Recent developments in aromatic heteroatom coupling reactions

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1 Introduction

This review highlights the recent advances in the addition of heteroatom nucleophiles to aromatic or heteroaromatic substrates throughout the period 1/6/96 to 31/12/97. The review will cover the transition metal catalysed addition of nitrogen, oxygen, sulfur and phosphorus nucleophiles. This chemistry typically involves palladium or nickel based catalysts containing phosphine ligands. In addition to catalytic coupling reactions, we will review the recent developments in nucleophilic aromatic substitution reactions (S$_{b}$Ar). The recently developed macrocyclisation reaction based on an intramolecular S$_{k}$Ar reaction has enjoyed many applications in the synthesis of large-ring natural products. In addition to typically nucleophilic heteroatoms, electrophilic heteroatoms such as boron, oxygen, sulfur and phosphorus nucleophiles. This chemistry involves bis(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high-yielding, catalytic cross-coupling of aryl bromide 3 with tert-butylamine to give 4 in 98% yield using only 0.05 mol% of catalyst!

2 Catalytic heteroatom coupling reactions

One of the most exciting developments in catalysis over the last few years is undoubtedly the advent of a practical, mild and efficient protocol for catalytic carbon–heteroatom coupling reactions. In independent investigations, Buchwald et al. and Hartwig et al. reported the first catalytic aminations of aryl bromides with free amines. For the palladium catalysed reaction has enjoyed many applications in the synthesis of large-ring natural products. In addition to typically nucleophilic heteroatoms, electrophilic heteroatoms such as boron, silicon, tin and germanium have also been coupled to aryl electrophiles. A summary of the general reaction pathways of these C–X bond forming processes can be found elsewhere. The Buchwald group found that a combination of Pd$_2$(dba)$_3$ and BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] in the presence of sodium tert-butoxide performed as a superior catalyst for the cross-coupling of amines with aryl bromides to afford amine derivatives 2 (Scheme 1). The efficiency of BINAP as a ligand may be attributed to its ability to inhibit the formation of catalytically inactive palladium bis(ammine) aryl halide complexes. This remarkable protocol is illustrated by the catalytic cross-coupling of aryl bromide 3 with n-hexylamine to give 4 in 98% yield using only 0.05 mol% of catalyst!

The Hartwig group discovered that (DPPF)PdCl$_2$. DPPF = 1,1’-bis(diphenylphosphino)ferrocene] catalyst provided high yields of mixed, secondary aryl amines 2 from aryl halides and primary amines, notably in examples that gave low to moderate yields with the Pd(0)/P(0-tolyl)$_3$ catalyst system. This study revealed several important concepts; firstly, the catalytic cycle involves bis(phosphate) intermediates. Second, sterically encumbered phosphines are not necessary for the high-yielding, intermolecular amination of aryl halides. For example, Hartwig reports the catalytic cross-coupling of aryl bromide 5 with aniline to afford product 6 in 94% yield (Scheme 1). Finally, the observed favourable selectivity for reductive elimination over β-hydrogen elimination results from chelation and large bite angle, rather than from steric effects. For further discussion of the kinetics and mechanisms involved in the amination chemistry, Hartwig has written two excellent accounts.

Although a general protocol had been developed for the palladium catalysed cross-coupling of primary and secondary amines with aryl bromides, the use of sodium tert-butoxide as base presented problems with a number of common functional groups. Buchwald discovered that the ligand (rac)-PPF-OME 7 was superior for effecting aminations with acyclic secondary amines. Therefore, this new protocol was a major step forward for the development of more general methods for cross-coupling reactions.
Furthermore, it was noted that the combination of Pd₃(dba)₃ and (rac)-PPF-OMe 7 allowed the reaction to proceed with the weaker base caesium carbonate. These new reaction conditions are sufficiently mild to tolerate the presence of methyl and ethyl esters, aldehydes, enolisable ketones and nitro groups, which are incompatible with reaction conditions which employ sodium tert-butoxide as the stoichiometric base. Thus, the reaction of ketone 8 with primary amine 9 proceeds efficiently to afford a 73% yield of aniline 10 (Scheme 2).

![Scheme 2]

A further improvement in procedure has been reported by Buchwald which allows the catalytic amination of aryl iodides at room temperature. For example, the reaction of p-iodotoluene 11 with piperidine 12 in the presence of stoichiometric quantities of sodium tert-butoxide and 18-crown-6 and a catalytic amount of Pd₃(dba)₃/BINAP proceeds to completion in 6 hours at room temperature (Scheme 2). The product 13 is isolated in 85% yield. This is a significant advance for reactions involving thermally sensitive molecules or where it may be inconvenient to heat reactions such as large parallel syntheses or applications in combinatorial chemistry.

The first palladium catalysed coupling reaction of aryl chlorides with amines was reported by Beller. Crucial to the success of the reaction was the use of potassium tert-butoxide as base. The coupling of aryl chloride 14 and piperidine 12 was catalysed by trans-di(μ-aceto)-bis[α-(di-o-tolyphosphino)-benzyl]palladium(II) (palladacycle) to give the product 15 in 98% yield (Scheme 3). Further aminations of aryl chlorides have been reported by Buchwald. The mild nickel catalysed procedure tolerates a variety of functional groups including ethers, nitriles, acetics and non-enolisable ketones. For example, 4-chlorotoluene 16 and amine 17 gave the desired tertiary amine 18 in 91% yield by employing a Ni(COD)₂/DPPF catalyst (Scheme 3). Interestingly, the chelating nitrogen ligand 1,10-phenanthroline, which is not effective in palladium catalysed aminations, proved useful in the nickel catalysed reaction. This is demonstrated in the preparation of 21 by a nickel catalysed cross-coupling of 4-chlorobenzonitrile 19 with morpholine 20 (Scheme 3).

The conversion of phenols to aryl amines clearly has considerable synthetic value. Given the simple conversion of phenols to aryl triflates, and the application of aryl triflates in Stille and Suzuki couplings, it was no surprise that Hartwig and Buchwald independently extended their amination chemistry to include aryl triflates as coupling partners. Under the standard conditions, Hartwig reports the conversion of aryl triflate 22 into aryl amine 23 in 96% yield as an example of the utility of this methodology (Scheme 4). Similarly, Buchwald reports that the combination of Pd(OAc)₂/BINAP is an effective catalyst system for this valuable transformation. Once again, by changing the stoichiometric base from sodium tert-butoxide to caesium carbonate, a greater functional group tolerance is allowed the reaction to proceed with the diphenyl ketimine product 28. The products can be purified and stored as masked amines or the benzophenone imine can be
cleaved directly to the primary amine \( \text{29} \) by catalytic hydrogenation or treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF (Scheme 5).

The synthesis of aminopyridines is important to many branches of chemistry; for example, they find applications as ligands, as components of fluorescent dyes, and are stimulants to the central nervous system. The Buchwald group have revealed that the palladium catalysed amination strategy can be effectively applied to the synthesis of aminopyridines and this protocol represents a significant improvement relative to existing procedures which often require activated substrates and harsh reaction conditions.

The reaction of 2-bromopyridine \( \text{30} \) with 2-aminopyridine \( \text{31} \) produced the interesting product \( \text{32} \) in 87% yield. This was also an effective strategy for preparing diarylated diamines \( \text{34} \), as shown by the reaction of four equivalents of 2-bromopyridine \( \text{30} \) with diamine \( \text{33} \) (Scheme 6).

In an alternate amination reaction, Beletskaya and Guilard have shown that polyamines such as \( \text{35} \) react with aryl bromides, for example \( \text{5} \), to afford monoarylated products \( \text{36} \). This strategy provides a convenient method of arylation of di-, tri- and tetra-amine compounds (Scheme 7).

Frost and Mendonça have reported the successful implementation of an iterative palladium catalysed amination strategy to prepare an array of peptide analogues \( \text{37} \) by parallel synthesis (Scheme 8). The combination of \( \text{Pd(II)}_3 \) \text{DBA} /\text{DPPF} proved to be an effective catalyst for the efficient introduction of different nitrogen functionality. Two groups have reported methods for the solid phase synthesis of aryl amines employing the palladium catalysed amination protocol. Willoughby and Chapman note that the \( \text{Pd(II)}(\text{tolyl})_3 \) catalyst system is effective in the coupling of secondary amines such as \( \text{39} \) with polymer bound aryl bromide \( \text{38} \) to afford high yields of product \( \text{40} \) (Scheme 9). The use of \( \text{BINAP} \) as a ligand allowed the coupling of primary amines in high yields and with excellent purities. Ward and Farina independently report similar findings. This methodology will no doubt prove useful for constructing combinatorial libraries of aniline derivatives for biological screening.
Buchwald has reported the palladium catalysed coupling of enantiomerically enriched amines with aryl bromides to afford the corresponding N-aryl derivatives. The choice of ligand is crucial to the formation of the anilines without racemisation. The Pd(0)/P(o-tolyl)$_3$ combination catalyses the intramolecular aryl amination to produce optically pure products, intermolecular coupling reactions with this catalyst system lead to racemised products. However, intermolecular cross-couplings employing Pd(0)/BINAP afford products in excellent yields with no erosion of enantiopurity. This is illustrated by the reaction of aryl bromide 41 with the protected amino alcohol derivative 42 to afford the enantiopure product 43 (Scheme 10). The application of the intramolecular process to the synthesis of 44 a potent ACE inhibitor has been demonstrated. Further studies by Ma and Yao have described the Pd–Cu catalysed couplings of enantiopure o-amino acids and aryl halides.

The group of Senanayake have reported the application of a unique palladium catalysed amination reaction in a concise synthesis of the potent H$_1$-antihistaminic norastemizole 47 (Scheme 11). Using the standard conditions derived by Buchwald, the amine 46 is coupled to the 2-chlorobenzimidazole core 45 in 85% yield. This is a remarkably efficient process considering a primary amine is being selectively coupled in the presence of a secondary amine.
The amination methodology has recently found application in polymer synthesis. The reaction of aryl dibromide 48 with secondary diamine 49 proceeds smoothly in the presence of stoichiometric sodium tert-butoxide and catalytic PdCl$_2$-[P(o-tolyl)$_3$)$_2$ to give new poly(aryleneamine) (Scheme 12). Poly(aminopyridine-2,6-diylimino-1,3-phenylene) has been prepared in an analogous way.  

Scheme 12

The efficiency of the catalytic amination methodology is further demonstrated by Hartwig in the preparation of high molecular weight triarylamine dendrimers. The first generation dendrimer 52 is prepared from tris(4-bromophenyl)amine 50 and lithium diphenylamide 51 (Scheme 13). The yield for the reaction is 84% which is far superior to the modest yields obtained by copper-mediated Ullmann chemistry. The power of the technique is illustrated by the preparation of the largest reported triarylamine starburst dendrimer.

Scheme 13

The group of Pye and Rossen have reported a fascinating kinetic resolution of racemic dibromide 53 employing an enantiomerically pure ligand in a palladium catalysed amination (Scheme 14). The combination of Pd$_2$(dba)$_3$([S]-[2.2]-PHANEPHOS 54 is effective in providing practical enantio-meric discrimination when halide is removed from the reaction mixture using the halide scavenger TlPF$_6$. The products from the reaction are the monoaddition compound 55, the bis-(benzylamine) 57 and the dehalogenated compound 56. After 90% conversion the remaining 10% of 53 is enantiomerically pure at $>$99.9% ee!

Scheme 14

2.3 Carbon–oxygen bond formation
An example of a palladium catalysed aromatic carbon–oxygen bond forming reaction was reported by Buchwald, an intramolecular ipso substitution of an aryl halide to produce oxygen heterocycles. Related work by Hartwig described the palladium catalysed formation of tert-butyl ethers. More recently the Buchwald and Hartwig groups have independently disclosed practical, efficient methods for catalytic, intermolecular carbon–oxygen bond formation. Buchwald promotes the use of a Pd$_2$(dba)$_3$/tol-BINAP combination to achieve a successful intermolecular coupling. Hartwig has also disclosed that a Pd$_2$(dba)$_3$/DPPF catalyst system is effective in the preparation of diaryl ethers such as 60, by coupling aryl bromide 58 with sodium aryl oxide 59 (Scheme 15). It was also noted that electron poor DPPF derivatives led to increased reaction yields. Hartwig has also disclosed that a combination of Ni(COD)$_2$/DPPF or Ni(COD)$_2$/BINAP mediates the formation of protected phenols from aryl halides. Buchwald has also developed a general procedure for the copper catalysed coupling of a wide range of activated and unactivated aryl halides 61 with phenols 62 using caesium carbonate as a base (Scheme 16). The choice of copper catalyst was not critical, however the use of 1-naphthoic acid as an additive was important for the efficient coupling of less soluble phenoxides.

2.4 Carbon–sulfur bond formation
The synthesis of unsymmetrical sulfides by a palladium catalysed cross-coupling reaction of 9-organothio-9-borabicyclo-[3.3.1]nonane derivative 63 and aryl iodide 64 has been reported by the Miyaura group (Scheme 16). It has also been reported that S-allyl thio-carbonates 65 serve as convenient allylsulfonylating agents in the coupling of various aryl halides under typical Heck conditions (Scheme 17). This is a very practical method that enables the preparation of allyl aryl sulfides without having to use allylthiostannanes or allyl thiois, both reagents being notorious for their stench, instability and toxicity.

Another convenient method for the palladium catalysed preparation of mixed aryl sulfides 66 employs samarium(III) thiolates generated in situ from aryl thiacyanates 66 (Scheme 18). Once again, the main advantage with this method is that there is no need to isolate the intermediate thiol.

The palladium catalysed cyclisation of indolyl iodide 68 with the internal thiol group furnishes the product 69 in 74% yield (Scheme 19). This intermediate was then converted to chuangxinmycin, an antibacterial agent, by hydrolysing the methyl ester to the carboxylic acid.

2.5 Carbon–phosphorus bond formation
Laneman reports the findings that tertiary phosphines 71 can be prepared from aryl triflates or halides 70 by nickel catalysed cross-coupling with Ph$_2$P(Cl) in the presence of zinc (Scheme 20). The use of a cheap phosphorus reagent coupled with the
3 Nucleophilic substitution of activated aromatics

In recent times there has been substantial progress in the development of mild, efficient methods for the nucleophilic substitution of aromatic rings. Notably, Pearson has developed a novel approach to diaryl or triaryl ethers by activating chloroarenes to nucleophilic substitution via complexation with transition metals such as FeCp, RuCp or Mn(CO)₃. This strategy has allowed the construction of diaryl ethers from amino acid derivatives with no racemisation. Other methods to prepare diaryl ether linkages have also been developed, Zhu has reported a new macrocyclisation method based on an intramolecular S₅Ar reaction of 3-fluoro-4-nitrophenylalanine derivatives. Zhu has published an excellent review detailing the application of this methodology to the synthesis of 14-, 16- and 17-membered macrocycles as found in a variety of natural products.41

3.1 Transition metal complex promoted reactions

It is well established that tricarbonylchromium complexes of aryl halides undergo nucleophilic substitution more rapidly than the parent aryl halide. Perez exploits this in the synthesis of arylpiperazines.42 For example, the (η⁶-fluoroarene)tricarbonylchromium complex undergoes rapid nucleophilic substitution with piperazine. Decomplexation is performed in situ to afford the product arylpiperazine in 98% yield (Scheme 21). Related S₅Ar chemistry mediated by η⁶-cyclopentadienyliron complexes has been employed by Pearson to prepare a range of symmetrical and unsymmetrical tetraalkylp-phenylenediamines.43 The ease of performing sequential nucleophilic substitutions on p-dichlorobenzene–FeCpPF₆ facilitates the preparation of unsymmetrical pyrrolidine/prolinol derivative in high yield (Scheme 21).

Transition metal η⁶-complexes of protected aromatic amino acids can be used as coupling partners in peptide coupling reactions. Pearson demonstrates the utility of ruthenium complexes for the construction of the diaryl ether 77 under extremely mild conditions (Scheme 22). The synthesis of the anti-tumour agent OF 4949 III was completed by a cycloamidation reaction under high dilution conditions and deprotection steps.

The alternative approach of first performing the peptide coupling reaction then cyclising via an intramolecular S₅Ar reaction to afford cyclic biphenyl ether 78 in high yield is also an effective strategy as demonstrated by Rich (Scheme 23). The same paper reports preformed peptidyl ruthenium complexes have been used to prepare cyclic biphenyl ethers in a combinatorial fashion.

3.2 Nucleophilic substitution of activated arenes

Bernotas has reported an intramolecular nucleophilic substitution of an activated aryl fluoride 79 to furnish the product 80 in 71% yield. The reduction of 80 provided an efficient synthetic route to constrained aryl piperazines, exemplified by 81 (Scheme 24).46
A similar strategy is employed by Arán in the synthesis of cinnolin-3-yl oxide \(83\), a new class of heterocyclic betaine by an intramolecular cyclisation of an \(N^9,N^9\)-disubstituted (2-fluorophenyl)acetohydrazide \(82\) (Scheme 25).\(^{47}\)

The preparation of organic molecules on solid phase allows the rapid generation of diverse arrays of compounds for biological screening. Lee reports the assembly of a small library of quinoxalinones \(84\) on solid support, using a nucleophilic aromatic substitution reaction in the key coupling step (Scheme 26).\(^{48}\) Shapiro has established that \(^{19}\)F NMR is a good method for monitoring solid phase reaction kinetics in \(S_N\)Ar reactions where fluorine is the leaving group.\(^{49}\)

Many of the techniques for nucleophilic substitution of activated aromatics have been developed for the construction of vancomycin and other related glycopeptide antibiotics. Nicolaou reports the development of new synthetic technology for the synthesis of aryl ethers using a triazene unit situated ortho to a leaving group on an aromatic nucleus that acts as an ‘electron sink’.\(^{50}\) The practical utility of this methodology is
demonstrated by the synthesis of vancomycin type model system 85 (Scheme 27).

The nitroaromatic based S_N_Ar methodology has enjoyed numerous applications in synthetic approaches to various targets. The group of Rama Rao has reported a synthesis of the DE segment of vancomycin,^{51} and Zhu reports the synthesis of model tricyclic rings of teicoplanin by means of an efficient cycloetherification.^{52} Boger has also disclosed full details of the synthesis of fully substituted CD and DE rings of vancomycin.^{53}

The power of this methodology is illustrated in the report by the Evans group on the outstanding synthesis of orienticin C (bis-dechlorovancomycin) aglycon (Scheme 28).^{54} The heptapeptide 86 was cyclised to the product 87 in 90\% yield! Given the complexity and sensitivity of these natural products this is quite remarkable.

4 Conclusion

The use of transition metal catalysed reactions to achieve heteroatom-aromatic cross-coupling is an area of fervent interest. The excellent methodology being developed notably by the Buchwald and Hartwig groups is certain to enjoy numerous and diverse applications in synthesis. Some of the excellent chemistry which has been reported in the literature on the S_N_Ar macrocyclisation methodology will surely continue to progress towards even more complex total syntheses.

5 References

41 J. Zhu, Synlett, 1997, 133.