# 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 ($S_NAr$). The recently developed macrocyclisation reaction based on an intramolecular $S_NAr$ 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.[1]

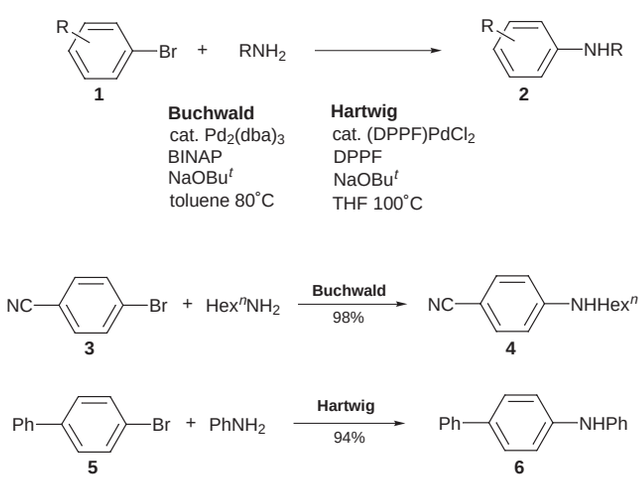
## 2 Catalytic heteroatom coupling reactions

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[2] *et al*. and Hartwig[3] *et al*. reported the first catalytic aminations of aryl bromides with free amines. For the palladium catalysed reaction to occur with good yields, both groups stressed the need to employ P(*o*-tolyl)$_3$ as ligand. Since the initial reports there have been many excellent contributions in this area and much of the chemistry discussed in this section is still actively being developed.

### 2.1 Carbon–nitrogen bond formation

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

The Buchwald group found that a combination of $Pd_2(dba)_3$ and BINAP [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 **1** to afford aniline derivatives **2** (**Scheme 1**).[4] 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 aryl bromide **3** with *n*-hexylamine to give **4** in 98% yield using only 0.05 mol% of catalyst!

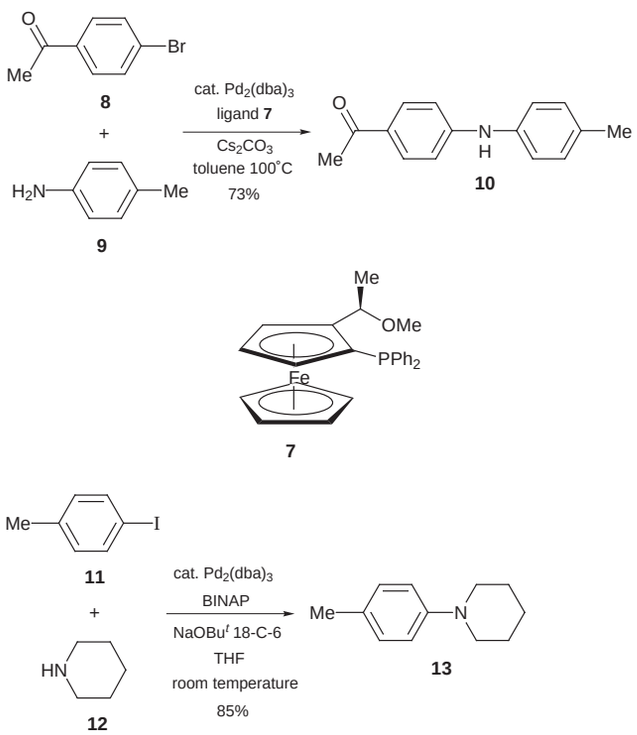



**Scheme 1**

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(*o*-tolyl)$_3$ catalyst system.[5] This study revealed several important concepts; firstly, the catalytic cycle involves bis(phosphine) intermediates. Second, sterically encumbered phosphines are not necessary for the high-yielding, intermolecular amination of aryl halides. For example, Hartwig reports the catalytic cross-coupling of 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.[6]

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.[7]

Furthermore, it was noted that the combination of $Pd_2(dba)_3$ 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.[8] Thus, the reaction of ketone **8** with primary amine **9** proceeds efficiently to afford a 73% yield of aniline **10** (**Scheme 2**).

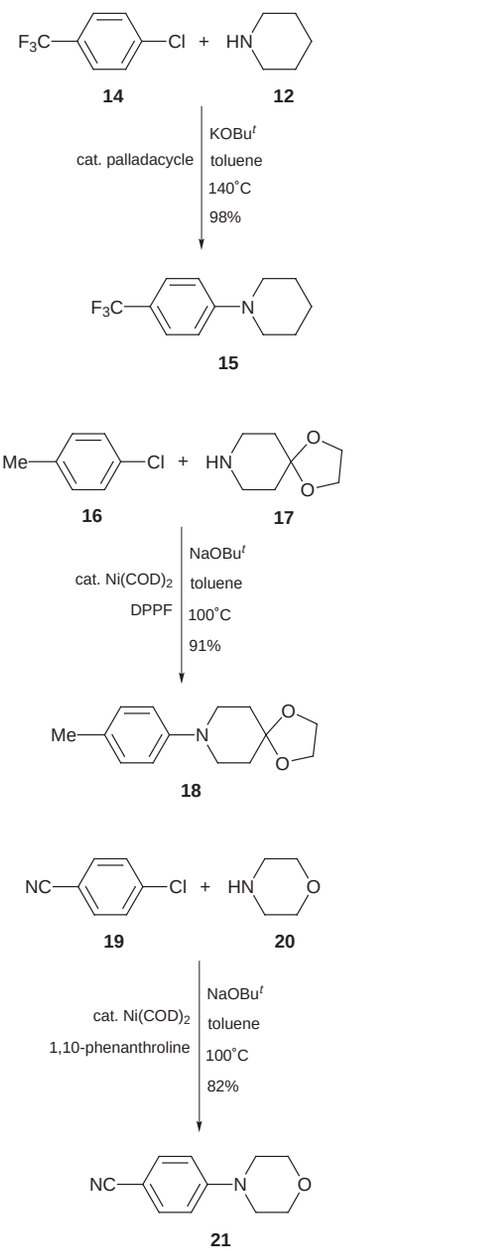



**Scheme 2**

A further improvement in procedure has been reported by Buchwald which allows the catalytic amination of aryl iodides at room temperature.[9] 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 $Pd_2(dba)_3$/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.[10] 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[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (palladacycle) to give the product **15** in 98% yield (**Scheme 3**). Further aminations of aryl chlorides have been reported by Buchwald.[11] The mild nickel catalysed procedure tolerates a variety of functional groups including ethers, nitriles, acetals 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

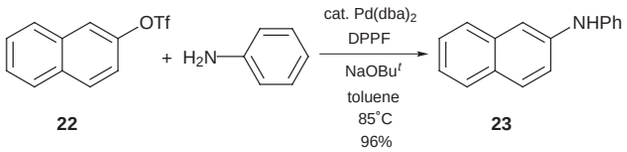


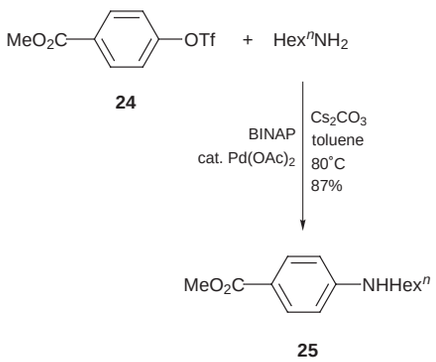

**Scheme 3**

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**).[12] Similarly, Buchwald reports that the combination of $Pd(OAc)_2$/BINAP is an effective catalyst system for this valuable transformation.[13] Once again, by changing the stoichiometric base from sodium *tert*-butoxide to caesium carbonate, a greater functional group tolerance is exhibited.[14] This is demonstrated by the conversion of the aryl triflate **24** into the amine **25** in 87% yield, the methyl ester is unaffected (Scheme 4).

### 2.2 Applications of C–N coupling reactions

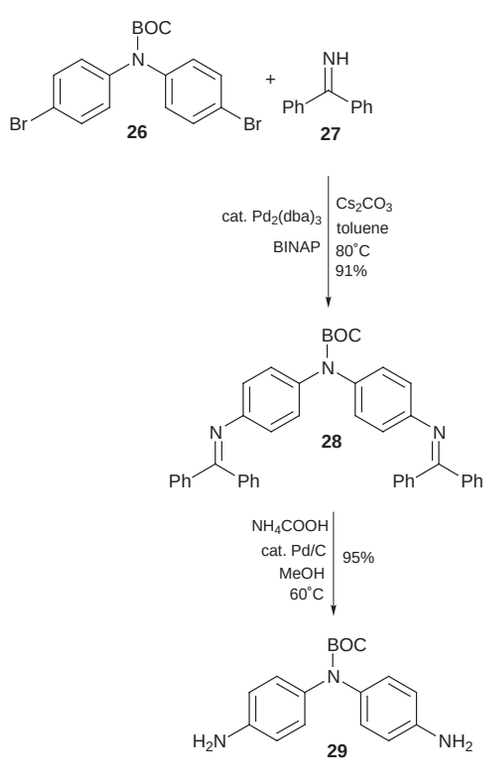
The discovery that benzophenone imine **27** serves as a convenient ammonia equivalent in the palladium catalysed amination of aryl halides and triflates has been reported by Buchwald.[15] The catalytic amination of **26** proceeds in high yield to afford the diphenyl ketimine product **28**. The products can be purified and stored as masked amines or the benzophenone imine can be



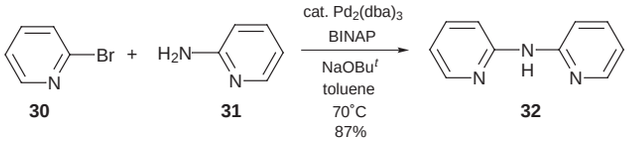

**Scheme 4**

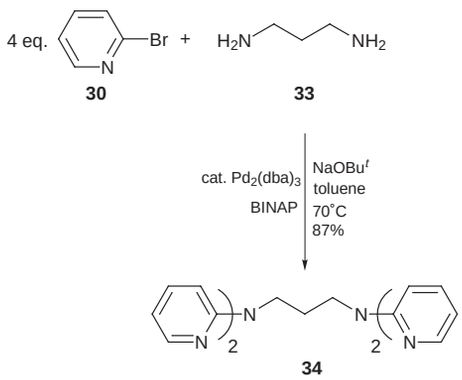
cleaved directly to the primary amine **29** by catalytic hydrogenation or treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF (**Scheme 5**).




**Scheme 5**

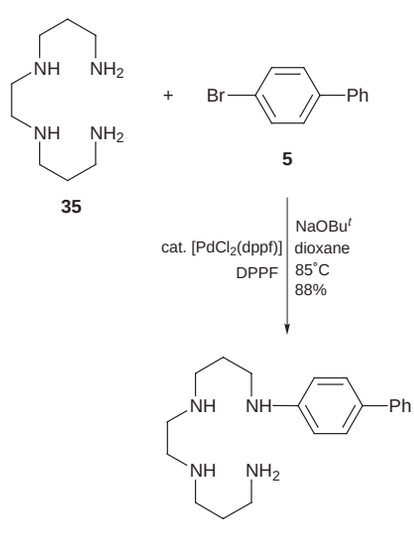
The synthesis of aminopyridines is important to many branches of chemistry; for example, they find applications as ligands, as components of fluorescent dyes, and are stimulants to the central nervous system. The Buchwald group have revealed that the palladium catalysed amination strategy can be effectively 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.[16] The reaction of 2-bromopyridine **30** with 2-aminopyridine **31** produced the interesting product **32** in 87% yield. This was also an effective strategy for preparing diarylated diamines **34**, as shown by the reaction of four equivalents of 2-bromopyridine **30** with diamine **33** (**Scheme 6**).



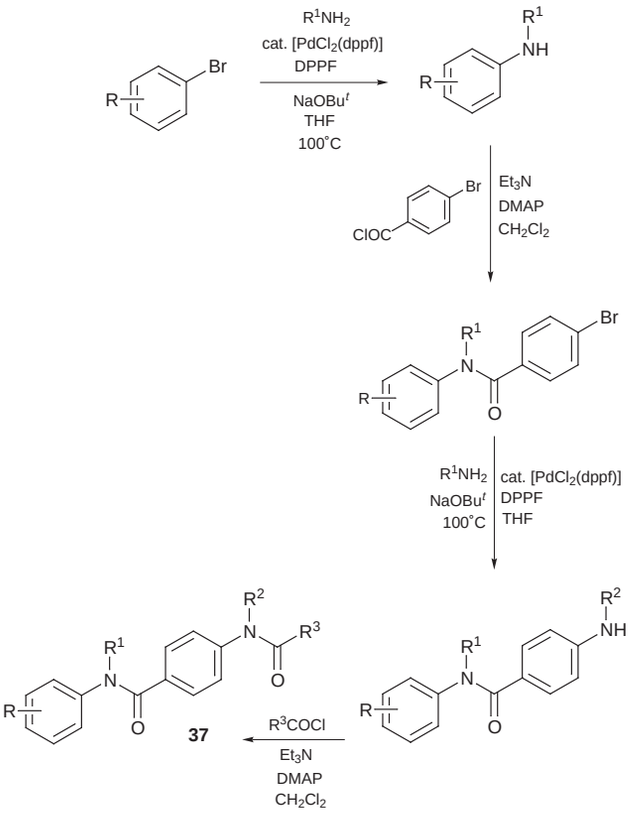

**Scheme 6**

In an alternate amination reaction, Beletskaya and Guilard have shown that polyamines such as **35** react with aryl bromides, for example **5**, to afford monoarylated products **36**.[17] This strategy provides a convenient method of arylation of di-, tri- and tetra-amine compounds (**Scheme 7**).

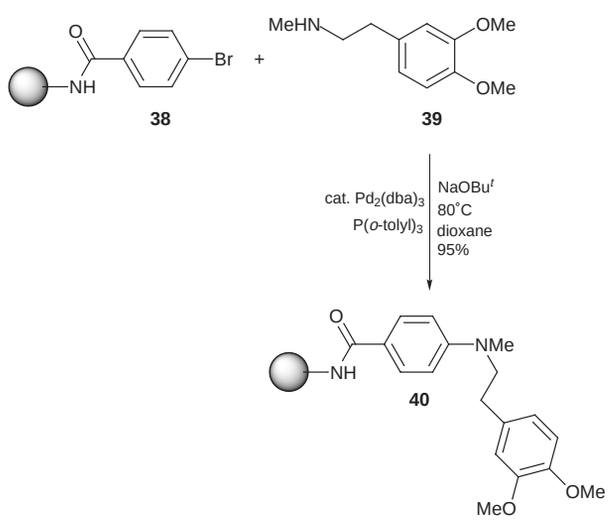



**Scheme 7**

Frost and Mendonça have reported the successful implementation of an iterative palladium catalysed amination strategy to prepare an array of peptide analogues **37** by parallel synthesis (**Scheme 8**).[18] The combination of $Pd_2(dba)_3$/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 Pd(0)/P(*o*-tolyl)$_3$ catalyst system is effective in the coupling of secondary amines such as **39** with polymer bound aryl bromide **38** to afford high yields of product **40** (**Scheme 9**).[19] The use of BINAP as a ligand allowed the coupling of primary amines in high yields and with excellent purities. Ward and Farina independently report similar findings.[20] This methodology will no doubt prove useful for constructing combinatorial libraries of aniline derivatives for biological screening.

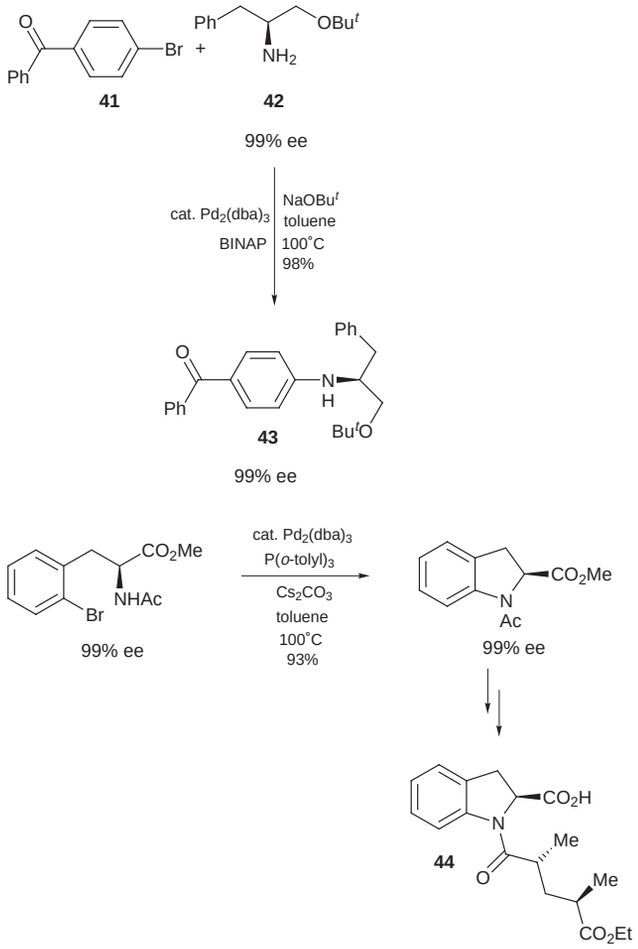


**Scheme 8**



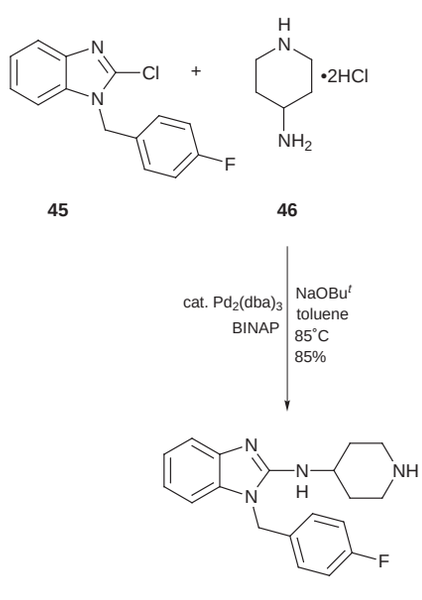
**Scheme 9**

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.[21] 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 α-amino acids and aryl halides.[22]



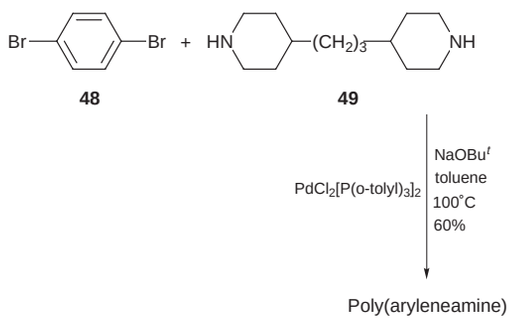
**Scheme 10**

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**).[23] 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.



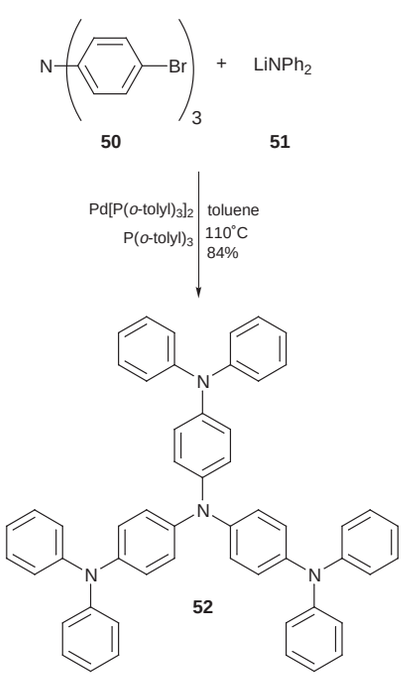
**Scheme 11**

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 $PdCl_2$-$[P(o\text{-tolyl})_3]_2$ to give new poly(aryleneamine) (**Scheme 12**).[24] Poly(iminopyridine-2,6-diylimino-1,3-phenylene) has been prepared in an analogous way.[25]



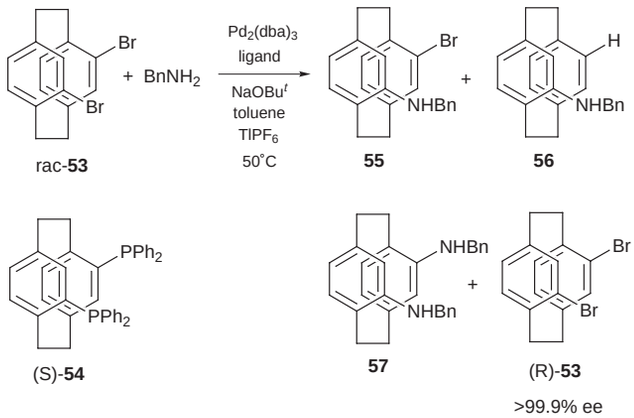

**Scheme 12**

The efficiency of the catalytic amination methodology is further demonstrated by Hartwig in the preparation of high molecular weight triarylamine dendrimers.[26] 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**).[27] The combination of $Pd_2(dba)_3$/(*S*)-[2.2]-PHANEPHOS **54** is effective in providing practical enantiomeric 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.[28] Related work by Hartwig described the palladium catalysed formation of *tert*-butyl ethers.[29] 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.[30,31] Hartwig has demonstrated that a $Pd(dba)_2$/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**).[32] 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.[33] 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 15).[34] 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

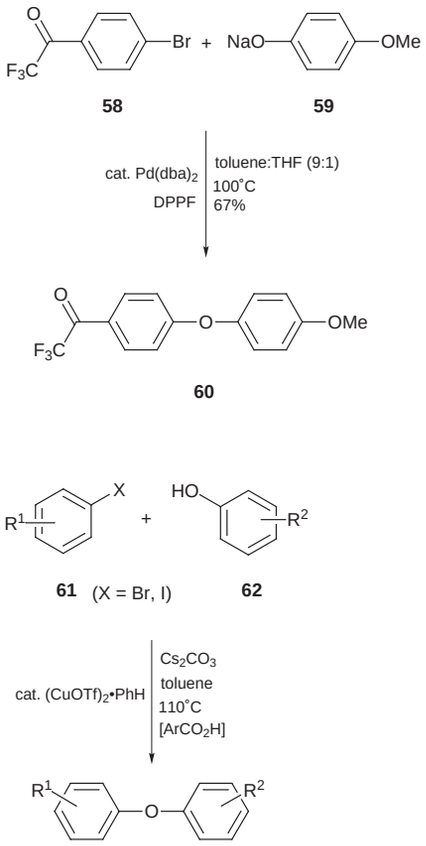
The synthesis of unsymmetrical sulfides by a palladium catalysed cross-coupling reaction of 9-organothio-9-borabicyclo-[3.3.1]nonane derivative **63** and aryl iodide **64** has been reported by the Miyaura group (**Scheme 16**).[35] It has also been reported that *S*-allyl thiocarbonates **65** serve as convenient allylsulfenylation agents in the coupling of various aryl halides under typical Heck conditions (**Scheme 17**).[36] This is a very practical method that enables the preparation of allyl aryl sulfides without having to use allylthiostannanes or allyl thiols, both reagents being notorious for their stench, instability and toxicity.

Another convenient method for the palladium catalysed preparation of mixed aryl sulfides **67** employs samarium(III) thiolates generated *in situ* from aryl thiocyanates **66** (**Scheme 18**).[37] Once again, the main advantage with this method is that there is no need to isolate the intermediate thiol.

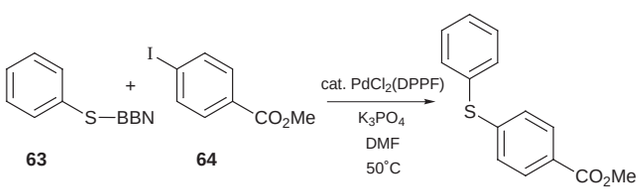
The palladium catalysed cyclisation of indolyl iodide **68** with the internal thiol group furnishes the product **69** in 74% yield (**Scheme 19**). This intermediate was then converted to chuangxinmycin, an antibacterial agent, by hydrolysing the methyl ester to the carboxylic acid.[38]

## 2.5 Carbon–phosphorus bond formation

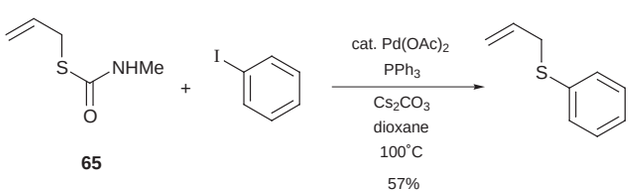
Laneman reports the findings that tertiary phosphines **71** can be prepared from aryl triflates or halides **70** by nickel catalysed cross-coupling with $Ph_2PCl$ in the presence of zinc (**Scheme 20**).[39] The use of a cheap phosphorus reagent coupled with the




**Scheme 15**




**Scheme 16**

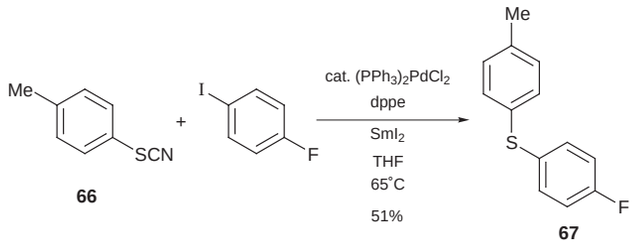



**Scheme 17**

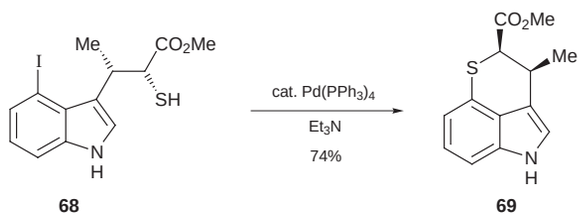
tolerance of the reaction to a wide variety of functional groups and amenability to large scale makes this a useful approach to phosphorus ligands.

## 3 Nucleophilic substitution of activated aromatics

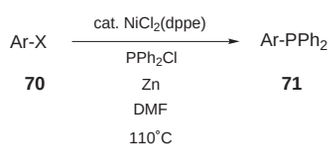
In recent times there has been substantial progress in the development of mild, efficient methods for the nucleophilic substitution of aromatic rings. Notably, Pearson has developed a novel approach to diaryl or triaryl ethers by activating chloroarenes to nucleophilic substitution *via* complexation with transition metals such as FeCp, RuCp or $Mn(CO)_3$.[40] 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 $S_NAr$ reaction of 3-fluoro-4-nitrophenylalanine




**Scheme 18**




**Scheme 19**




**Scheme 20**

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

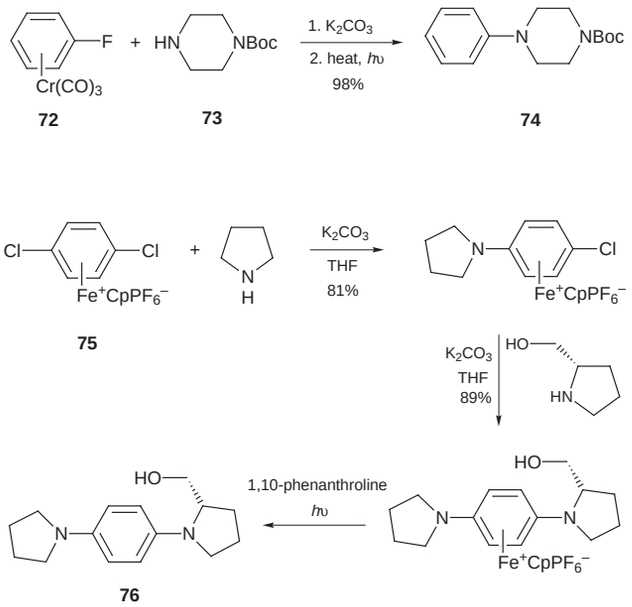
It is well established that tricarbonylchromium complexes of aryl halides undergo nucleophilic substitution more rapidly than the parent aryl halide. Perez exploits this in the synthesis of arylpiperazines.[42] For example, the ($\eta^6$-fluoroarene)tricarbonylchromium complex **72** undergoes rapid nucleophilic substitution with piperazine **73**. Decomplexation is performed *in situ* to afford the product arylpiperazine **74** in 98% yield (**Scheme 21**). Related $S_NAr$ chemistry mediated by $\eta^6$-cyclopentadienyliron complexes has been employed by Pearson to prepare a range of symmetrical and unsymmetrical tetraalkyl-*p*-phenylenediamines.[43] The ease of performing sequential nucleophilic substitutions on *p*-dichlorobenzene–$Fe^+CpPF_6^-$ **75** facilitates the preparation of unsymmetrical pyrrolidine/prolinol derivative **76** in high yield (Scheme 21).

Transition metal $\eta^6$-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**).[44] The synthesis of the anti-tumour agent OF 4949 III was completed by a cycloamidation reaction under high dilution conditions and deprotection steps.

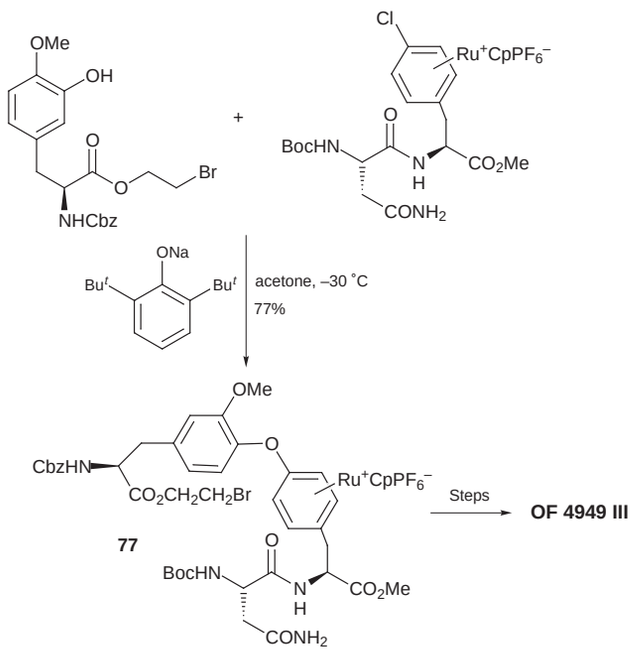
The alternative approach of first performing the peptide coupling reaction then cyclising *via* an intramolecular $S_NAr$ reaction to afford cyclic biphenyl ether **78** in high yield is also an effective strategy as demonstrated by Rich (**Scheme 23**).[45] The same paper reports preformed peptidyl 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]



Scheme 21

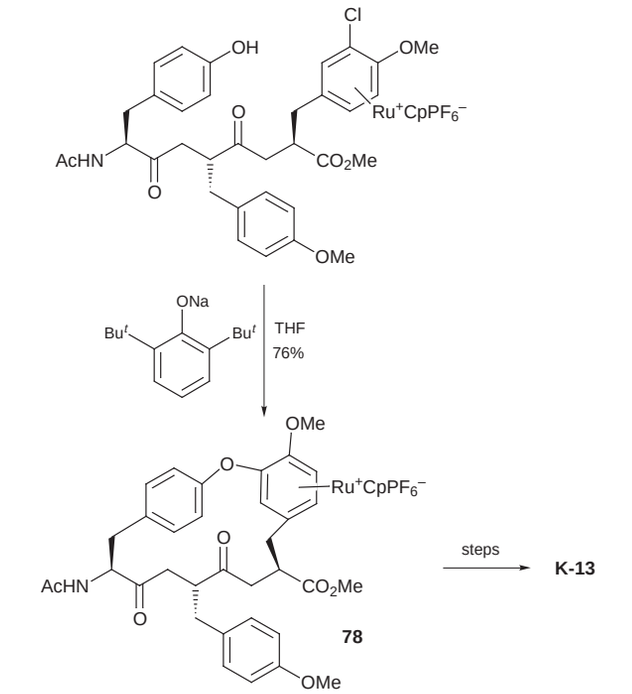


Scheme 22

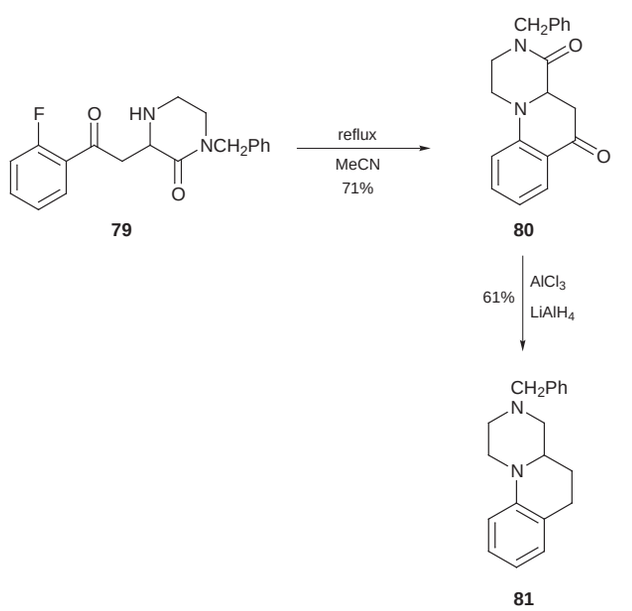
A similar strategy is employed by Arán in the synthesis of cinnolin-3-ylio oxide **83**, a new class of heterocyclic betaine by an intramolecular cyclisation of an *N*′,*N*′-disubstituted (2-fluorophenyl)acetohydrazide **82** (**Scheme 25**).[47]

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 $S_NAr$ reactions where fluorine is the leaving group.[49]

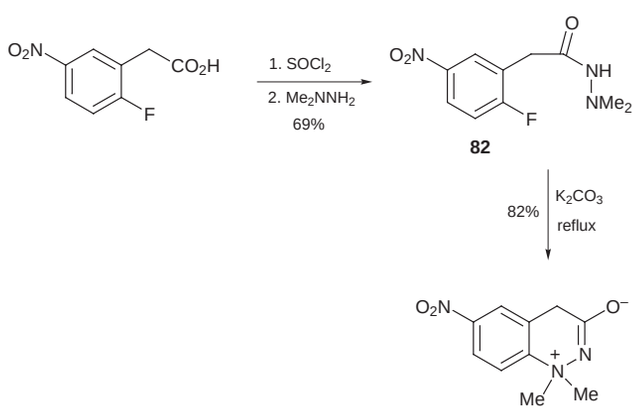
Many of the techniques for nucleophilic substitution of activated aromatics have been developed for the construction of vancomycin and other related glycopeptide antibiotics. Nicolaou reports the development of new synthetic technology for the synthesis of aryl ethers using a triazene unit situated *ortho* to a leaving group on an aromatic nucleus that acts as an 'electron sink'.[50] The practical utility of this methodology is



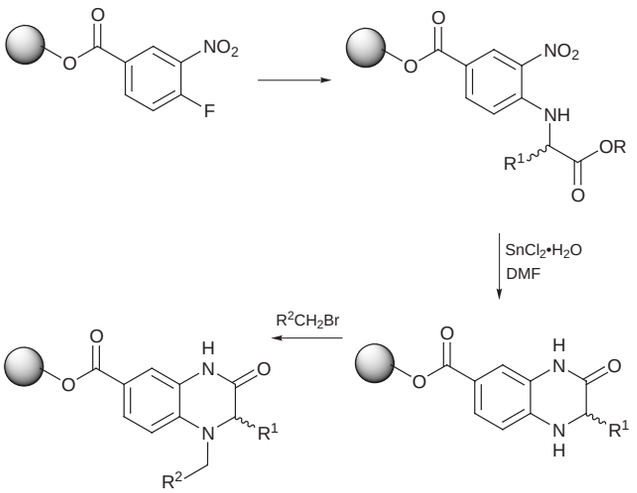
Scheme 23



Scheme 24

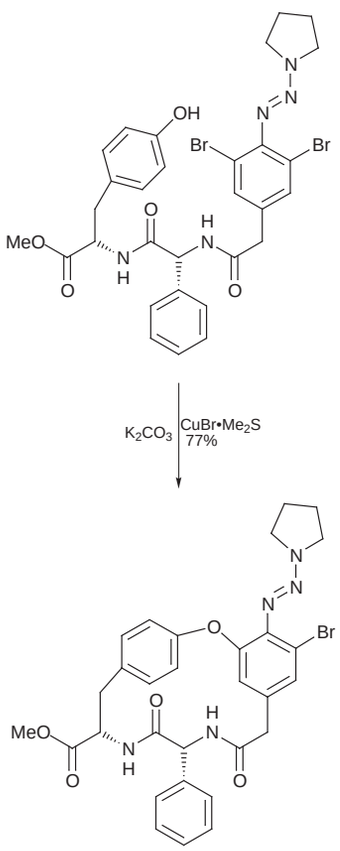


Scheme 25




**84**

**Scheme 26**



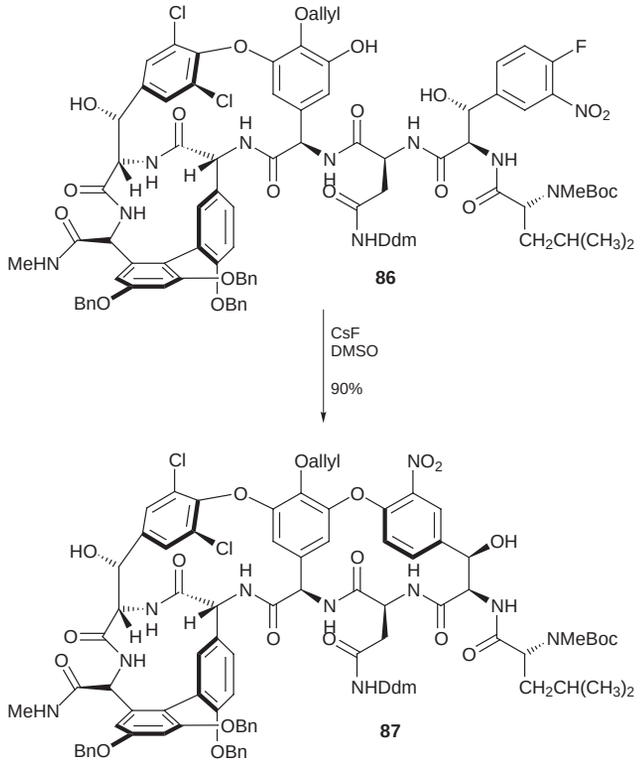

**85**

**Scheme 27**

demonstrated by the synthesis of vancomycin type model system **85** (**Scheme 27**).

The nitroaromatic based $S_NAr$ 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




**86**

**87**

**Scheme 28**

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 $S_NAr$ macrocyclisation methodology will surely continue to progress towards even more complex total syntheses.

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