphino- 1,1'-binaphthyl (MAP), and showed it to have an accelerating effect on the *N*-phenylation of binaphthyl amino-

**Figure 2**

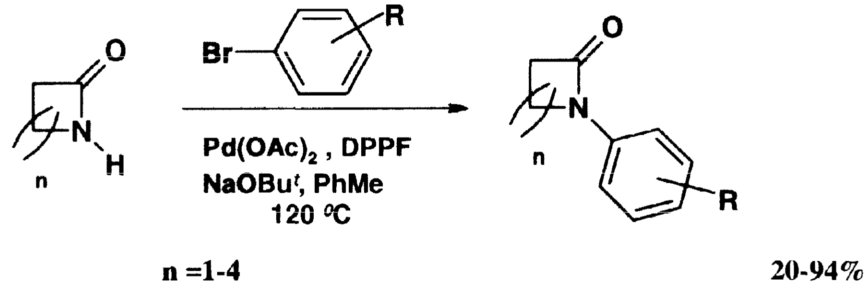


**Ligand 2** **Ligand 3**

alcohol and diamino derivatives when used in place of BINAP. Buchwald has also reported[40b] the synthesis of similar BINAP analogues.

In 1999, Shakespeare reported[41] the coupling of lactams to aryl bromides using the DPPF ligand in conditions identical to those of Hartwig (Scheme 21). It was found that the reaction yield depended on the electronic nature of the aryl ring and the ring size of the lactam. A five membered lactam ring was found to be optimal, but the coupling of other lactams could be facilitated by the use of electron poor aryl bromides.

**Scheme 21**

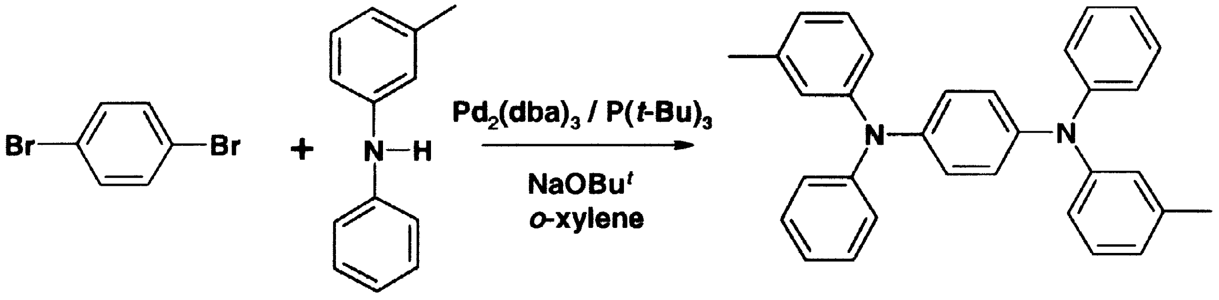


## 2.2 Some Applications of Palladium Catalysis

These advances in Pd-catalyzed amination have been put to practical uses in the total synthesis of many useful products. As long ago as 1985, Boger[42] used a stoichiometric amount of palladium-tetrakis complex to catalyze an intramolecular cyclisation amination in the total synthesis of the natural antitumor antibiotic lavendamycin methyl ether, (Figure 3, Compound 1).

High molecular weight triarylamine dendrimers have become compounds of great interest due to their use as building blocks for high-spin polyradicals, conductive polymers and especially due to their applications in electroluminescent display devices. Previously their synthesis had typically been achieved *via* an Ullman reaction using high temperatures and a stoichiometric amount of copper, often resulting in poor yields. Hartwig[43] provided a route to these molecules in yields of up to 99% by using a variety of ligands. The best yields, however, were observed when amino-lithium compounds were used as aminating agents. Yamamoto[44] provided a route to triarylamines, which did not require the use of amino-lithium compounds, using P(*t*-Bu)$_3$ as the ligand. For this synthesis, this catalyst system was shown to be more active than that reported by Hartwig; reactions were carried out using typically, *N*-(3-methylphenyl)aniline together with mono-, di-, or tri-halobenzene together with the catalyst and NaOBu$^t$ in *o*-xylene. Yields were generally good, ranging from 77-99% (Scheme 22).

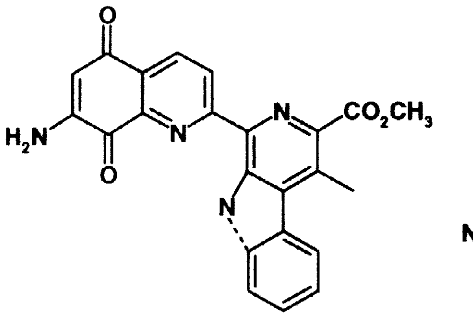
**Scheme 22**



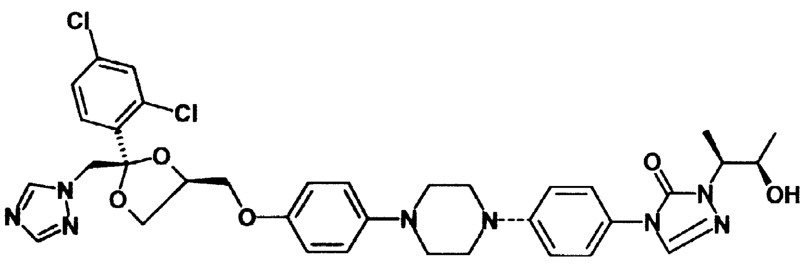
**80%**

In 1998, Buchwald reported[45] a palladium-catalyzed synthesis of oligoanilines, which have been shown to be environmentally stable conductive polymers and are used in rechargeable batteries, electrochromic displays and anticorrosion coatings for steel. The wide scope and ease of this method allows for the production of many novel oligoanilines, which may be end-functionalised,[46] and of a controlled chain length with an odd or even number of the monomer.

**Figure 3** **Compound 1**



**Compound 2**



------ = newly formed bond

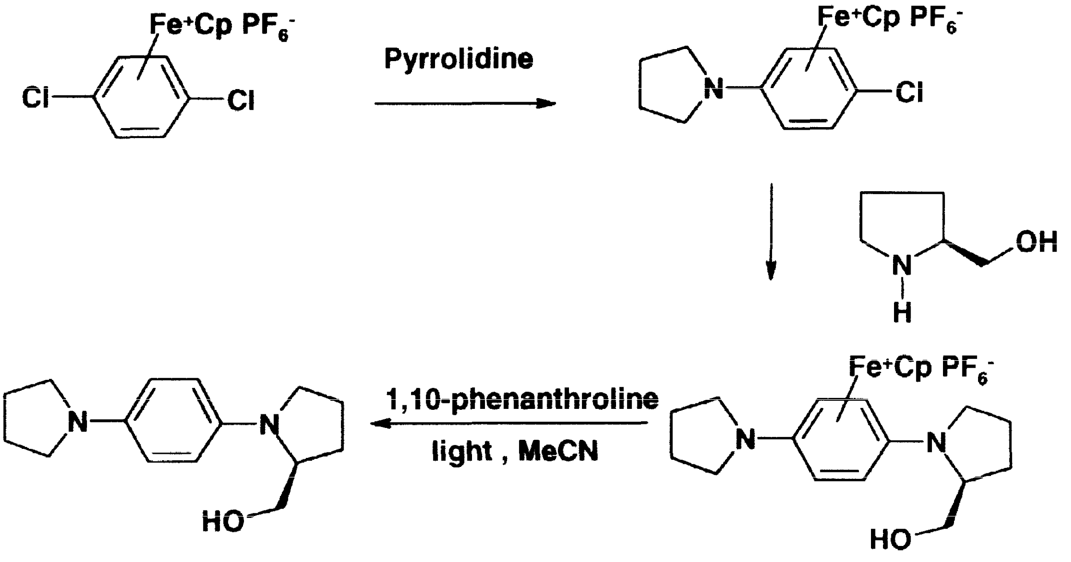
Later in 1998, Morita[47] used palladium catalyzed amination to synthesize a phenylpiperazine intermediate in the total synthesis of a derivative of a metabolite of the antipsychotic agent aripiprazole. Also in 1998, Tanoury[48] applied palladium catalyzed amination in the total synthesis of hydroxyitraconazole enantiomers (Compound 2). The two halves of the molecule were individually prepared and then a piperidine coupled to an aryl bromide *via* palladium catalysis. Since both coupling partners in this convergent route are highly functionalised, this synthesis shows the versatility of the catalyst system by demonstrating its tolerance to functional groups.

## 2.3 Other Transition Metal Catalysts

Recent advances in nucleophilic aromatic amination are not only limited to palladium catalyzed reactions, but have involved other transition metal catalysis.

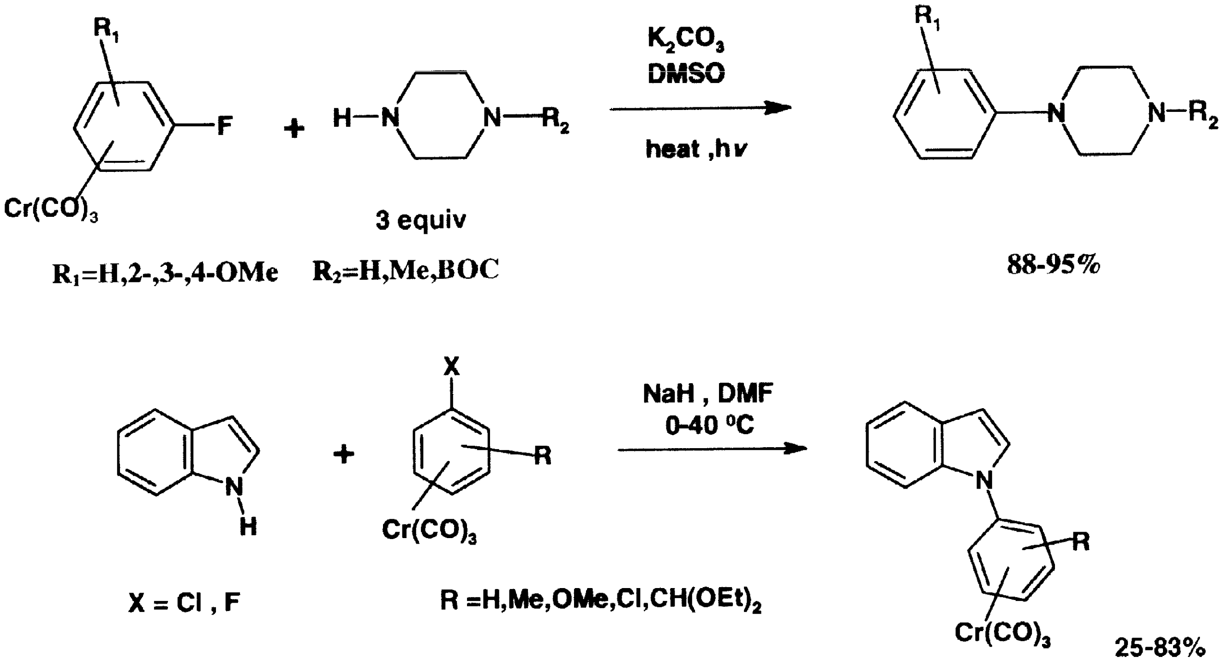
Pearson[49] has described the synthesis of unsymmetrical and/or functionalised tetra alkyl-*p*-phenylene diamines from cyclopentadienyl(1,4-dichlorobenzene)iron(I+) complexes. High yields of unsymmetrical (80% and above) compounds were isolated (Scheme 23). Tricarbonylchromium complexes of $\eta^6$-flouroarenes have been shown by Perez [50] to catalyze the synthesis of arylpiperazines (Scheme 24). Maiorana,[51] in 1997, also used chromium tricarbonyl complexes, in the *N*-arylation of indoles using chloride or fluoride as a leaving group (Scheme 24). Mild reaction temperatures (0-40 °C) were used in the presence of sodium hydride and DMF. Further developments in the copper salt catalyzed amination of triarylbismuth (Bi III) and pentavalent bismuth (Bi V) compounds have occurred.[52] Banfi[53] has reported the synthesis of functionalised *N*-arylpiperidines, especially those substituted in the *meta* position, (Scheme 25).

**Scheme 23**



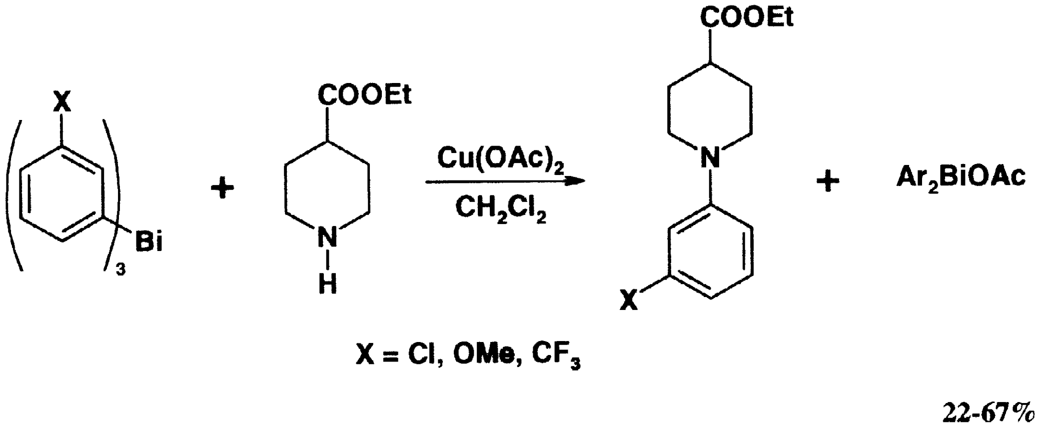
In further studies of organobismuth reagents described by Barton,[52] a combination of $Ar_3Bi(OAc)_2$ and the soluble catalyst $Cu(OPiv)_2$ was found to be the most efficient catalyst system, with

**Scheme 24**



quantitative yields often being obtained. The effect of the steric hindrance of the aryl groups in these pentavalent bismuth compounds on the amination, and other coupling reactions has been investigated by Finet.[54]

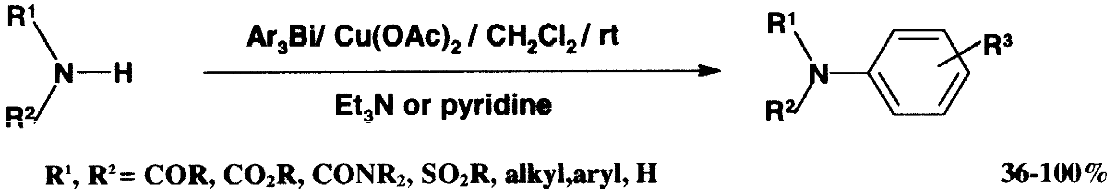
**Scheme 25**



Chan,[55] in 1996, reported that the arylation of N-H bonds in amines, amides and imides, was facilitated by triarylbismuth and cupric acetate (Scheme 26). The reactions require the presence of a 'tertiary amine promoter' of either pyridine or triethylamine to enable the reaction to proceed or to give reasonable yields.

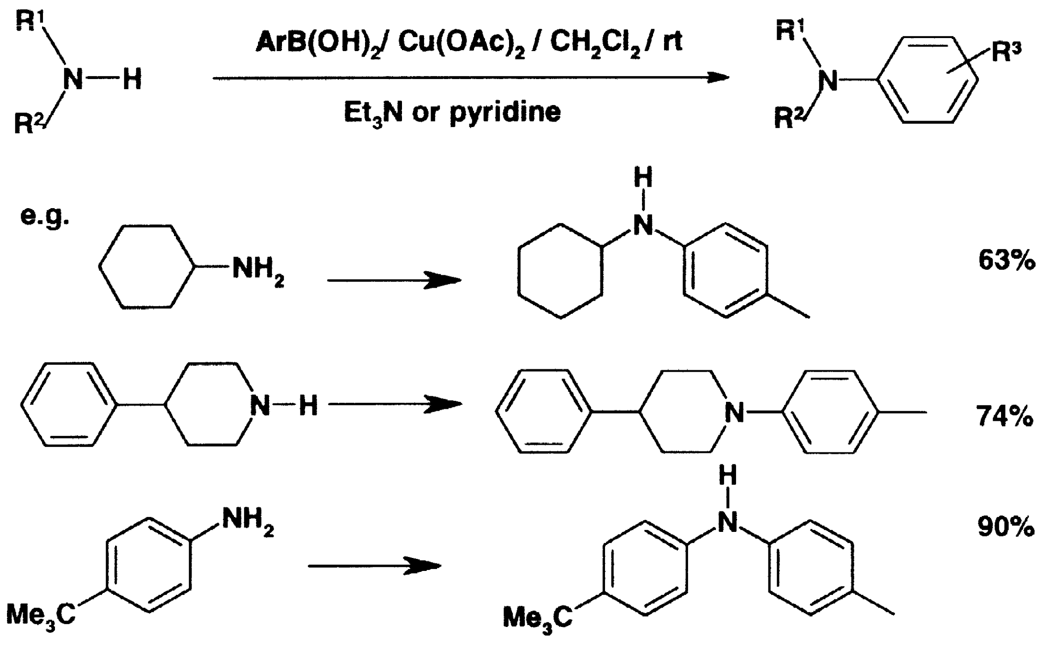
Later, in 1998, Chan[56] reported (Scheme 27) a modification of this reaction in which aryl boronic acids were used in place of triarylbismuth in otherwise identical reactions. The reaction involves mild conditions (room

Scheme 26



temperature, mild amine base), is applicable to a large range of amines and related functionalities (primary, secondary, anilines, amides, imides, ureas, carbamates and sulfonamides) and is tolerant to many functional groups on the boronic acid.

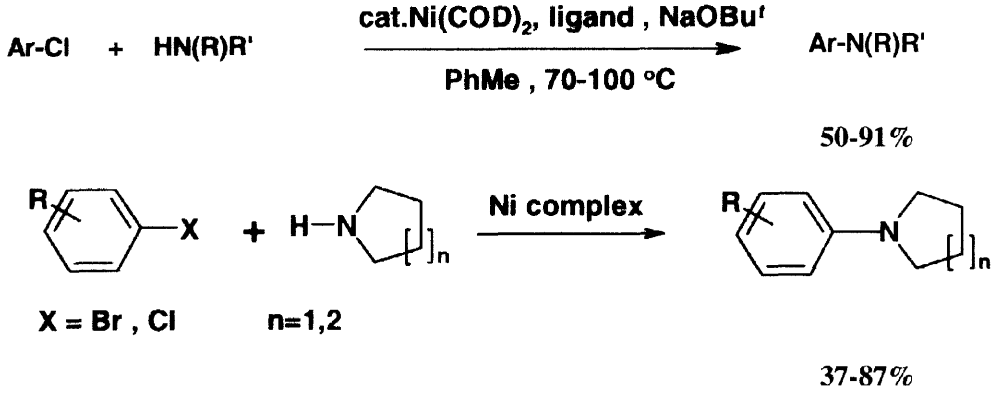
Scheme 27



At the same time, Lam[57] applied these reaction conditions in the coupling of arylboronic acids to N-H containing heteroaryl systems (such as imidazoles and triazoles), which may contain alkyl substituents or be fused to a phenyl ring. It was also found that aryltrialkylstannanes could be used instead of the arylboronic acids, but a large drop in the yield was observed and the use of tin creates disposal and potential toxicity problems. Lam later applied the boronic acid-copper acetate coupling technique to the formation of C-N aryl/heteroaryl bonds on solid support, providing a useful route to chemical libraries.[58]

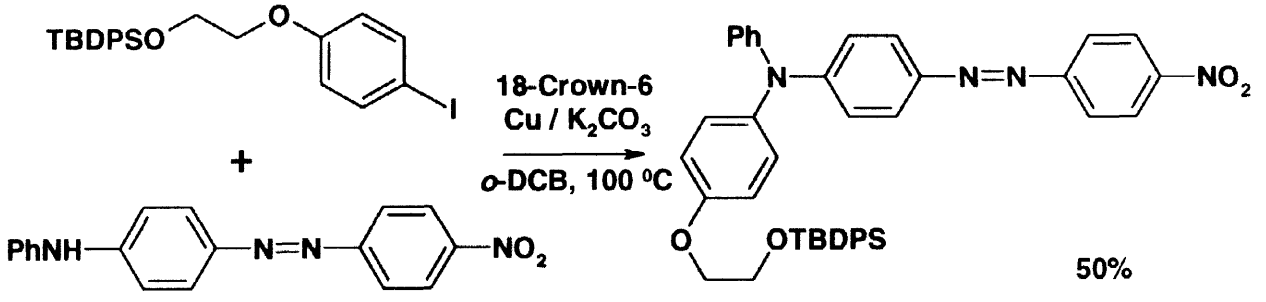
In 1996, Buchwald developed a nickel-based catalyst system for the amination of aryl chlorides.[59] This was important at the time because at this point there was no existing palladium catalyst system for this reaction. It was limited to the leaving groups bromide, iodide and triflate, although, as mentioned earlier, chloride equivalents were subsequently developed. The catalyst system used was Ni(COD)$_2$ (COD = cyclooctadiene) with DPPF as a ligand (Scheme 28). This method may be used to couple both electron-rich and electron-poor aryl chlorides and chloro-pyridines to primary and secondary amines under relatively mild reaction conditions. Later, to eliminate the use of the air-sensitive Ni(COD)$_2$, a method using DPPF with NiCl$_2$ and MeMgBr was developed.[3] Nickel(0) was also used as a catalyst by Fort.[60] The catalyst system used is a known combination from the synthesis of C-C bonds, and was a mixture of NaH, NaOAm$^t$, Ni(OAc)$_2$ and 2,2'-bipyridine (in a ratio of 2:2:1:2) in THF with 0.5 of an equivalent of styrene. It was used to aminate bromo- and chlorophenyls with cyclic secondary amines (Scheme 28).

**Scheme 28**



The synthesis of a series of 4-(*N,N*-diarylamino)-4-nitroazobenzenes has been reported by Miller[61] using

**Scheme 29**



a phase transfer mediated Ullman reaction performed using 18-crown-6 in either *o*-chlorobenzene or triethylene glycol dimethyl ether. Given the harsh reaction conditions used, reasonable yields are obtained (19-81%) and the reaction is tolerant of functionality, e.g. a TBDPS ether survives the reaction conditions (Scheme 29).

Goodbrand[62] has described the rate acceleration of classical Ullman coupling reactions by the addition of the copper binding ligand, 1,10-phenanthroline, in equimolar amounts to the Cu(I) catalyst used.

This also allows for milder temperatures to be used and improved yields of 61-85% were observed. This effect has been described as ligand-accelerated catalysis.

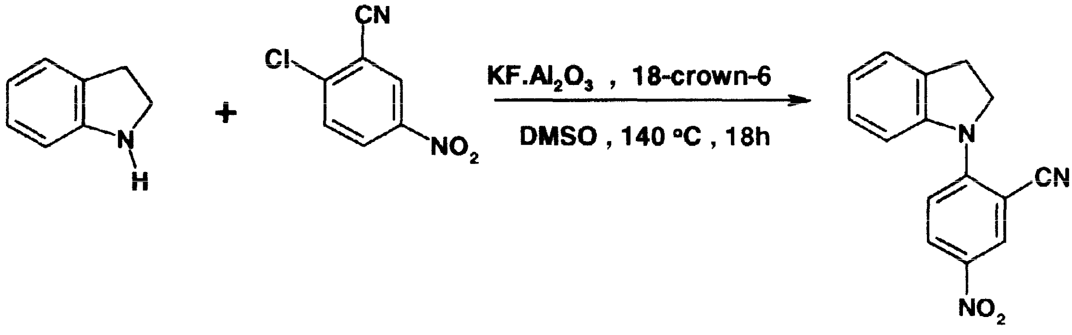
## 3 Transition Metal-Free Methods

Advances also continue to be made in non-metal catalyzed and non-catalyzed nucleophilic aromatic amination, often by using forcing reaction conditions and varying solvents .

Sawyer[63] has demonstrated the formation of diarylamines by potassium fluoride-alumina and 18-crown-6 catalysis (Scheme 30). The method has been adapted from their system for the formation of diaryl ethers and diaryl thioethers and involves the coupling of an amine to an activated aryl chloride in the presence of the catalysts and DMSO at 140 °C.

In 1990, Kotsugi[64a] reported the successful synthesis of aromatic amines from phenols containing EWGs under pressure. The activated phenols were converted into the corresponding triflates using triflic anhydride and triethylamine and the triflate reacted with the amine to produce the arylamine. Reactive amines (*e.g.* piperidine) simply react on heating under reflux in acetonitrile but unreactive amines, such as aniline, do not react on heating and instead require 10 kbar pressure. The pressure procedure is also used for less-activated triflates such as *p*-cyano and *p*-benzoyl, and was employed for activated aromatic fluorides.[64b]

**Scheme 30**



82%

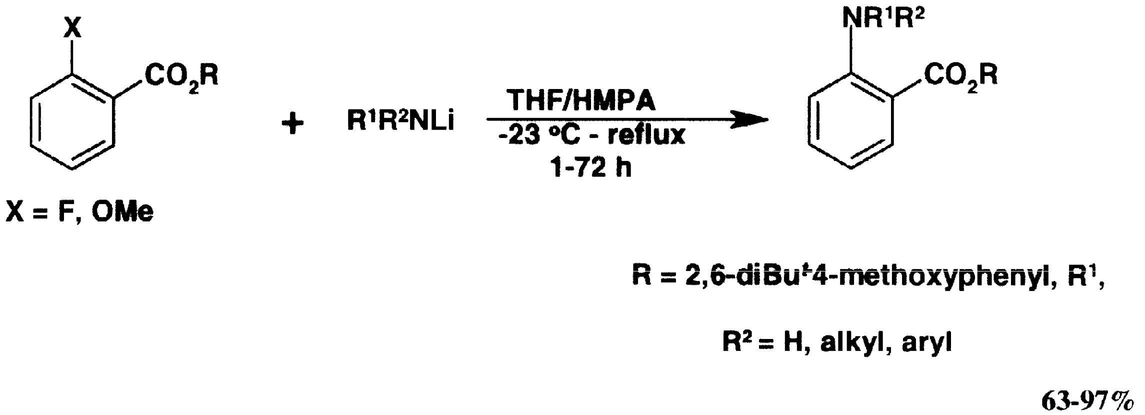
Since 1991 high pressure routes to aryl amines from aryl halides have been extensively developed by Ibata.[65] Previously such reactions had been limited to certain fluorides and chlorides with strong EWGs (e.g. *o*-/*p*-nitro). Here, reactions were carried out using activated aryl halides (with Br, Cl, F, I) and primary and secondary amines in THF at 50 °C under a pressure of 7.2 kbar. The reaction is also viable for cyclic amines and di- and tri-haloarenes. In 1993, Ibata investigated nitro-group substitution in 2,3,5,6-tetrachloronitrobenzene[66] using a variety of primary and secondary amines, derived from his earlier work showing no nitro group substitution in mono- di- and tri-chloronitrobenzenes. These findings indicated that the bulkiness of the attacking amine determined the ratio of nitro group to chlorine atom substitution, the less bulky the group the higher the yield of nitro group substituted product.

The comparatively low nucleophilicity of tertiary amines in relation to primary and secondary amines has meant that their nucleophilic substitution reaction with aromatic halides has been difficult to achieve and few examples of this $S_NAr$ reaction exist. Ibata[67] reported the use of high pressure for this reaction using the coupling of *N*-methyl substituted cyclic amines and mono-, di-, and tri-chloronitrobenzenes. Reaction were carried out at pressures of between 0.60 and 0.75 GPa, and in most cases gave mixtures of products. Depending on the amine used and the position of the substituents within the ring, demethylation and ring-opened products were observed in varying ratios. Similar reactions were carried out using *p*-chloronitrobenzene[68] as substrate with *N*-methyl and *N*-benzyl cyclic amines giving similar product variation.

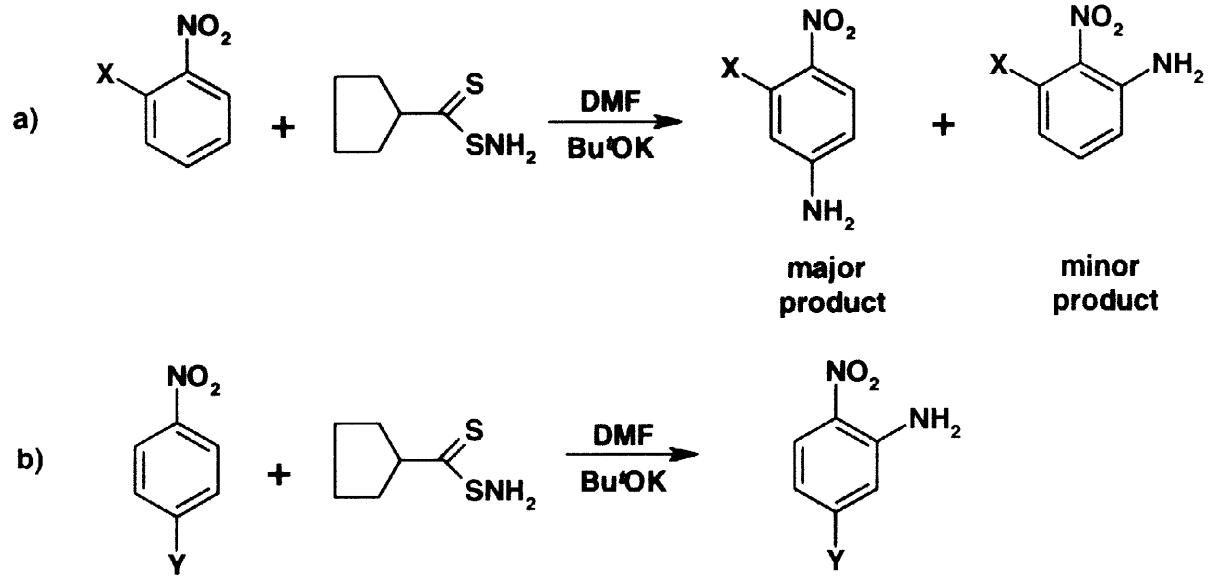
Wynberg[69] has reported the formation of aromatic amines by the direct substitution of aromatic ethers by lithium amides. Aromatic methoxy, phenyl and benzyl ethers were used as substrates and reacted with lithium amines in THF under reflux. Reactions were found to proceed well with secondary amines, but poor yields were observed with primary amines and hindered secondary amines. Lithium was also used by Periasamy[70] for the *N*-phenylation of amines *via* the reaction of bromo- and chlorobenzenes and amine. The synthesis of phenylamines in preference to the biphenyl product was promoted by using an excess of halobenzene and lithium with respect to the amine. Secondary amines and certain primary amines reacted in good yields (70-86%) but reaction was poor with secondary phenylamines.

Miyano[71] showed that the introduction of a 2,6-di-*tert*-butyl-4-methoxy phenyl ester into an aromatic system *ortho* or *para* to a fluoro or methoxy group facilitated the synthesis of 2- or 4-(diarylamino)benzoates in good to excellent yields, *via* substitution of the fluoro or methoxy group by a primary or secondary lithium amide (Scheme 31).

**Scheme 31**



**Scheme 32**

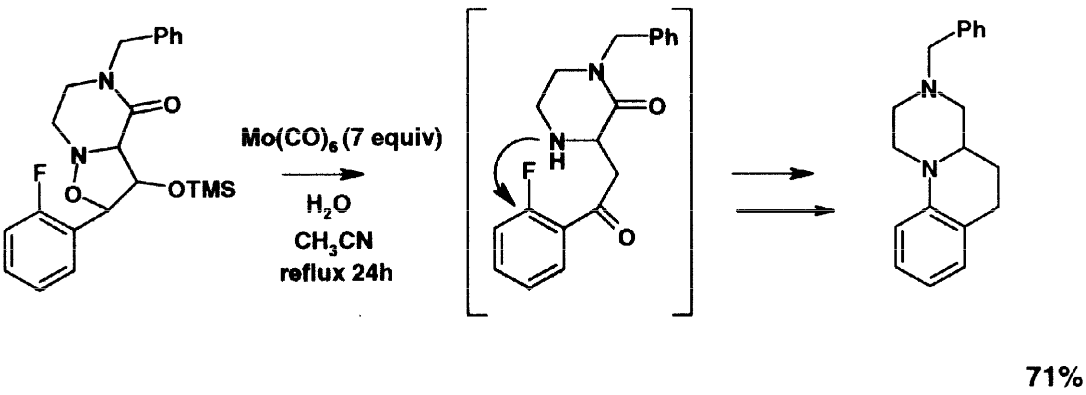


X=H,$NO_2$,CN,$CF_3$,Cl Y= $NO_2$,$CF_3$,Cl,F,OMe a)21-72% b)4-63%

Pagoria[72] reported the use of 1,1,1-trimethylhydrazinium iodide as a reagent for the vicarious nucleophilic substitution of hydrogen. Reactions were carried out on 3-substituted nitro-benzenes and 1,3-dinitrobenzene and the reagent was found to be reactive enough to give substitution both *ortho* and *para* to the nitro group. Vicarious nucleophilic substitution has also been developed by Makosza,[73] who reacted sulphenamides with nitroarenes under basic conditions to give access to a range of substituted nitroanilines. By varying the structure of the sulphenamide and nature of the base, some degree of control of the orientation of the amination was obtained (Scheme 32).

In 1996, Bernotas and Adams[74] developed a non-catalyzed synthesis for constrained arylpiperizines *via* intramolecular aromatic amination of flouroarenes by piperazine (Scheme 33). The molybdenum complex used

**Scheme 33**

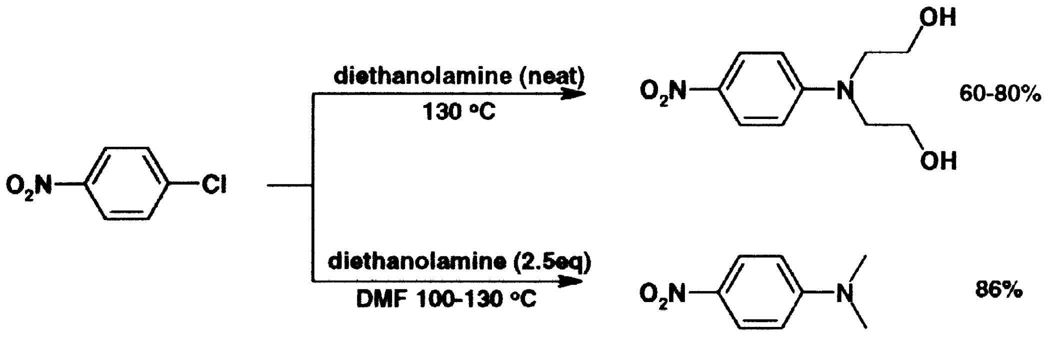


in the reaction does not act as a catalyst, but is used to cleave the isoxazole. Once cleaved the intermediate immediately undergoes substitution to form the arylpiperazine .

Synthesis of arylamines on solid phase *via* non-catalyzed methods has been reported by Lee,[75] who coupled a solid-supported fluoroarene to α-amino esters using DIEA and DMF as a route to a quinoxalinone library.

In 1997, Cho and Park[76] discovered a convenient new method of producing dimethylaminobenzenes from activated arylamines. When *p*-nitrochlorobenzene (PNBC) is reacted with diethanolamine at 130 °C, the substituted product is observed. When DMF was used as a solvent, however, it reacts with PNBC, not ethanolamine, and the dimethylamino product was obtained. The reaction was also demonstrated with bromide as the leaving group and with halopyridines, quinolines and pyrimidines (Scheme 34).

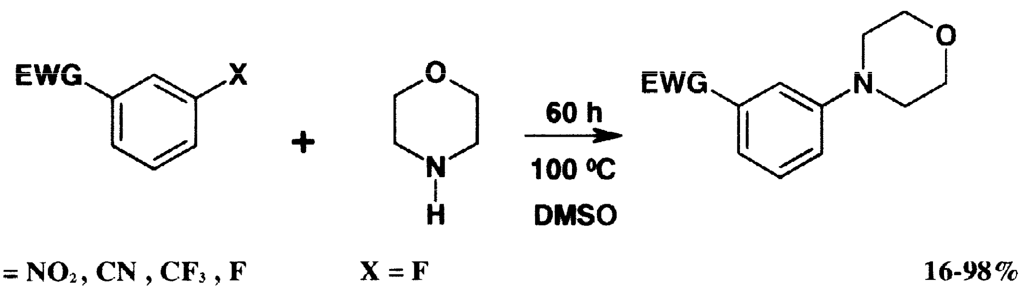
**Scheme 34**



In 1998, Salmoria[77] reported a method of shortening the reaction times for the reaction of halobenzenes with nucleophiles, including amines, using microwave radiation. The reactions were carried out homogeneously under reflux at atmospheric pressure in a microwave oven. The same reactivity order among the nucleophiles and leaving groups was observed as in the non-microwave aided reaction, but rate increases of between 2.7 and 12 times were observed.

Recently, in this laboratory, Brown[78] reported a method for the high yield synthesis of *meta*-substituted amination products (Scheme 35). Morpholine was used as the attacking amine and the substrate was a

**Scheme 35**



EWG = $NO_2$, CN , $CF_3$ , F    X = F    16-98%

fluorobenzene (chloro and bromo were tried, but failed to give any product) containing one or two *meta* positioned EWGs ($NO_2$> CN>$CF_3$). Reaction conditions were optimized so that morpholine was used in 5.5 equivalents and also acted as the base in the reaction. The reaction was conducted in a small amount of DMSO as solvent and was heated at 100 °C for 60h to give *meta*-substituted yields as high as 98%. This work indicates that high yielding *meta*-aminations are possible when the intermediate cyclohexadienyl ion is stabilized inductively by EWGs.

## 4. Overview and Synthetic Options

Although the nucleophilic aromatic substitution of benzenes with amines is a long-established and extensively studied reaction, many advances have been made recently to give improved synthetic yields without regioisomer problems, so that it is now the method of choice over electrophilic substitution approaches. These advances have accelerated since 1994 by the extensive work carried out by Buchwald's[3] and Hartwig's[4] research groups into the development of palladium catalyzed reactions. Both groups have developed distinctive catalyst systems, which have led to palladium catalyzed methods suitable for a wide range of substrates and amine nucleophiles. Other workers have also developed palladium catalysis and have applied the catalyzed reaction to the total synthesis of important compounds. An important recent development is the achievement of palladium catalyzed substitutions with solid phase reagents[23,24] that may be useful in the important developing area of combinatorial chemistry. Other metals have also been developed for use as catalysts, but some of these methods require stoichiometric amounts of metal, and would lead to residue disposal issues in larger scale use. Information from the palladium catalysis work (e.g. the ligand systems) has been applied to these other metals, creating high yielding and potentially cheaper processes.

Non-catalyzed methods also continue to be developed, mainly through varying reaction conditions, but the rate of advance has been slower here.

Overall this report has hopefully demonstrated that the last few years have seen considerable progress in the development of aromatic nucleophilic amination chemistry, and it is now the method of choice for the synthesis of many aromatic amino derivatives. Publications in this field continue to appear frequently, and further advances are anticipated.

### Synthetic options

We have covered a wide range of substitution methods in this report, and here we provide an outline guide to synthetic methods of choice.

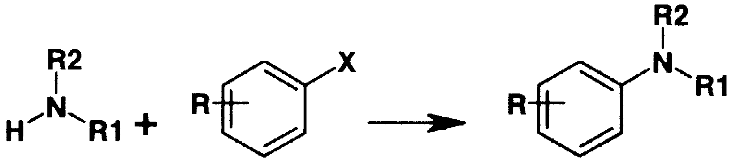
- **General** - Nucleophilic substitution is preferred to electrophilic approaches, and palladium catalyzed methods are the most versatile. Conventional non-metal nucleophilic substitution is the optimal method when EWGs are present.

- **Amine Nucleophiles** - There is now no restriction on the range of amines that can be used in palladium catalyzed reactions (except for the general steric restrictions found in organic chemistry), and this method is particularly useful for substitution with anilines, where the DPEphos catalyst[37] is valuable. Direct amination can be achieved in good yield with benzophenone imine[33] as the amine source.

- **Leaving groups** - Fluoride is the best leaving group for conventional substitutions, and has permitted substitutions to proceed in *meta*-substitution positions.[78] Bromide is a superior leaving group in palladium reactions where NaOBu$^t$ is the optimal base.[3,4] Triflate has the advantage that it gives access to the wide range of phenols available as starting materials; here caesium carbonate is the base required.

- **Aromatic Ring Substitution** - When strong EWGs are present non-catalysed substitution in DMSO is optimal for *ortho*- and *para*-substitution,[8] and for good yields in *meta*-substituted compounds it is essential to use the recently reported reaction conditions of 60 h at 100 °C,[78] employing fluoride as the leaving group. For benzenes containing donor groups, palladium chemistry must be used for good results.

- **Summary Table of Best Options**



| R | Amine, R$_1$, R$_2$ | | |
|---|---|---|---|
| | Aniline | Primary | Secondary |
| *Ortho*-EWG | Pd | Pd or Nu | Nu |
| *Meta*-EWG | Pd | Pd or Nu | Pd or Nu |
| *Para*-EWG | Pd | Pd or Nu | Nu |
| *Ortho,meta, para* donor group | Pd | Pd | Pd |

Pd = palladium catalyzed method; Nu = conventional nucleophilic substitution, X = leaving group.

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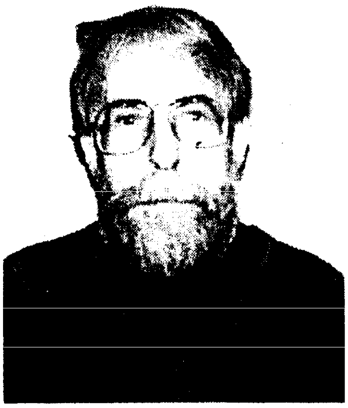
# Biographical sketch

Andrew J. Belfield

George R. Brown



Alan J. Foubister

**Andrew Belfield** was born in Stockport in 1978 and is studying for an honours degree in chemistry with industrial chemistry at Liverpool University. At present he is working at AstraZeneca on a project involving nucleophilic aromatic substitution. He has investigated novel substitution reactions and has made a major contribution to this report.

**George Brown** was born in London and received his BSc degree in chemistry from London University in 1962. He became Abbott Research Worker at Brunel University and completed an MSc thesis (London) in 1968 on synthetic oestrogens. In 1970 he joined ICI Pharmaceuticals and has worked in a number of medicinal chemistry research areas. He has published widely in medicinal and organic chemistry, and is currently a Principal Medicinal Chemist with AstraZeneca.

**Alan Foubister** was born in Ellon Scotland and was awarded a BSc in chemistry from Aberdeen University in 1966. After working on process chemistry in the dyestuff industry, he joined ICI Pharmaceuticals in 1974. He has worked on the synthesis of a wide range of aromatic and heterocyclic systems, and has discovered novel ring enlargements and contractions. Currently he is a Principal Synthetic Chemist at AstraZeneca.