Practical Palladium Catalysts for C-N and C-O Bond Formation

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The development of new palladium catalysts for the arylation of amines and alcohols with aryl halides and sulfonates is reviewed. Initial systems as well as mechanistic issues are discussed briefly, while subsequent generations of catalysts are described in greater detail. For these later generations of catalysts, substrate scope and limitations are also discussed. The review is organized by substrate class. Modifications and improvements in technical aspects of reaction development are described where appropriate. In addition, applications of this technology toward natural product synthesis, new synthetic methodology, and medicinal chemistry are chronicled. This review is organized in a manner that is designed to be useful to the synthetic organic chemist.

Keywords. Amination, Arylation, Catalyst, Ligand, Palladium

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Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	*n*-butyl
t-Bu	*tert*-butyl
cat	catalyst, catalytic
conc	concentrated
Cy	cyclohexyl
Dba	dibenzylideneacetone
de	diastereomeric excess
DME	1,2-dimethoxyethane
DPPP	1,3-bis(diphenylphosphino) propane
ee	enantiomeric excess
equiv	equivalent(s)
Et	ethyl
h	hour(s)
LHMDS	lithium hexamethyl disilazide
Me	methyl
mol	mole(s)
Nf	nonafluorobutylsulfonyl
Ph	phenyl
PMB	4-methoxybenzyl
i-Pr	*iso*-propyl
RT	room temperature
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl

THF	tetrahydrofuran
TMS	trimethylsilyl
o-tol	2-methylphenyl
p-tol	4-methylphenyl
Troc	triphenylmethoxycarbonyl
Ts	tosyl, 4-toluenesulfonyl

1 Introduction

Arylamines and aryl ethers are ubiquitous in numerous fields of chemistry. Arylamines are commonly encountered in natural products [1] pharmaceuticals [2] xerographic and photographic materials [3] as well as conducting polymers [4]. Similarly, aryl ethers are commonly found in natural products [1] and biologically active compounds [2] as well as polymeric materials [5]. Traditionally, the preparation of alkylarylamines has been carried out by the reductive amination of aniline derivatives or arene nitration/reduction protocols [6, 7]. These methods, although often effective, suffer from a relatively limited substrate generality and functional group tolerance. Additionally, these synthetic strategies often require multiple steps or the use of expensive reagents in stoichiometric amounts. The preparation of aryl ethers has most often been achieved via the Ullman ether synthesis [8]. Though useful, the Ullman reaction suffers from a limited substrate scope; the reaction typically works best for the coupling of electron-deficient and sterically unhindered aryl halides.

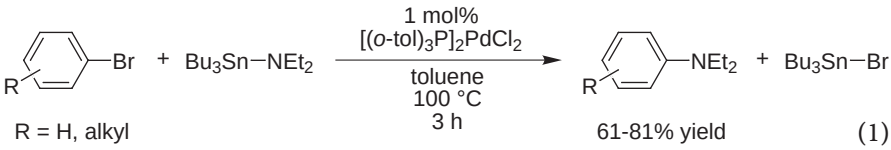
Thus, the transition metal catalyzed arylation reactions of amines and alcohols would constitute powerful tools for synthetic chemists. We have been developing practical procedures for the palladium-catalyzed arylation of amines and alcohols with aryl halides or sulfonates. During the course of our investigations [9] as well as those of John Hartwig and co-workers [10] the substrate scope of these transformations has been incrementally expanded. With each cycle of this catalyst improvement process, advances in mechanistic understanding and ligand design have also been made.

This review covers the literature through December, 2000 and is designed to be of greatest use to the synthetic organic chemist. Thus, the mechanistic studies will be not be covered in detail, and it is left to the reader to refer to the literature describing such studies [11]. In addition, the reader is encouraged to consult previous reviews on amine and alcohol arylation [9, 10, 12]. Procedures detailing other transition metal catalysts (e. g., Ni and Cu) effective in amine and alcohol aryl couplings have also been reported, but because of space limitations, are beyond the scope of this review [13]. Experimental procedures were chosen based on the general utility of the procedure as well as the commerical availability of the catalyst precursors.

2
Palladium-Catalyzed Amine Arylation

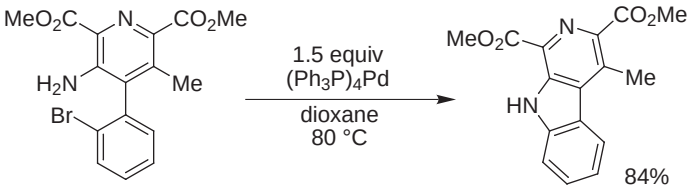
2.1
Initial Systems

The first palladium-catalyzed formation of aryl C-N bonds was reported in 1983 by Migita and co-workers, Eq. (1) [14]. The reaction of electronically neutral aryl bromides and aminotin compounds in the presence of catalytic $[(o\text{-tol})_3P]_2PdCl_2$ resulted in the efficient preparation of the corresponding aniline in moderate to good yield. This seminal discovery was limited by the necessity to use the thermally and moisture sensitive tributyltin amides, however.



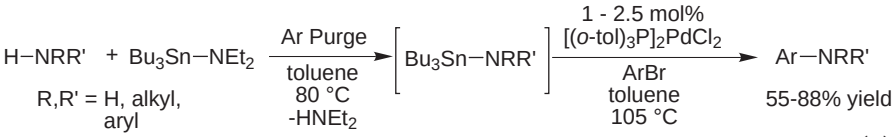
(1)

Additionally, Boger and Panek reported an intramolecular amine arylation mediated by stoichiometric quantities of Pd (0), Eq. (2) [15]. Efforts to render this transformation catalytic in palladium were fruitless, however. The resulting heterocycle was utilized in the total synthesis of lavendamycin.



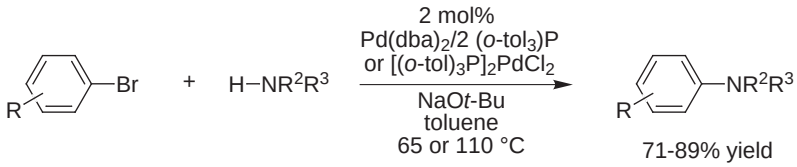
(2)

In 1994, Buchwald and Guram reported a new catalytic procedure based on Migita's amination procedure where the tin amide could be generated *in situ* by an amine exchange reaction, Eq. (3) [16]. Thus, by pre-mixing *N*,*N*-diethylaminostannane with the reacting amine followed by removal of the volatile diethyl amine by argon purge, they were able to cleanly produce the desired aminotin compound. This intermediate was found to undergo coupling with several aryl bromides in moderate to good yields, although this procedure still necessitated the use of stoichiometric tributyltin compounds.



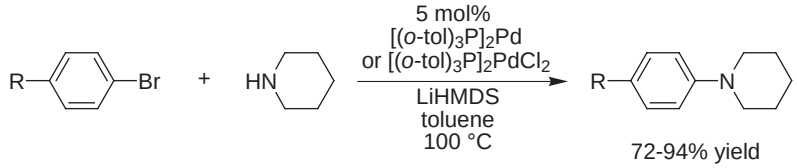
(3)

The limitations associated with the use of tin compounds in this chemistry was overcome by the Buchwald and Hartwig groups concurrently in 1995. By using NaO*t*-Bu as base, the Buchwald, Guram, and Rennels were able to effect catalytic C-N bond formation, Eq. (4) [17]. Thus, the sodium amide generated *in situ* by deprotonation of the reacting amine could be used instead of the corresponding aminotin species. They reported that the isolated complex $[(o\text{-tol})_3P]_2PdCl_2$ or a catalyst generated by mixing Pd_2dba_3 and two equivalents of $(o\text{-tol})_3P$ achieved the C-N bond formation with comparable efficiency.



(4)

Similarly, Hartwig and Louie reported that LiHMDS was also a useful base for such transformations, Eq. (5) [18]. They also reported two different complexes as catalysts; $[(o\text{-tol})_3P]_2PdCl_2$ and $[(o\text{-tol})_3P]_2Pd$ effectively catalyzed the amine arylation reaction.

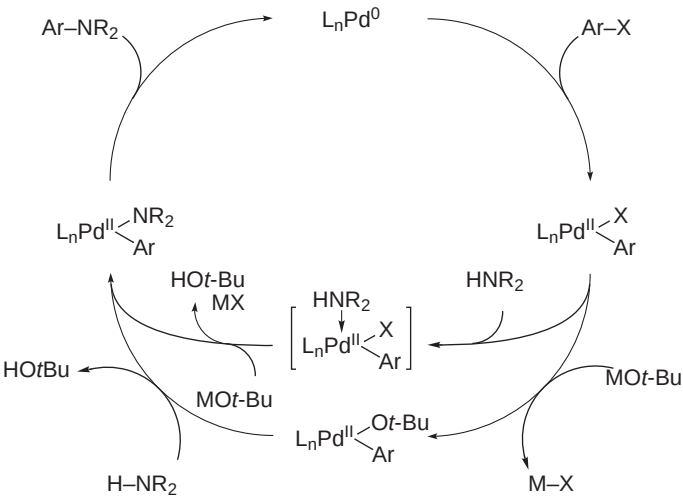


(5)

Although both of these reports greatly expanded the scope and utility of the amine arylation reaction, these catalytic systems enjoyed a relatively narrow substrate scope compared to subsequent generations of catalysts developed both by the Buchwald and Hartwig groups. Through iterative cycles of ligand design, methodological studies, and mechanistic investigations, highly active and broadly useful catalyst systems have been developed.

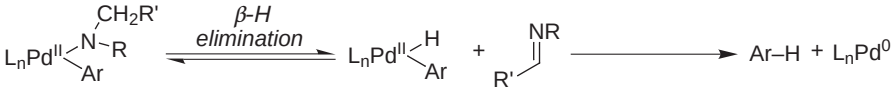
The generally accepted mechanism for the amine arylation is shown in Scheme 1. The catalytic cycle begins with the oxidative addition of the aryl halide (or sulfonate) by Pd (0). The palladium (II) aryl amide can be formed either by direct displacement of the halide (or sulfonate) by the amide or via the intermediacy of a palladium (II) alkoxide [19]. Reductive elimination of the C-N bond results in the formation of the desired arylamine and regeneration of the Pd (0) catalyst [11e, 20].

In the coupling of more challenging substrates, reduction of the aryl halide is frequently observed [21]. Specifically, in the reaction of electron-rich aryl halides or sulfonates, reduced arene is a major by-product. Presumably, this side-product arises when the palladium amide can undergo β-hydride elimination to generate an imine and a palladium (II) aryl hydride (Scheme 2). Subse-



Scheme 1

quent reductive elimination yields the reduced arene and regenerates the Pd (0) catalyst. Thus, one of the major challenges confronted in the development of more efficient amine arylation catalysts was to shut down this unwanted side reaction.



Scheme 2

2.2
N-Arylation of Secondary Amines

2.2.1
Reaction of Cyclic Secondary Amines with Aryl Bromides

The initial catalyst systems described above were effective with aryl bromides and a relatively narrow array of amines, although these procedures found utility in the preparation of diaminofluorenes [22], poly(aryleneamines) [23], certain *N*-aryl-aza-crown ethers [24], *N*-arylpiperazines [25], and diaminobenzenes [26] (Fig. 1). These original methods often proved reasonably effective in the coupling of cyclic amines. Presumably, cyclic amines are less challenging substrates for the palladium-catalyzed coupling because the cyclic palladium (II) amide intermediates are less prone to β-H elimination compared to their acyclic counterparts.

Although the arylation reaction could be effected with $(o\text{-tol})_3P$ as ligand, Buchwald and co-workers investigated the use of BINAP (**1**) and other diphosphine ligands in the C-N bond forming reaction. (±)-BINAP often provided better yields of the desired product with both cyclic and acyclic amines, and lower

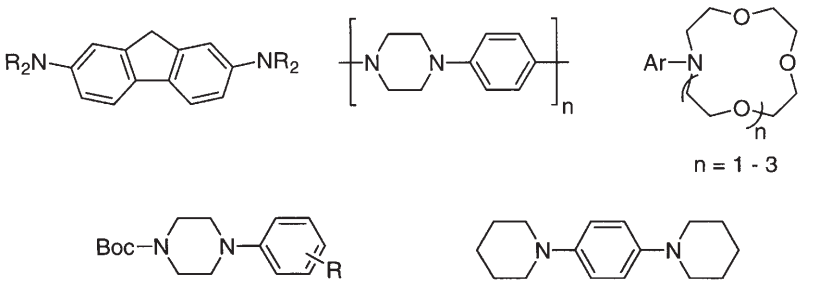
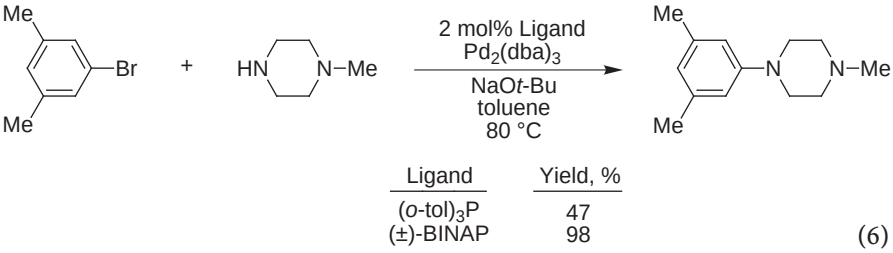


Fig. 1. Compounds prepared by the $[(o\text{-tol})_3P]_2PdCl_2$-catalyzed amine arylation

amounts or aryl bromide reduction were observed [27, 28]. While the coupling of *N*-methylpiperazine with 3,5-dimethylbromobenzene proceeded in 47% isolated yield when the $(o\text{-tol})_3P$–based protocol was used, the (±)-BINAP-derived catalyst effected the reaction in 98% yield, Eq. (6). In fact, a 94% yield of the desired product was obtained when the (±)-BINAP/Pd-catalyst was used in only 0.05 mol% in the absence of solvent. Substantial improvements in yield in the coupling of acyclic secondary amines were also observed with the BINAP system as well as well as a DPPF (**2**)-based catalyst reported by Hartwig [29]. Like the $(o\text{-tol})_3P$/Pd system, NaO*t*-Bu is most often used as base, however, recently a Novartis group has reported that alkoxide bases containing β-hydrides such as NaOMe or NaO*i*-Pr can also be used [30]. Additionally, milder bases such as Cs_2CO_3 and K_3PO_4 are often compatible with these methods.



Ligand	Yield, %
$(o\text{-tol})_3P$	47
(±)-BINAP	98

(6)

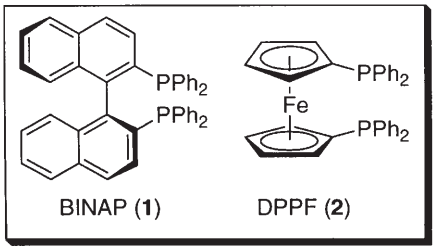
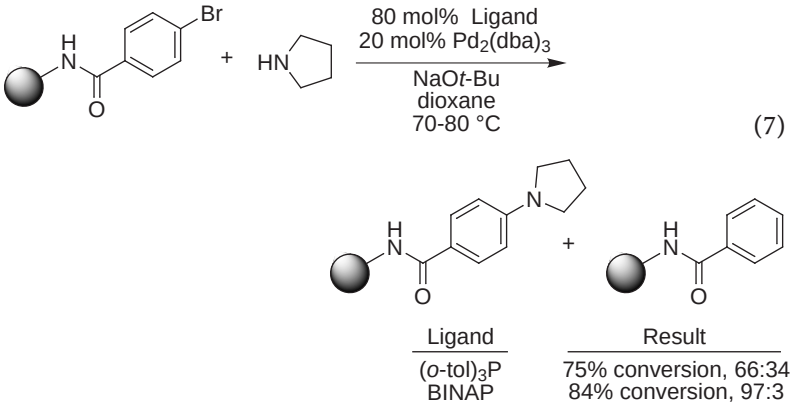


Fig. 2

General Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Bromides using BINAP/Pd: (Excerpted with permission from [27]. © 2000 American Chemical Society) An oven-dried Schlenk flask was charged with

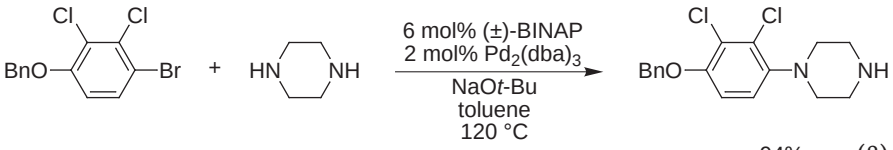
sodium *tert*-butoxide (134.5 mg, 1.4 mmol), $Pd_2(dba)_3$ (2.3–9.2 mg, 0.0025–0.01 mmol), and BINAP (4.7–18.7 mg, 0.0075–0.03 mmol). The Schlenk flask was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2–9 ml), aryl bromide (1.0 mmol), and amine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (15 ml), filtered, and concentrated. The crude reaction mixture was then purified further by flash chromatography on silica gel.

Numerous groups have used the BINAP/Pd- and DPPF/Pd-based reaction protocols for the arylation of cyclic secondary amines. Independently, Ward and Farina [31] as well as Willoughby and Chapman [32] disclosed that the palladium-catalyzed arylation reaction could be effected on resin-bound amines, Eq. (7). Both groups reported that while the (*o*-tol)$_3$P-based catalysts were often inferior to the BINAP-based system, using DPPF as ligand often resulted in comparable yields and reaction rates. They also observed that BINAP-derived catalysts usually yielded smaller amounts of reduced arene by-products.



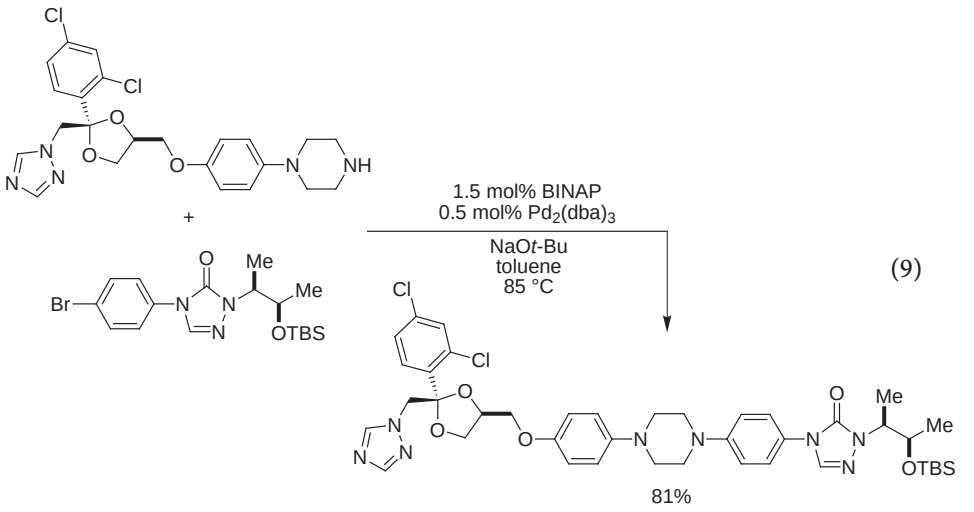
(7)

Morita and co-workers have utilized the BINAP/Pd-catalyst system to prepare arylpiperazines which are metabolites of Aripiprazole, an anti-psychotic agent, Eq. (8) [33].



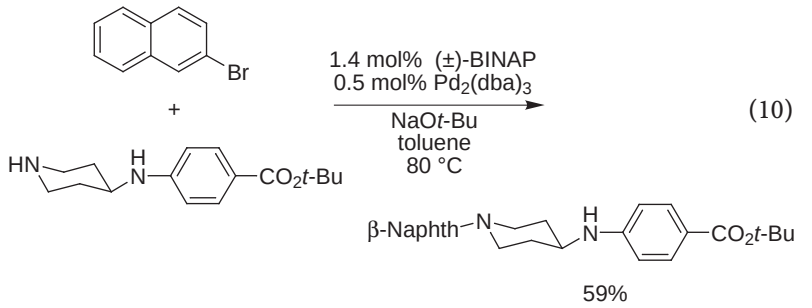
94% (8)

Tanoury, Senanayake, and co-workers utilized the BINAP/Pd-based catalyst in the synthesis of hydroxitraconazole, an antifungal agent [34]. The key C-N bond formation reaction provided the TBS-protected compound in 81% yield, Eq. (9).



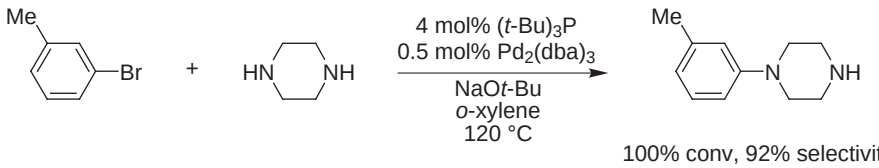
(9)

Similarly, Kung and co-workers utilized the (±)-BINAP/Pd-catalyst to prepare various aryl analogues of a novel quinazoline antibacterial agent [35]. For example, the coupling below proceeded in 59% isolated yield with 1 mol% palladium, Eq. (10). The moderate yield was likely due to cleavage of the *tert*-butyl ester.



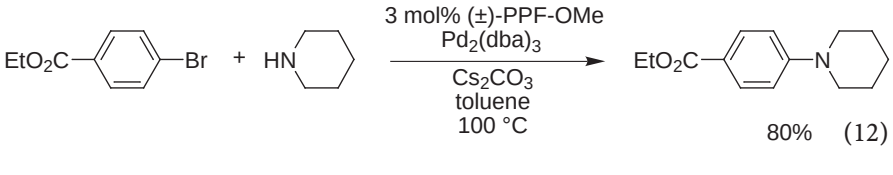
(10)

Other ligands are useful in the C-N bond coupling of aryl bromides and cyclic amines. In 1998, Nishiyama and co-workers at Tosoh corporation reported that tri-*tert*-butylphosphine is an effective supporting ligand for the palladium-catalyzed arylation of piperazine [36]. The $(t\text{-Bu})_3$P/Pd-catalyst provided the product with 1 mol% Pd in high selectivity, Eq. (11).



(11)

The Buchwald group subsequently disclosed that sterically hindered ferrocene-based monophosphines such as PPF-OMe (**3**), were useful ligands that extended the substrate scope of the amine arylation reaction, particularly with acyclic secondary amines [37, 38, 39]. In addition, during the development of catalysts derived from **3,** it was discovered that Cs_2CO_3 could be used as base in the amine arylation, resulting in greater functional group tolerance. Esters, enolizable ketones and nitroalkane functional groups were now compatible with the C-N bond forming reaction, Eq. (12) [40]. Cesium carbonate was also an effective base when used with the (±)-BINAP/Pd-based catalyst, Eq. (13) [27a]. Recently, Torisawa and co-workers have reported that the use of catalytic amounts of 18-crown-6 (10 mol%) improved the yield in certain arylation reactions where Cs_2CO_3 was used as base [41].



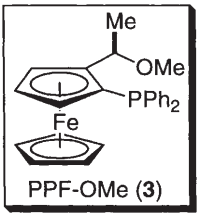
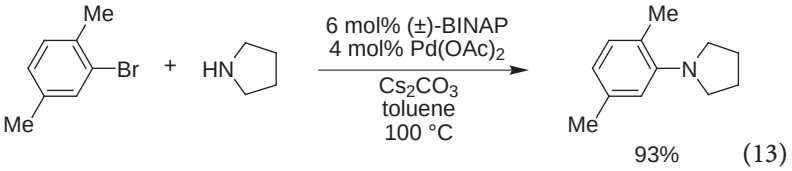
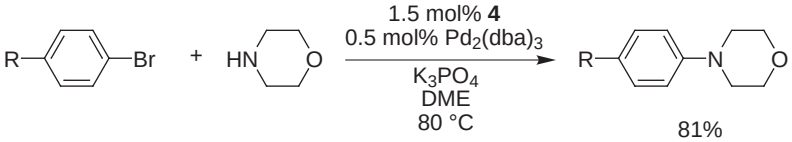


Fig. 3



The catalyst derived from aminophosphine **4** enjoys very high reactivity and a similar substrate scope as ligand **3**. In addition, mild bases could be employed in the arylation of dialkylamines [42, 43, 44]. With the catalyst derived from $Pd_2(dba)_3$ and **4**, 4-bromomethylbenzoate reacted cleanly with morpholine in the presence of K_3PO_4, Eq. (14). With stronger bases such as NaO*t*-Bu, ester



R	Yield, %
-CO_2Me	81
-COMe	82

(14)

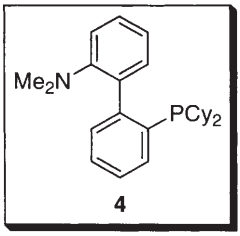
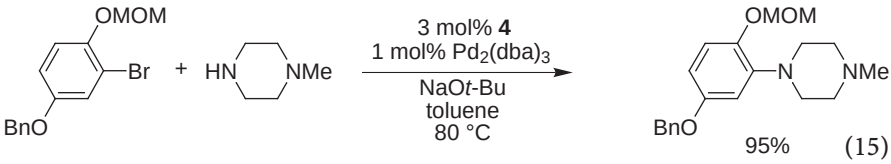


Fig. 4

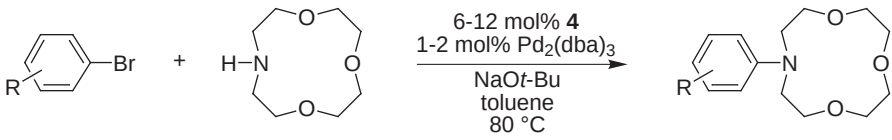
cleavage by-products are observed. 4-Bromoacetophenone was coupled with morpholine in high yield and without unwanted aldol side-reactions.

Schmalz and co-workers utilized the **4**/Pd-catalyzed arylation to prepare several novel chiral bidentate ligands [45]. For example, the arylation of *N*-methylpiperazine below proceeded in 95% yield to furnish the desired ligand building block, Eq. (15).



95% (15)

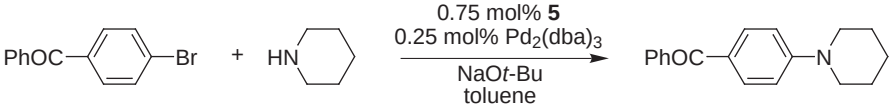
Zhang and Buchwald have recently reported that the **4**/Pd-catalyst is particularly effective in the arylation of aza-crown ethers [46]. These reactions proceed in high yield when with *meta*- or *para*-substituents on the aryl bromide; *ortho*-substituted aryl bromides react in moderate yield, Eq. (16).



R	Yield, %
p-*t*-Bu	87
o-Me	41

(16)

Guram has reported similar P,N- and P,O-chelating ligands useful in the amine arylation reaction [47]. For example, the coupling of piperidine with 4-bromobenzophenone proceeds in 98% yield with as little as 0.5 mol% of the palladium catalyst resulting from ligand **5**, Eq. (17).



98% (17)

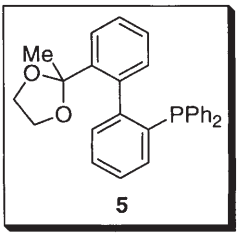
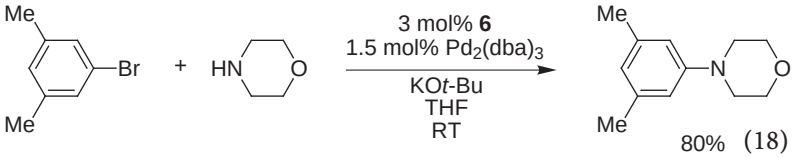


Fig. 5

In 1999, Wolfe and Buchwald reported the synthesis of hindered, electron-rich phosphine **6** and its use in the amine arylation reaction. Use of this new ligand resulted in a catalyst capable of effecting the room temperature reaction between cyclic amines and aryl bromides [42a, 44, 48, 49]. The catalyst derived from $Pd_2(dba)_3$ and **6** couples 3,5-dimethybromobenzene with morpholine in 80% yield while stirring for 20 hours at room temperature, Eq. (18). This new highly active catalyst efficiently arylates a variety of amines with aryl bromides as well as chlorides at room temperature.



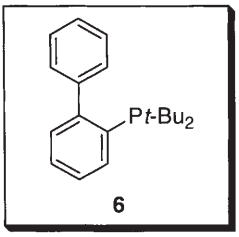
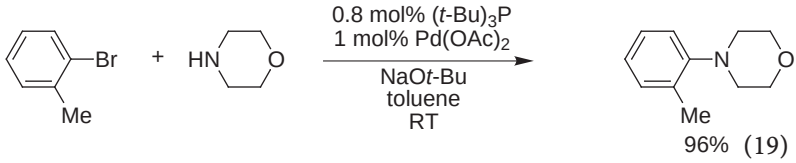
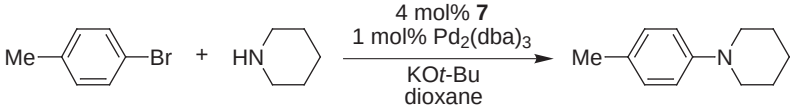


Fig. 6

Concurrently with this contribution from Buchwald and co-workers, the Hartwig group reported that the $P(t\text{-Bu})_3P$/Pd-catalyst system first reported by Koie and co-workers [36] is sufficiently active to couple aryl bromides with secondary amines at room temperature [50]. For example, 2-bromotoluene is efficiently aminated with morpholine at in 96% yield, Eq. (19). This catalyst is capable of the room temperature coupling of acyclic secondary amines and aryl bromides as well as the coupling of aryl chlorides at elevated temperatures.



Recently, heterocyclic carbene ligands, first investigated by Arduengo [51] have been utilized as ligands for palladium in the arylation reaction. Nolan reported the use of ligands derived from heterocycles such as **7** in the arylation of piperdine using 4-bromotoluene. The reaction proceeds in 83 % yield at room temperature, Eq. (20) [52].



83% (20)

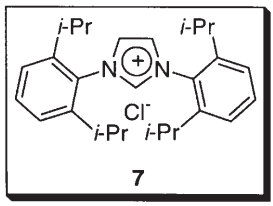
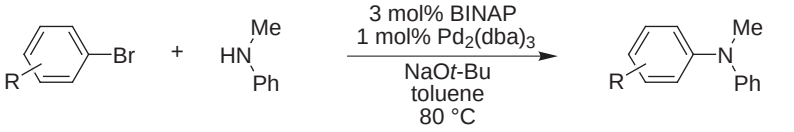


Fig. 7

2.2.2
Reaction of Acyclic Secondary Amines with Aryl Bromides

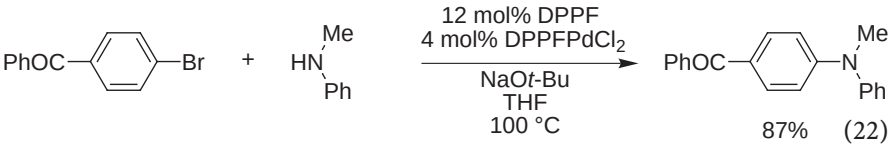
Acyclic secondary amines often are more challenging substrates for the palladium-catalyzed amine arylation due to their greater propensity for β-hydride elimination, and a screening of different ligands in the reaction of acyclic secondary amines revealed a stronger dependence of the reaction efficiency on the ligand relative to their cyclic counterparts. Early on, the Buchwald group discovered that the use of (±)-BINAP as a ligand in these reactions resulted in the clean coupling of *N*-methylaniline with aryl halides that possess electron-donating groups or moderate steric hindrance, Eq. (21) [27, 28].



R	Ligand	Yield, %
3,5-Me_2	P(*o*-tol)$_3$	5
3,5-Me_2	BINAP	79
2-NMe_2	P(*o*-tol)$_3$	0
2-NMe_2	BINAP	65

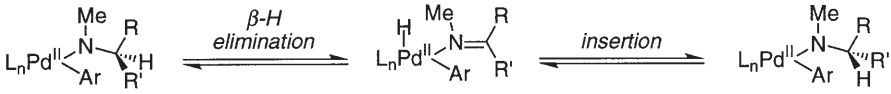
(21)

Hartwig and co-workers simultaneously described an improved procedure employing DPPFPdCl_2, and added DPPF, as catalyst, Eq. (22) [29]. Considerable improvements in yield were observed using this DPPF/Pd catalyst to couple primary as well as acyclic secondary amines compared to (*o*-tol)$_3$P-based systems.



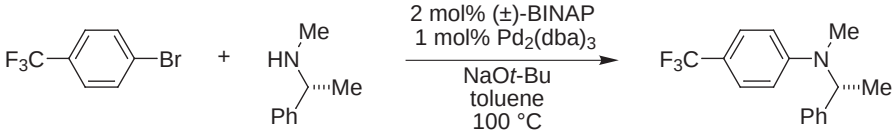
87% (22)

Presumably, the use of a bidentate ligand such as (±)-BINAP or DPPF results in the occupation of a vacant coordination site, preventing β-hydride elimination of the Pd (II) amide intermediate [53]. Dissociation of the imine and C-H bond reductive elimination results in formation of the reduced aryl bromide. If this β-hydride elimination is rapid relative to reductive elimination and reversible, then significant erosion of the enantiomeric excess of optically active α-substituted amines may be observed during the reaction (Scheme 3).



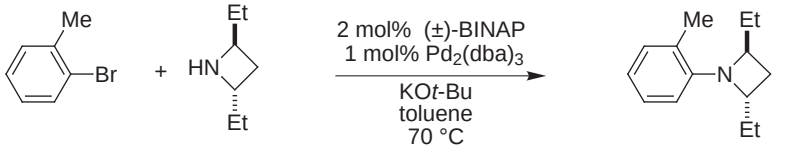
Scheme 3

Buchwald and co-workers investigated this β-hydride elimination/reinsertion phenomenon in the coupling of optically active amines. They observed significant epimerization of the α-stereocenter during the coupling of (*R*)-*N*-methyl-α-methylbenzylamine and 4-bromo-α,α,α-trifluorotoluene when the $(o\text{-tol})_3$P-derived catalyst was used. In contrast, the use of (±)-BINAP/Pd-based system resulted in retention of the integrity of the α-stereocenter, Eq. (23) [54]. It should be noted that the chirality of the ligand is inconsequential to the reaction since racemic BINAP was used in these studies. The Buchwald group reported that use of the Pd/DPPF-based catalysts prevents the epimerization of the α-stereocenter as well.



(23)

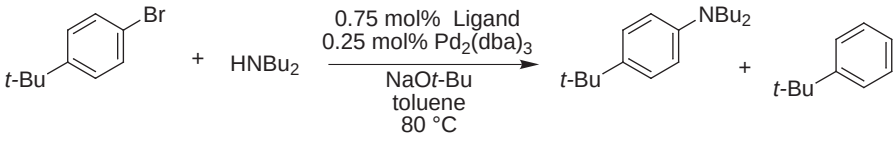
This observation was exploited by Marinetti in the *N*-arylation of chiral azetidines [55]. For example, 2,4-diethylazetidine was coupled with *ortho*-bromotoluene in high yield using the (±)-BINAP-based protocol, Eq. (24). No stereoisomerization of the amine was observed during the arylation reaction. Other groups have utilized the BINAP/Pd-system to couple α-chiral primary amines.



85% (24)

Despite the significant improvements in substrate scope that were enjoyed in the development of these new bisphosphine-based protocols, significant aryl bromide reduction side products were observed with other secondary amines. Specifically, the coupling of certain acyclic secondary amines was often accompanied by a large amount of aryl bromide reduction. While *N*-methylarylamines were good substrates for this reaction, substituents larger than methyl were not well tolerated and significant amounts of aryl bromide reduction was observed. Additionally, large amounts of arene side products were observed when electron rich aryl bromides were used. Thus, it was necessary to design new catalyst systems to broaden the scope of the amine arylation reaction.

The use of ferrocene-based ligands such as **3** and PPFA (**8**) result in the formation of catalysts that extended the scope of the arylation reaction to more difficult transformations [37, 38, 56]. For example, di-*n*-butylamine could now be effectively coupled with electronically neutral as well as electron-deficient aryl bromides. Reaction of 4-*tert*-butylbromobenzene with di-*n*-butylamine with the (±)-BINAP/Pd- or DPPF/Pd-based catalysts resulted in significant amounts of *tert*-butylbenzene formation, however the use of ligands **3** and **8** resulted in formation of the desired product in excellent yield, Eq. (25).



Ligand	Ratio	Yield, % (GC)
(±)-BINAP (**1**)	1.0:5.2	8
DPPF (**2**)	1.0:4.9	9
(±)-PPFOMe (**3**)	39:1.0	97
(±)-PPFA (**8**)	12.5:1.0	92

(25)

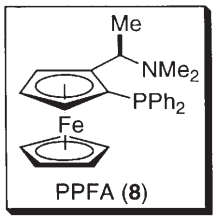
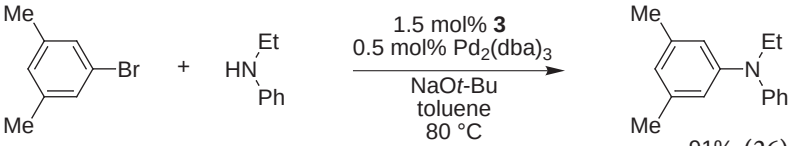


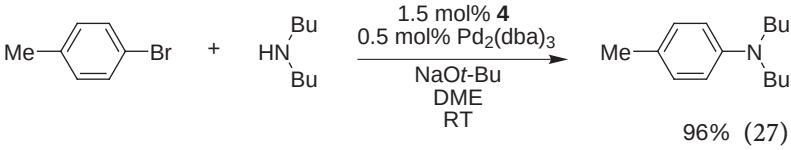
Fig. 8

The use of PPF-OMe (**3**) also allowed the coupling of secondary alkylarylamines that possess alkyl groups other than methyl. The reaction of *N*-ethylaniline and 5-bromo-*meta*-xylene proceeds in excellent yield with no reduced arene formation, Eq. (26). It should be noted that the **3**/Pd-catalyst system tolerates the use of Cs_2CO_3 as base.



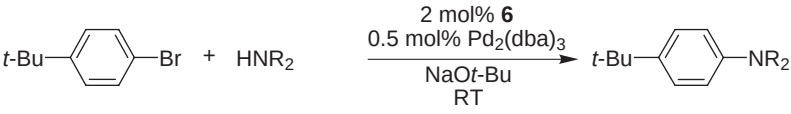
91% (26)

Commercially available aminophosphine **4** provided even better yields in the coupling of acyclic secondary amines [42]. The resulting catalyst was found to be so active that the reaction could often be conducted at room temperature. For example, Di-*n*-butylamine was efficiently reacted with 4-bromotoluene in 96% isolated yield at room temperature, Eq. (27). In addition, electron-rich, electronically neutral, and electron-deficient aryl bromides were effectively utilized with this new system. The **4**/Pd-based catalysts also mediate the coupling of *N*-alkylanilines that bear electron-donating substituents on the amine partner. A Xantphos/Pd-catalyst is effective in the coupling of electron-poor alkylarylamines with electron-poor aryl bromides.



96% (27)

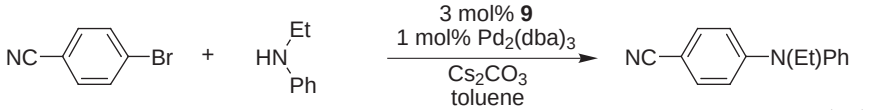
As was the case with ligand **4**, 2-biphenyldi-*tert*-butylphosphine (**6**) effects the amination of acyclic secondary amines at room temperature [42a, 48]. The catalyst derived from this commercially available ligand and $Pd_2(dba)_3$ promotes the coupling of 4-bromo-*tert*-butylbenzene and di-*n*-butylamine or *N*-methylaniline in excellent yields at room temperature, Eq. (28).



Amine	Solvent	Yield, %
H-NBu_2	toluene	92
H-N(Me)Ph	DME	83

(28)

The use of Xantphos (**9**), first reported by Van Leeuwen [57], as supporting ligand allows for the efficient coupling of alkylarylamines and aryl bromides [58]. For example, the reaction of 4-bromobenzonitrile and *N*-ethylaniline proceeds in 85% isolated yield, Eq. (29). This ligand is particularly effective in the coupling of electron-deficient alkylarylamines and electron-deficient aryl bromides.



85% (29)

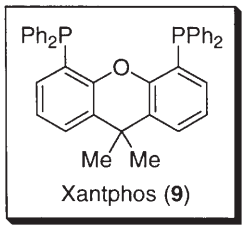
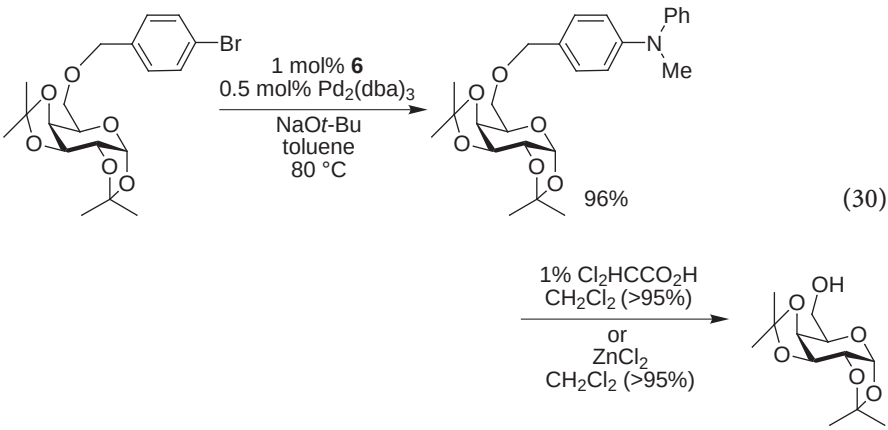


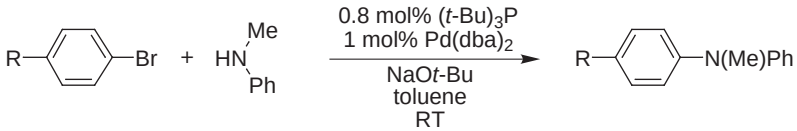
Fig. 9

Seeberger and Buchwald have reported the use of the **6**/Pd-catalyzed amine arylation reaction as a method for protecting group activation [59]. The 4-bromobenzyl protecting group may be easily aminated to furnish the corresponding 4-aminobenzyl ether derivative, Eq. (30). The resulting electron-rich benzyl ether can be easily deprotected by use of a Brønsted or Lewis acid under very mild conditions. Notably, this strategy can be further elaborated by the selective reaction of 4-chloro- and 4-iodobenzyl protecting groups as well.



(30)

Hartwig's group disclosed that $(t\text{-Bu})_3$P/Pd-based catalysts were sufficiently active such that the coupling of secondary amines and aryl bromides may be performed at room temperature, Eq. (31) [50]. This system tolerates electron-withdrawing, electronically neutral, as well as electron-donating substituents on the aryl bromide.

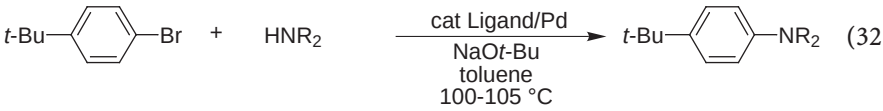


R	Yield, %
CN	95
OMe	99

(31)

Other groups have described systems that catalyze the arylation of acyclic secondary amines using aryl bromides, Eq. (32). Uemura reported the use of

chromium arene based ligands such as **10** in the Pd-catalyzed C-N bond forming reaction [60]. Similar to PPFA (**8**), ligand **10** effects the coupling of numerous aryl bromides with *N*-ethylaniline. The catalyst derived from $Pd_2(dba)_3$ and phosphinoether **5** promotes the amination of acyclic secondary amines and aryl bromides as well [47]. Related ligands were found useful in the coupling of aryl chlorides. Hayashi has reported the use of DPBP (**11**) in the amine arylation reaction [61]. It is expected that **11** would behave similarly to BINAP in these transformations, since it possesses similar electronic properties and bite angle.



(32)

Amine	Ligand (mol%)	Pd Source (mol %)	Yield, %
H-NEt_2	**10** (3)	$Pd(dba)_2$ (1)	90
H-N(Et)Ph	**10** (3)	$Pd(dba)_2$ (1)	90
H-N(Me)Bn	**5** (6)	$Pd_2(dba)_3$ (2)	83
H-$N(Oct)_2$	**5** (6)	$Pd_2(dba)_3$ (2)	93
H-(Me)Bn	**11** (7.5)	$Pd_2(dba)_3$ (2.5)	97

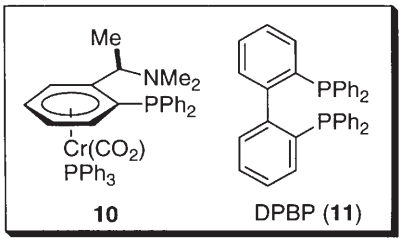
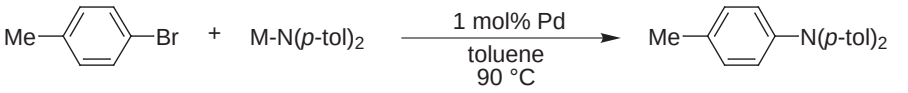


Fig. 10

Heterogeneous catalysts have also been reported to effect the arylation of secondary amines using aryl bromides. Buchmeister reported the preparation of a polymer-bound catalyst, which effects the arylation reaction at elevated temperatures. No attempts to recycle the catalyst were reported, however [62]. Djakovitch and co-workers reported the use of Pd particles immobilized on metal oxides or Pd-loaded zeolites as a catalyst [63]. The yields and selectivities for the reaction were diminished compared to homogeneous systems previously described.

2.2.3
Reaction of Diarylamines with Aryl Bromides

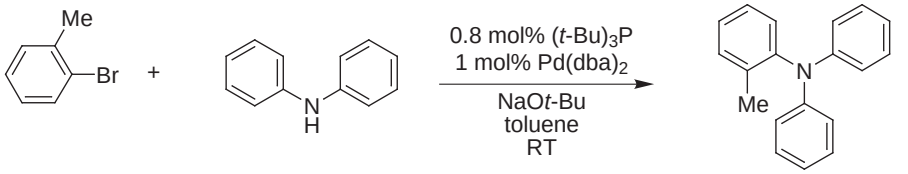
Hartwig first reported the arylation of diarylamines using both (*o*-tol)$_3$P/Pd- and DPPF/Pd-catalysts, Eq. (33) [29, 64]. The Yale group utilized the (*o*-tol)$_3$P/Pd- and DPPF/Pd-based protocols for the preparation of triarylamine-containing dendrimers and cyclophanes, respectively.



M	Reaction Conditions	Yield, %
Li	$[(o\text{-tol})_3P]_2Pd$	99
H	$[(o\text{-tol})_3P]_2Pd$, Base = NaO*t*-Bu	92
H	$Pd(dba)_2$, DPPF, Base = NaO*t*-Bu	89

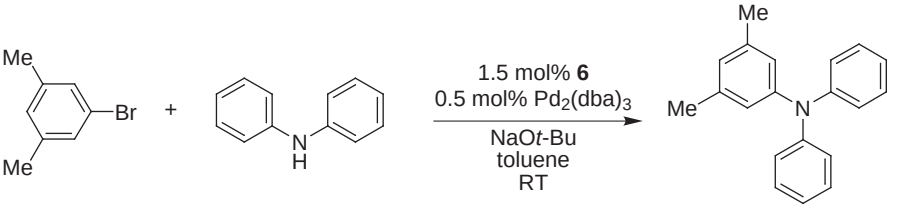
(33)

Nishiyama, and co-workers first reported that the catalyst derived from $Pd(OAc)_2$ and $(t\text{-Bu})_3P$ effects the C-N bond formation to produce triarylamines in excellent yield [65]. This system also is useful in the coupling of diarylamines and aryl chlorides. Hartwig and co-workers found this protocol optimal for the preparation of triarylamines. The $(t\text{-Bu})_3P$/Pd-catalyst was sufficiently active such that the coupling of diarylamines and aryl bromides can be performed at room temperature, Eq. (34) [50]. The $(t\text{-Bu})_3P$/Pd-system has been used to produce new triarylamine-based polymers [64a–d].



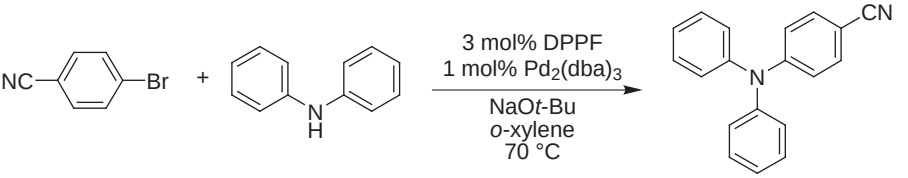
97% (34)

The highly active **6**/Pd-catalyst is capable of effecting C-N bond formation between and aryl bromide and a diarlyamine at room temperature [42a, 48]. Using, NaO*t*-Bu as base, the reaction below proceeded in 89% yield over 23 h, Eq. (35).



89% (35)

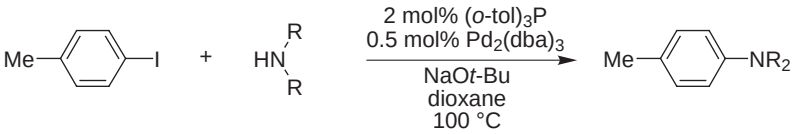
Recently, Stupp and co-workers, as well as others, have utilized the DPPF or $t\text{-Bu}_3P$/Pd-catalyst to prepare substituted triarylamines in high yield, Eq. (36) [66]. The product below was used to prepare 4-diphenylaminostysene, which was incorporated into an optoelectronic polymer.



83% (36)

2.2.4
Reaction of Secondary Amines with Aryl Iodides

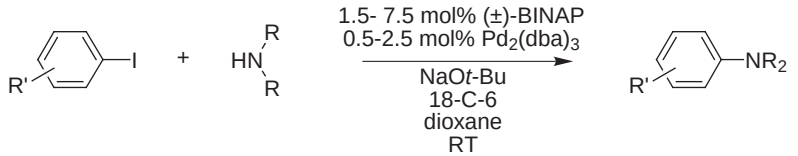
In 1996, Wolfe and Buchwald reported that the (*o*-tol)$_3$P/Pd catalyst system effectively couples secondary amines with aryl iodides, Eq. (37) [67]. This protocol allowed for the successful reaction of both cyclic and acyclic secondary amines; the use of dioxane as solvent was key to the success of these reactions. Similarly, Zhao and co-workers reported the coupling of aryl iodides and piperazines mediated by the (*o*-tol)$_3$P/Pd catalyst [25b].



Amine	Yield, %
H-N(Me)Bn	78
H-N(Bu)$_2$	68
H-N(Me)Ph	74
morpholine	73

(37)

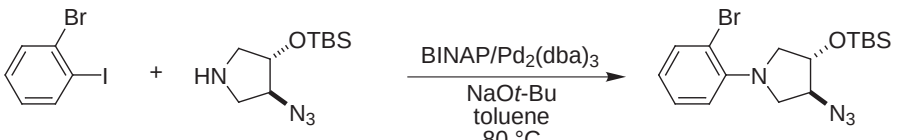
The room-temperature reaction of secondary amines and aryl iodides can be efficiently catalyzed by the (±)-BINAP/Pd system, Eq. (38) [68]. In order to achieve complete conversion, it was necessary to utilize stoichiometric 18-crown-6 as an additive. However, role of the crown ether is not entirely clear. Notably, aryl iodides react exclusively under these conditions while aryl bromides are left unchanged.



R'	Amine	Yield, %
p-*t*-Bu	H-N(Me)Ph	90
p-*t*-Bu	morpholine	71
o-Br	morpholine	78

(38)

The difference in reactivity between the aryl iodide and bromide was exploited by Sulikowski in the synthesis of a mytomycin skeleton [69]. The desired arylamine was prepared in 66% yield with exclusive reaction at the iodide, Eq. (39).



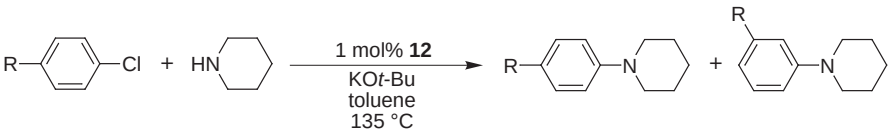
66% (39)

Nishiyama, Yamamoto, and Koie also reported that the $(t\text{-Bu})_3$P/Pd-based catalyst is effective in the C-N bond forming reaction between an aryl iodide as well as an aryl bromide and piperazine [36].

2.2.5
Reaction of Cyclic Secondary Amines with Aryl Chlorides

The use of aryl chlorides in the palladium catalyzed C-N bond forming reaction is highly desirable since aryl chlorides are often less expensive the analogous bromides and because there are a greater number of aryl chlorides which are commercially available. However, the use of aryl chlorides as reactants in numerous palladium-catalyzed processes has until recently been an elusive goal.

The first palladium-catalyzed coupling between a secondary amine and an aryl chloride was described by Beller, Hermann and co-workers in 1997 [70]. Use of palladacycle **12** as catalyst resulted in C-N bond formation in good yield for several secondary amines and electron-deficient aryl chlorides, Eq. (40). In these transformations, varying amounts of the regioisomeric product was observed, indicative that to some degree the reaction proceeds via a benzyne intermediate.



R	Yield, %	Ratio
CF_3	74	7:1
COPh	40	>50:1

(40)

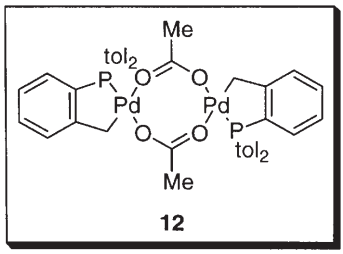
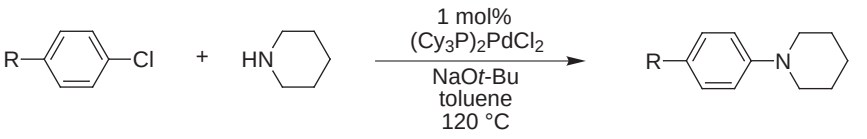


Fig. 11

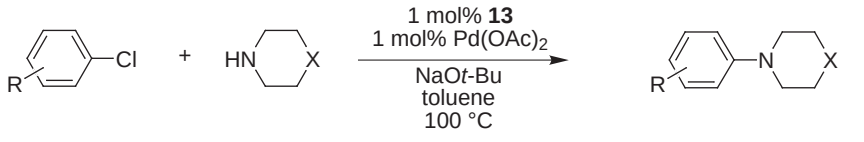
Reddy and Tanaka reported that $(Cy_3P)_2PdCl_2$ catalyzes the coupling of secondary amines with aryl chlorides, Eq. (41) [71]. With this catalyst system based on the use of sterically hindered, electron-rich trialkylphosphines, electron-poor and electronically neutral aryl halides were reacted at elevated temperatures. Similarly, Nishiyama, Yamamoto and Koie reported the formation of an arylpiperazine from chlorobenzene using a $(t\text{-Bu})_3$P/Pd catalyst [36].



R	Yield, % (GC)
CN	65
Me	56

(41)

In 1998, Hamann and Hartwig reported that electron-rich, ferrocene-based diphosphines such as **13** allowed for the coupling of cyclic amines with aryl chlorides [72, 73]. The known ligand **13** proved to be most generally useful for this transformation, Eq. (42). The **13**/Pd-catalyzed arylation reaction was performed with cyclic amines as well primary amines, however, no reactions with acyclic secondary amines were reported.



R	X	Yield, %
m-OMe	CH_2	81
p-Me	O	85

(42)

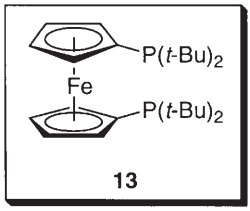
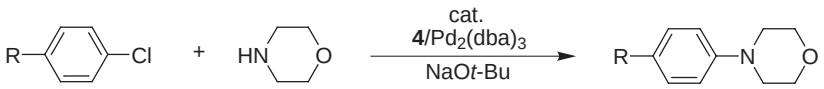


Fig. 12

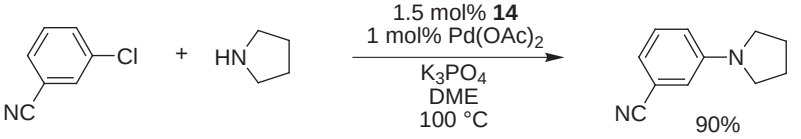
Almost concurrently with this report by Hartwig, Old, Wolfe, and Buchwald reported that catalysts derived from aminophosphine **4** are capable of effecting C-N bond formation with aryl chlorides cyclic amines [42]. This catalyst system effects the amination of aryl chlorides bearing electron-withdrawing, electronically neutral, and electron-donating groups. For the first time, the coupling of an activated aryl chloride, 4-cyanochlorobenzene, with morpholine could be performed at room temperature, Eq. (43). The reaction of a deactivated aryl chloride such as 4-chloroanisole and morpholine also proceeded in excellent yield in the presence of the **4**/Pd catalyst, although heating the reaction to 80 °C was necessary.



(43)

R	mol% $Pd_2(dba)_3$	mol% **4**	Reaction Conds.	Yield, %
-CN	2.5	7.5	DME, RT	96
-OMe	0.5	1.5	toluene, 80 °C	91

Dicyclohexyl-*o*-biphenylphosphine (**14**) is an excellent supporting ligand for the Pd-catalyzed C-N bond forming reaction, particularly when the coupling involves a functionalized aryl chloride, Eq. (44) [42a, 44, 74].



(44)

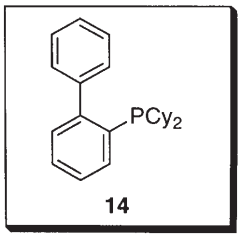
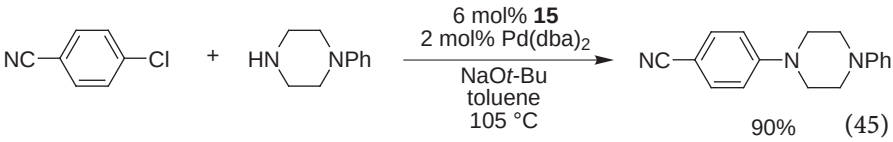


Fig. 13

Guram and co-workers at Symyx prepared phosphinoether ligand **15** that allows the efficient coupling of aryl chlorides with cyclic amines [47, 75]. For example, *N*-phenylpiperazine is reacted with 4-chlorobenzonitrile in the presence of **15**/Pd(dba)$_2$ in high yield, Eq. (45).



(45)

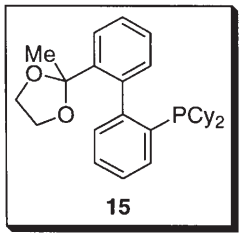
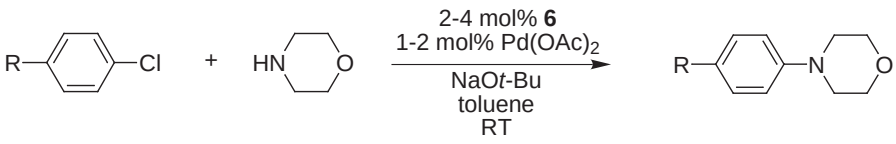


Fig. 14

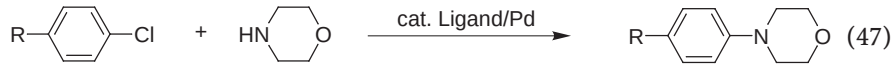
As was observed in the reactions of aryl bromides, the catalyst derived from commercially available ligand **6** displayed very high reactivity; as a result, it was now possible to couple a large variety of aryl chlorides with cyclic amines at room temperature [42a, 48]. Morpholine was reacted with both electron-rich and electron-deficient aryl chlorides in excellent yield, Eq. (46). Mild bases such as Cs_2CO_3 and K_3PO_4 can be used with this system, although elevated temperatures are necessary. This new catalyst system enjoys greater substrate scope in the arylation of acyclic secondary amines, and primary amines with aryl chlorides.



R	Yield, %
OMe	90
CN	86

(46)

Nolan's heterocyclic carbene-based system (7 + KO*t*-Bu/$Pd_2(dba)_3$) was effective in the coupling of secondary amines with aryl chlorides at elevated temperatures, Eq. (47) [52]. This protocol could be used for the room-temperature amination of aryl bromides as well. Hartwig reported that the saturated heterocyclic carbene ligand prepared by deprotonation of **16** forms a catalyst that is considerably more reactive than the system reported by Nolan. The resulting complex formed was capable of coupling aryl chlorides with cyclic amines at room temperature [76].



(47)

R	L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
Me	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	82
OMe	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	80
Me	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	99
OMe	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	96

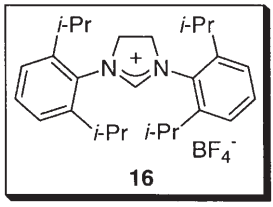
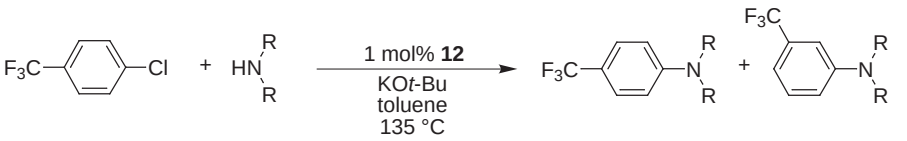


Fig. 15

2.2.6
Reaction of Acyclic Secondary Amines with Aryl Chlorides

As was the case with aryl bromides, the reaction of acyclic secondary amines with aryl chlorides is more challenging than their cyclic counterparts due to competitive formation of the reduced arene by-products.

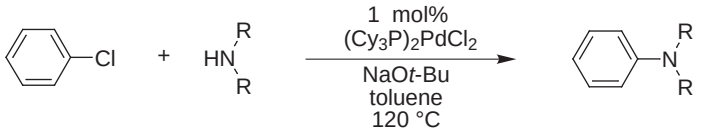
Beller's palladacycle (**12**) catalyzes the arylation of *N*-methylaniline and di-*n*-butylamine with an activated aryl chloride, Eq. (48) [70]. As was observed in the reactions of cyclic amines, significant amounts of the regioisomeric product was formed, indicative of reaction through a benzyne intermediate.



Amine	Yield, %	Ratio
H-N(Me)Ph	60	10:1
H-NBu$_2$	60	20:1

(48)

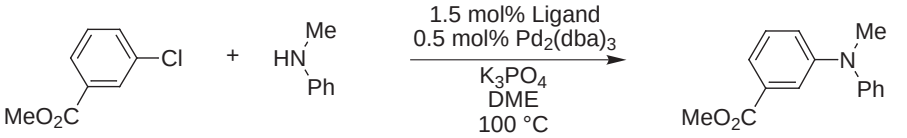
Reddy and Tanaka's procedure provides moderate to good yields in the arylation of cyclic amines as well as *N*-methylaniline, low yields were observed when dialkylamines were used, Eq. (49) [71].



Amine	Yield, %
H-N(Me)Ph	60
H-NHex$_2$	20

(49)

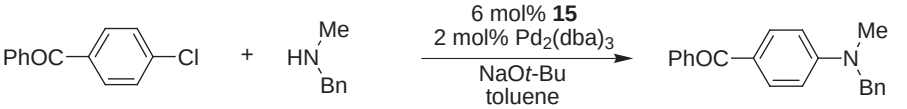
The **4**/Pd-based catalyst is effective in the arylation of acyclic secondary amines with functionalized aryl chlorides at elevated temperatures, Eq. (50) [42]. Similarly, ligand **14** is useful in these transformations. Strong bases such as NaO*t*-Bu and milder bases such as K_3PO_4 have found utility with both **4**- and **14**-based catalysts.



Ligand	Yield, %
4	83
14	88

(50)

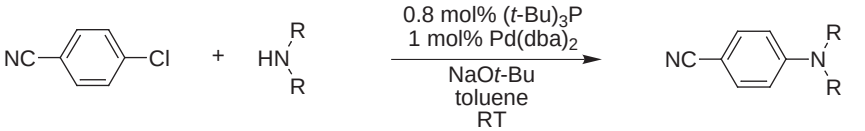
Guram's phosphinoether **15** mediates the coupling of acyclic secondary amines and aryl chlorides, Eq. (51) [47, 75].



96% (51)

Yamamoto, Nishiyama, and Koie first reported that the (*t*-Bu)$_3$P/Pd-catalyst is effective in coupling chlorobenzene and diphenylamine at elevated tempera-

tures (130 °C) [65]. Hartwig subsequently demonstrated, however, that this catalyst system enjoyed considerable substrate scope and in the case of activated aryl chlorides, the reaction could be performed at room temperature, Eq. (52) [50].

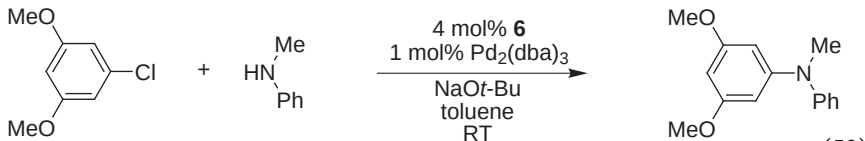


Amine	Yield, %
H-N(Me)Ph	90
H-NPh$_2$	89

(52)

Representative for the Palladium-Catalyzed Arylation of Amines with Aryl Chlorides using (t-Bu)$_3$P/Pd: (Reproduced with permission from [50]. © 1999 American Chemical Society) In a dry box, aryl halide, amine, Pd(dba)$_2$, (t-Bu)$_3$P, and sodium *tert*-butoxide were weighed directly into a screw cap vial. A stir bar was added followed by 1.0 – 2.0 ml of toluene to give a purple mixture. The vial was removed from the dry box, and the mixture was stirred at room temperature. After 5.5 h, the reaction mixture was adsorbed onto silica gel and chromatographed with 50 % toluene/hexanes to give 242 mg (90 %) of *N*-(4-cyanophenyl)diphenylamine as a white solid.

The catalyst derived from phosphine **6** and palladium is among the most active catalysts for the arylation of acyclic secondary amines with aryl chlorides [42a, 48]. The **6**/Pd-system is able to effect C-N bond formation at room temperature in many cases, Eq. (53).

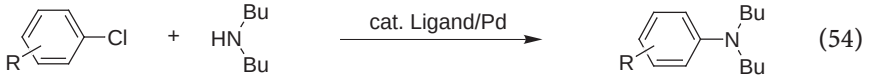


97% (53)

General Procedure for the Room-Temperature Palladium-Catalyzed Arylation of Amines with Aryl Chlorides using 6/Pd: (Excerpted with permission from [50]. © 2000 American Chemical Society) An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was evacuated and backfilled with argon and then capped with a rubber septum. The flask was charged with Pd(OAc)$_2$ (2.2 mg, 0.01 mmol, 1 mol%), **6** (6.0 mg, 0.02 mmol, 2 mol%), and sodium *tert*-butoxide (135 mg, 1.4 mmol). Toluene (0.5 ml), the aryl chloride (1.0 mmol), the amine (1.2 mmol), and additional toluene (0.5 ml) were added through the septum (aryl halides or amines that were solids at room temperature were added as solids following the addition of NaO*t*-Bu). The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was stirred at room temperature until the starting aryl chloride had been completely consumed as judged by GC analysis. During the course of the reaction, the mixture was observed to form a gel (at around 50 % conversion) and then

liquify again as the reaction proceeded to completion. Following complete consumption of the aryl chloride starting material, the mixture was diluted with ether (20 ml), filtered through Celite, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

Nolan reported that the use of the carbene ligand derived from the deprotonation of **7** results in the formation of an efficient catalyst for the reaction of aryl chlorides and acyclic secondary amines [52]. For example, di-*n*-butylamine efficiently reacts with 4-chloroanisole at 100 °C in the presence of this catalyst, Eq. (54). Hartwig disclosed that the saturated carbene ligand derived from the deprotonation of **16** yields a considerably more reactive catalyst which is capable of coupling acyclic secondary amines and aryl chlorides at room temperature [76].



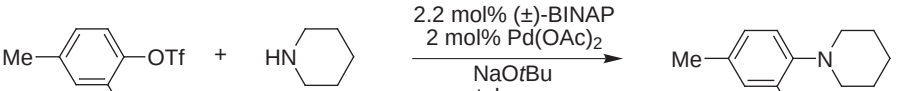
(54)

R	L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
p-OMe	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	98
o-Me	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	97
p-CN	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	97

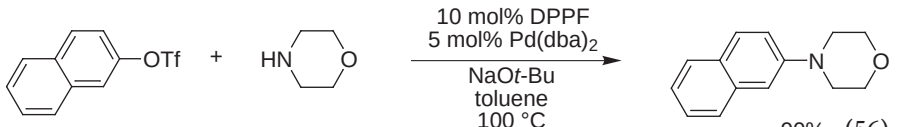
2.2.7
Reaction of Cyclic Amines with Aryl Sulfonates

The use of aryl triflates or other sulfonates in the amine arylation reaction is highly desirable from a synthetic standpoint since a large variety of phenols are easily accessed and derivatized. Aryl and vinyl triflates have enjoyed great utility in other Pd-catalyzed transformations such as the Stille [77] and Suzuki [78] couplings, and the Heck [79] reaction.

In 1997, the Buchwald and Hartwig groups reported the efficient couplings of aryl triflates with cyclic amines [80, 81]. In general, both groups obtained moderate to good yields of the desired products when electronically neutral or electron-rich aryl triflates were used (Eqs. 55, 56). Yields were lower in the reactions of electron-deficient aryl triflates due to competitive triflate cleavage under the reaction conditions. Hartwig first showed that slow addition of the aryl triflate could minimize this unwanted side reaction.



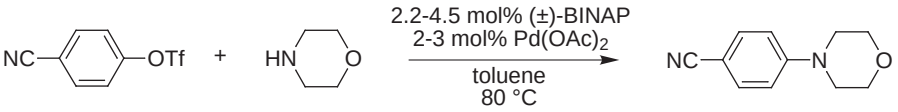
76% (55)



90% (56)

Later that year, the Åhman and Buchwald reported an improved procedure for the reaction of triflates and cyclic secondary amines [82]. The use of Cs_2CO_3 as base allowed numerous electron-deficient aryl triflates to be coupled in high yield. The reaction between the 4-cyano-substituted aryl triflate and morpholine in the presence of (±)-BINAP/Pd provided the desired arylamine in 28% yield, Eq. (57). However, when the triflate was added over the course of 30 minutes, the desired product was isolated in 60% yield. The use of Cs_2CO_3 as base improved the yield of arylamine to 84%. The use of a mild base also allowed for the use of functionalized aryl triflates in the C-N bond forming reaction.

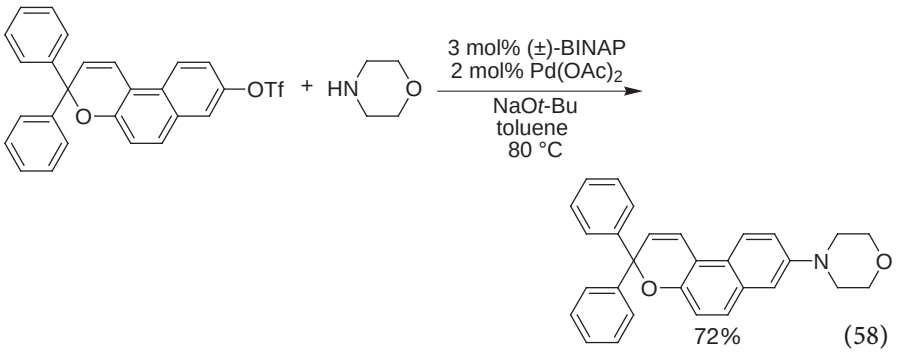
General Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Triflates using a BINAP/Pd-Catalyst and Cs_2CO_3 as Base: (Excerpted with permission from [82]. © 1997 Pergamon Press). An oven-dried Schlenk tube was charged with cesium carbonate which had been finely ground with a mortar and pestle. The tube was then charged with $Pd_2(dba)_3$ (4.6 – 9.2 mg, 0.005 – 0.01 mmol) and BINAP (9.3 – 18.7 mg, 0.015 – 0.03 mmol). The Schlenk flask was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2 ml), aryl bromide (1.0 mmol), and amine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 100 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (20 ml), filtered, and concentrated. The crude reaction mixture was then purified further by flash chromatography on silica gel.



Rxn. Conditions	Yield, %
NaO*t*-Bu	28
NaO*t*-Bu, slow addition	60
Cs_2CO_3	84

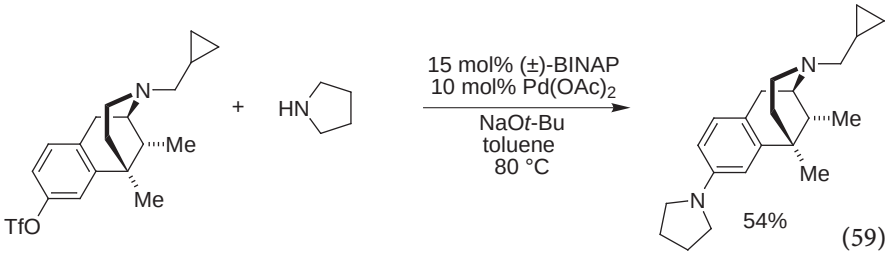
(57)

Other groups have utilized the (±)-BINAP/Pd-catalyst to prepare several interesting products by the amination of aryl triflate precursors. For example, the 3*H*-naphth[2,1-*b*]pyran triflate below was coupled in 72% yield, providing a photochromic material, Eq. (58) [83]



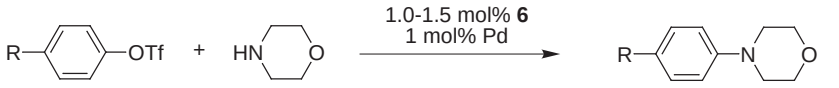
(58)

Wentland and co-workers reported that amine-substituted analogues of the analgesic cyclozine could be easily prepared by the Pd-catalyzed C-N bond forming reaction [84]. For example, the pyrrolide-substituted compound was prepared by using the (±)-BINAP/Pd-catalyst in 54% yield, Eq. (59). Several cyclic, acyclic secondary, and primary amines were coupled with this triflate utilizing both (±)-BINAP and DPPF as supporting ligands.



(59)

The **6**/Pd-system is the most efficient catalyst for the coupling of cyclic amines and aryl triflates [42a]. In the case of electron-rich or electronically neutral aryl triflates, the reaction can be performed at room temperature with NaO*t*-Bu as base, Eq. (60). In reactions of electron-deficient aryl triflates, use of K_3PO_4 as base and running the reaction at 80 °C results in clean C-N bond formation.

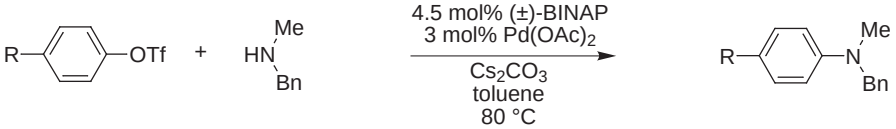


R	Reaction Conds.	Yield, %
t-Bu	$Pd(OAc)_2$, NaO*t*-Bu, Toluene, RT	79
OMe	$Pd(OAc)_2$, NaO*t*-Bu, Toluene, RT	81
NO_2	$Pd_2(dba)_3$, K_3PO_4, DME, 80 °C	76

(60)

2.2.8
Reaction of Secondary Acyclic Amines with Aryl Sulfonates

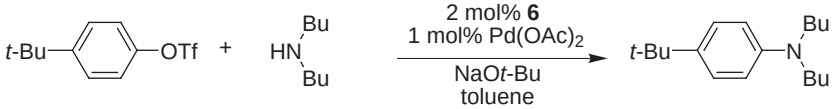
Using the conditions described above for the reaction between cyclic amines and electron-rich or electronically neutral aryl triflates, acyclic secondary amines can also be effectively coupled, Eq. (72) [80, 81]. As was observed with cyclic amines, the use of electron-deficient aryl triflates results in lower yields due to triflate cleavage. The use of a mild base such as Cs_2CO_3 allowed for the coupling of electron-deficient aryl triflates and acyclic secondary amines [82]. This protocol, which employed a (±)-BINAP/$Pd(OAc)_2$ catalyst, furnished the desired coupled products with good to excellent yield, Eq. (61).



R	Yield, %
CN	78
CO_2Me	85

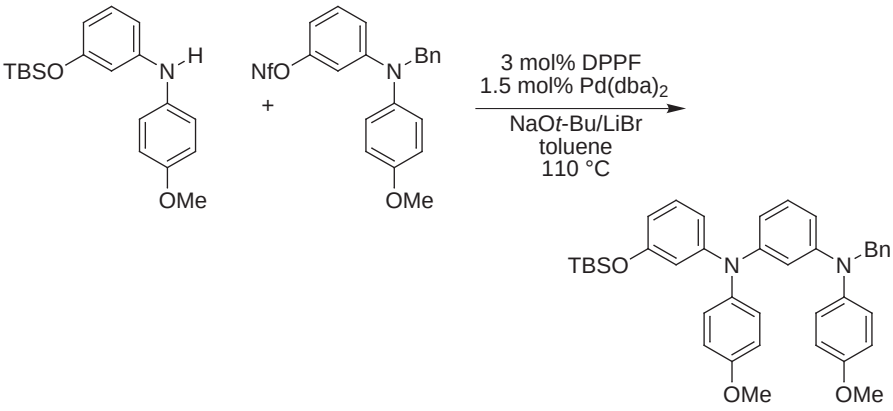
(61)

The **6**/Pd-catalyst system is very effective at the arylating acyclic secondary amines with aryl triflates in moderate to good yield, Eq. (62) [42a].



73% (62)

Hartwig has reported a DPPF/Pd-catalyzed C-N coupling reaction between a diarylamine and an aryl nonaflate, Eq. (63) [64b]. The coupling below proceeded in 95–100% yield (NMR) and was used in a strategy to prepare oligo(*m*-aniline) compounds.

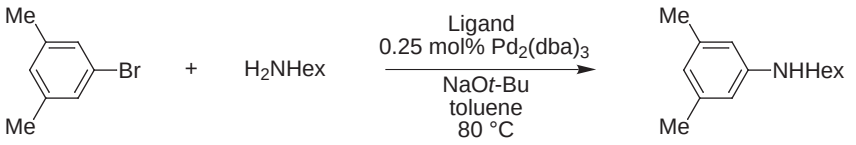


95-100% (NMR) (63)

2.3 N-Arylation of Primary Amines

2.3.1 *Reaction of Primary Aliphatic Amines with Aryl Bromides*

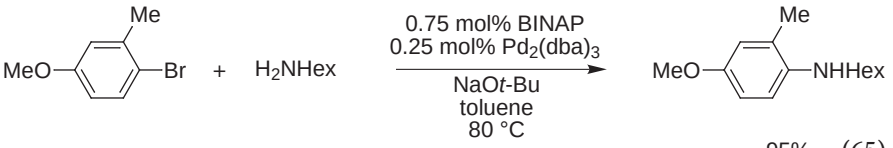
The coupling of aryl bromides with primary aliphatic amines often suffered from the formation of reduced arene by-products similar to the reactions with secondary amines. For example, the use of (±)-BINAP as a ligand greatly improved the yield in the coupling of 5-bromo-*meta*-xylene and *n*-hexylamine, Eq. (64) [27].



Ligand	Yield, %
(*o*-tol)$_3$P (1 mol%)	35
BINAP (0.75 mol%)	88

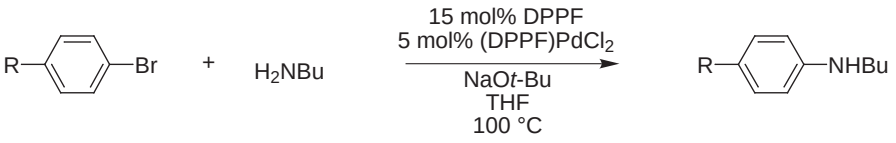
(64)

In addition, electron-rich aryl bromides were better tolerated with the BINAP/Pd-system, Eq. (65). Although NaO*t*-Bu is typically used as base, Prashad and co-workers recently reported that NaOMe and NaO*i*-Pr may also be used as well [30].



95% (65)

Simultaneously with the report by Buchwald, Hartwig demonstrated that the DPPF/Pd-catalyst efficiently couples primary amines and electron-deficient and electronically neutral aryl bromides [29]. For example, the couplings of *n*-butylamine with aryl bromides possessing nitrile and ketone functional groups proceed with excellent yields, Eq. (66).

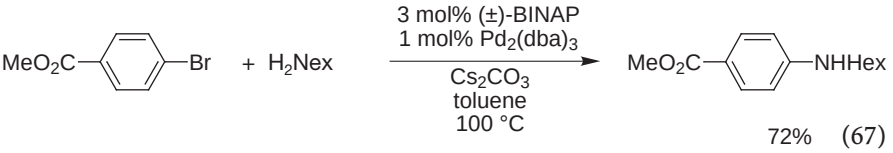


R	Yield, %
COPh	96
CN	93

(66)

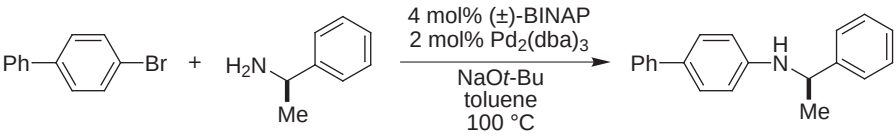
Representative Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Bromides using DPPF/Pd: (Excerpted with permission from [29]. © 1996 American Chemical Society) In an inert atmosphere dry box, $DPPFPdCl_2$ and 3.0 equiv. of DPPF/Pd were added to a solution of 20 equiv of bromobenzophenone and 25 equiv of sodium *tert*-butoxide in 8 ml of anhydrous THF. The reaction tube was sealed with a cap containing a PTFE septum and removed from the dry box. Butylamine (25 equiv) was added to the reaction mixture by syringe, and the mixture was heated to 100 °C for 3 h. The reaction was cooled to room temperature, the volatile materials were removed by rotary evaporation, and the product was isolated by either sublimation or silica-gel chromatography (20:1 hexane/EtOAc or 10:1 hexane/Et_2O followed by 4:1 hexane:Et_2O).

Weak bases such as Cs_2CO_3 and K_3PO_4 have been utilized in the BINAP/Pd-catalyzed reaction between aryl bromides and primary amines [27a, 40]. For example, the coupling of 4-bromomethylbenzoate with *n*-hexylamine can be performed in 72% yield without cleavage of the ester, Eq. (67).



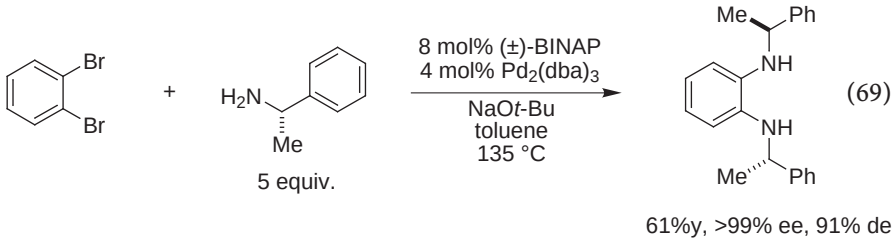
72% (67)

The efficacy of BINAP to shut down β-hydride elimination was demonstrated in the arylation of enantiomerically enriched primary amines as well [53, 54]. For example, the arylation of α–methylbenzylamine with 4-bromobiphenyl proceeded with preservation of optical activity when (±)-BINAP was used as the ligand, Eq. (68). In contrast, the use of $(o\text{-tol})_3P$ as ligand resulted in a significant erosion of enantiomeric excess (70 % ee).



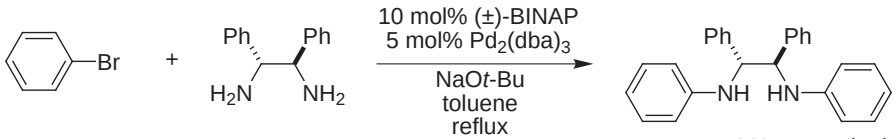
(68)

The efficacy of the BINAP/Pd-system to mediate C-N bond formation without stereochemical erosion has been taken advantage of by several groups. Diver and co-workers described the double amination or *ortho*-dibromobenzene with (*S*)-α-methylbenzylamine to yield the desired C_2-symmetric diamine in 61 % yield, > 99 % ee, and 91 % de, Eq. (69) [85]. Schmalz reported a similar coupling reaction to prepare new ligands for asymmetric catalysis [45].



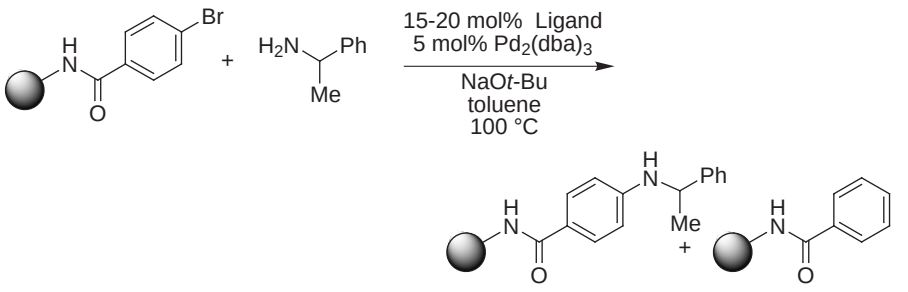
(69)

Mangeny doubly arylated (*R*,*R*)-1,2-diphenylethylenediamine with several aryl bromides to yield the desired chiral ligands in good to excellent yields [86]. For example, the reaction of bromobenzene mediated by the (±)-BINAP/Pd-catalyst furnished the desired compound in 89 % yield, Eq. (70).



(70)

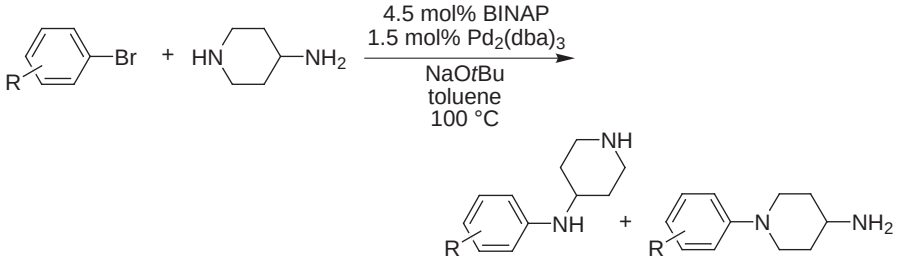
The coupling of primary amines with resin-bound aryl bromides was effected cleanly with both the (±)-BINAP/Pd- and DPPF/Pd-catalyst systems. Groups at Boehringer-Ingelheim and Merck have reported that BINAP/Pd- and DPPF/Pd-based protocols allow for efficient C-N bond formation, while use of $(o\text{-tol})_3P$/Pd-catalysis results in significant aryl bromide reduction, Eq. (71) [31, 32].



Ligand	Ratio
(*o*-tol)$_3$P	65:35
BINAP	100:0
DPPF	100:0

(71)

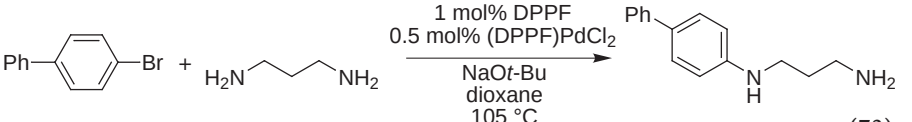
During their studies on the synthesis of norastemizol, Senanayake, Tanoury and co-workers reported that high levels of regioselectivity were observed in the amine arylation such that primary amines reacted in preference to secondary ones [87]. For example, the coupling of 4-aminopiperidine in the presence of the BINAP/Pd-catalyst resulted in reaction at the primary amine functional group, Eq. (72) [34].



R	Yield, %	Ratio
o-CN	87	59:1
p-CN	84	27:1

(72)

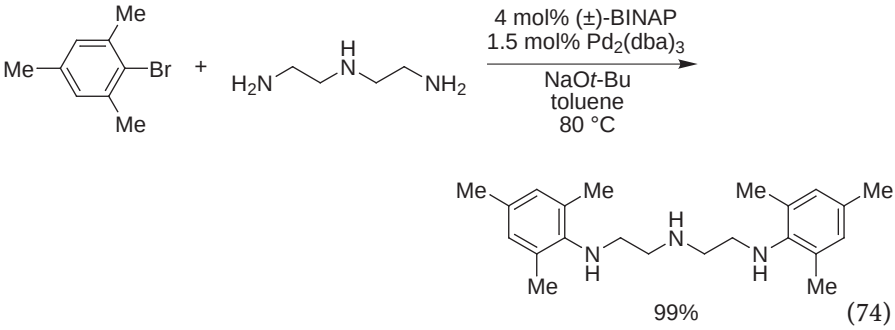
Beletskaya was able to prepare monoarylated propylenediamine derivatives by using an excess of the starting diamine and a DPPF/Pd-catalyst; the reaction below proceeded in 75% isolated yield, Eq. (73) [88].



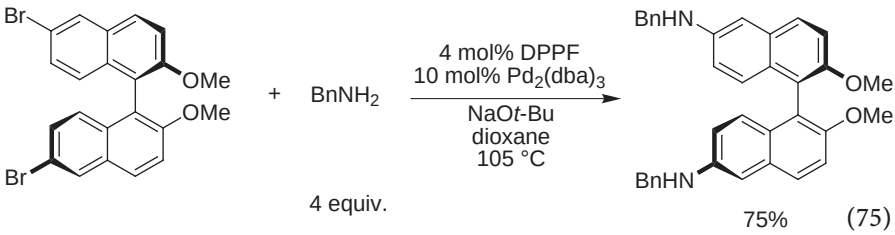
75% (73)

Similarly, Schrock utilized the (±)-BINAP/Pd-system to doubly arylate diethylene triamine to afford the ligand shown below in quantitative yield,

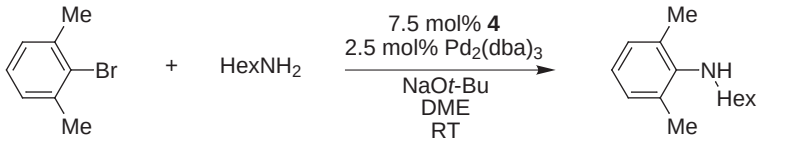
Eq. (74) [89]. Notably, the arylation is observed exclusively at the primary amino group. The MIT group prepared several polyamine-based ligands in this fashion.



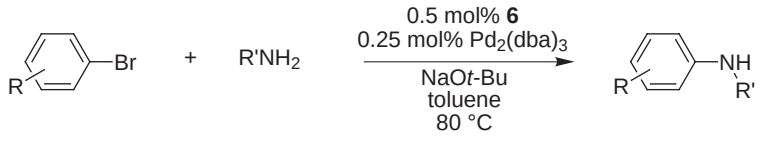
Lim and Lee coupled the binaphthol derivative below with benzylamine to yield the desired product in 75% yield, Eq. (75) [90]. Subsequent removal of the benzyl protecting groups was effected by hydrogenation, thus demonstrating that benzylamine may be used as an ammonia equivalent.



Aminophosphine **4** is an excellent supporting ligand in the room-temperature reaction of aryl bromides and primary amines [42]. The **4**/Pd-catalyst is capable of coupling a hindered aryl bromide such as 2-bromo-*meta*-xylene with *n*-butylamine in excellent yield, Eq. (76).



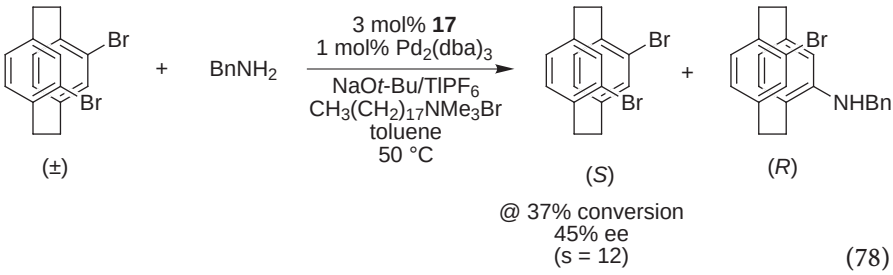
The catalyst derived from hindered phosphine **6** also is effective in the arylation of primary aliphatic amines with aryl bromides, Eq. (77). Although this system is capable of mediating such a reaction at room temperature, with more hindered substrates, heating is required [42a, 48].



R	R'	Yield, %
3,5-Me_2	Bn	86
2,6-Me_2	$CH_2CH{=}CH_2$	92

(77)

A Merck group reported an interesting kinetic resolution of a racemic dibromocyclophane via Pd-catalyzed amination [91]. While BINAP was a poor ligand for the reaction in terms of selectivity, the C_2-symmetric cyclophane-derived PHANEPHOS (**17**) proved to be optimal. Reaction of the cyclophane derivative with benzylamine afforded the unreacted dibromide in 45% ee after 37% conversion, corresponding to a selectivity factor of 12, Eq. (78).



(78)

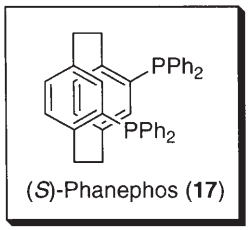
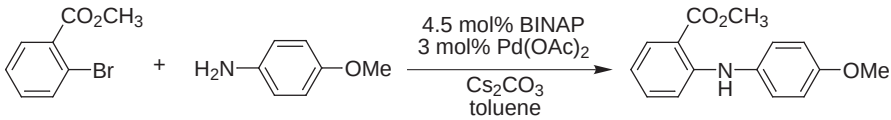


Fig. 16

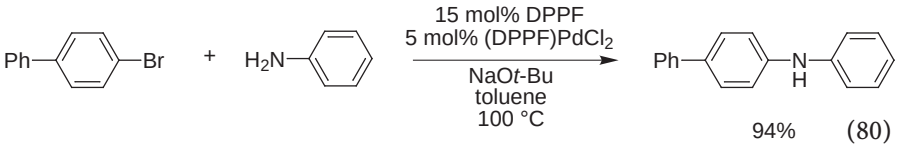
2.3.2
Reaction of Primary Aromatic Amines with Aryl Bromides

Buchwald's original BINAP/Pd-catalyst effectively couples aryl bromides with aniline derivatives, and either alkoxide bases [30] such as NaO*t*-Bu or mild bases such as Cs_2CO_3 may be used, Eq. (79) [27, 37]. Similarly, Hayashi et al. have reported the use of DPBP (**11**) in the coupling of an aryl bromide and aniline.



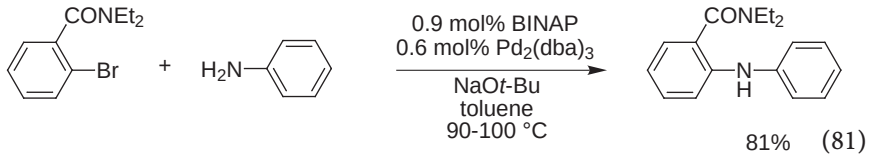
(79)

Hartwig's DPPF/Pd-based system is able to effect similar C-N bond formation reactions between aryl bromides and aniline derivatives, Eq. (80) [29].

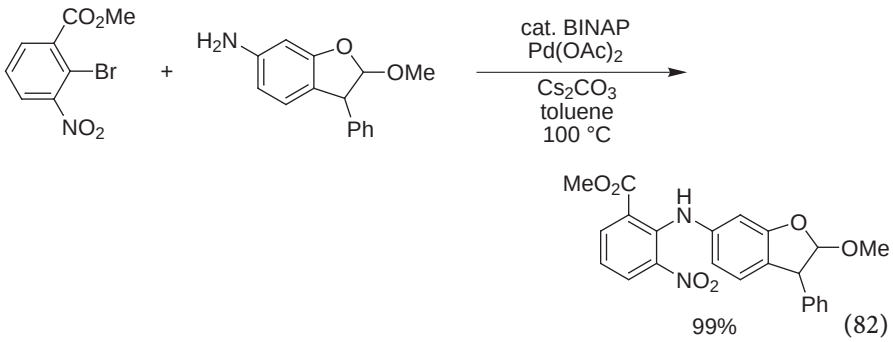


(80)

The BINAP/Pd- and DPPF/Pd-catalyst systems have been used by numerous groups to react aryl bromides with arylamines. Ward and Farina as well as Willoughby and Chapman performed the arylation reaction with arylamines and resin-bound aryl bromides [31, 32]. Snieckus reported the use of the Pd-catalyzed C-N bond forming reaction to prepare several acridone derivatives, Eq. (81) [92]. Kamikawa et al. prepared phenazine derivatives via an initial C-N bond coupling and subsequent cyclization, Eq. (82) [93].

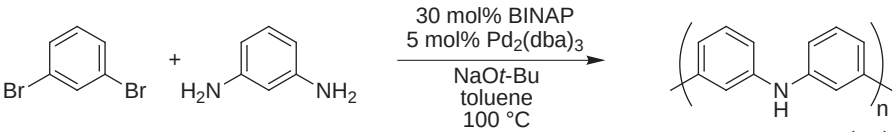


(81)

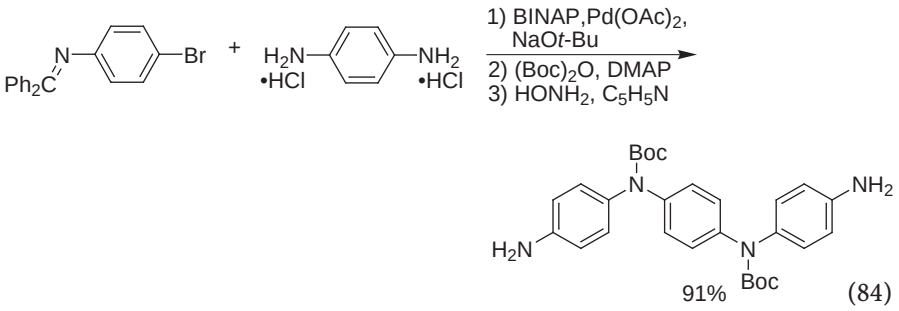


(82)

In 1997, Kanbara reported the preparation of poly(imino-1,3-phenylene) using Pd and several different supporting ligands. BINAP/Pd-catalysts provided the desired polymer in 86% yield, Eq. (83) [94]. Similarly, Singer, Sadighi, and Buchwald described the preparation well defined end-functionalized oligoanilines using the BINAP based-system [95]. The general strategy is outlined in Eq. (84); the double coupling reaction proceeded in 91% isolated yield. More reactive catalyst systems were later developed and used to prepare high molecular weight polyaniline.

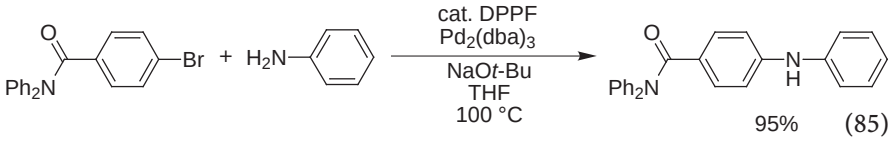


(83)



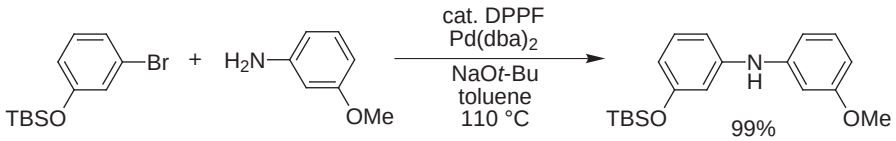
(84)

Frost and Medonça utilized an iterative amine arylation strategy to prepare benzamide-based peptidomimetics [96]. The researcher reported the DPPF/Pd-catalyzed coupling with several primary amines, including aniline, Eq. (85). Acylation of the resulting diarylamine with 4-bromobenzoylchloride furnished the substrate for the subsequent amination reaction. Schmalz reported a similar coupling to prepare new ligand precursors [45].



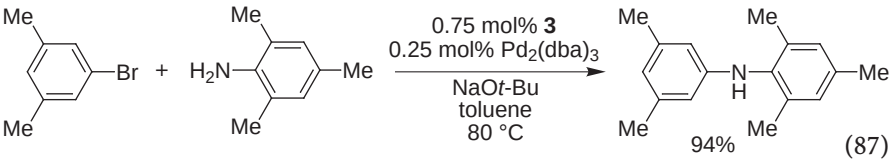
(85)

Louie and Hartwig described an application of the DPPF/Pd-catalyst toward the synthesis of oligo(*m*-anilines). The diarylamine monomer was prepared using this protocol in quantitative yield, Eq. (86) [64b]. Goodson and Hartwig have extended the method to synthesize other monomers for the preparation of poly(*N*-arylanilines) [54c].



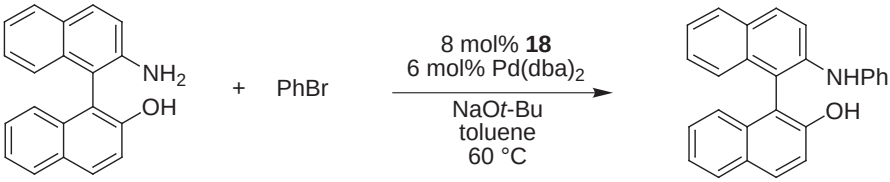
(86)

Phosphinoether PPF-OMe (**3**) is an effective supporting ligand in the palladium-catalyzed coupling of aryl bromides and arylamines [37]. For example, reaction of the hindered aniline below proceeded in 94% yield with as little as 0.5 mol% Pd, Eq. (87).



(87)

Kocovsky and co-workers reported the arylation of aminobinol mediated by a catalyst prepared from bulky aminophosphine **18** and $Pd(dba)_2$ [97]. Complete conversion was observed in less than 5 minutes at 60 °C using the **18**/Pd-system, Eq. (88); the BINAP/Pd-catalyst required 2 h for complete consumption of substrate under the same conditions.



100% conversion (88)

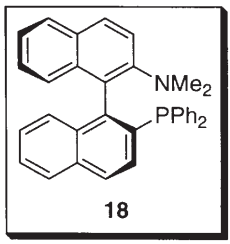
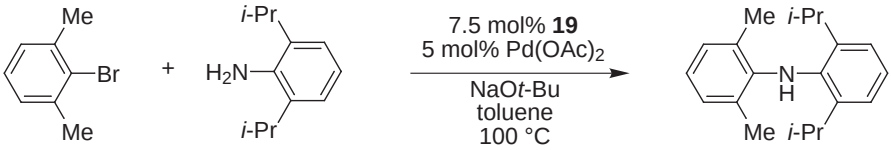


Fig. 17

DPEphos (**19**)/Pd-catalysts are effective in the coupling of arylamines and aryl bromides, particularly with sterically hindered coupling partners [57, 98]. For example, the coupling below proceeded in 90% yield when a **19**/$Pd(OAc)_2$-catalyst was used, Eq. (89).



90% (89)

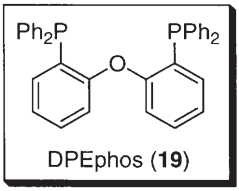
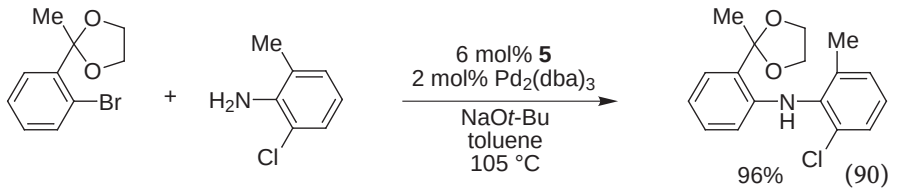


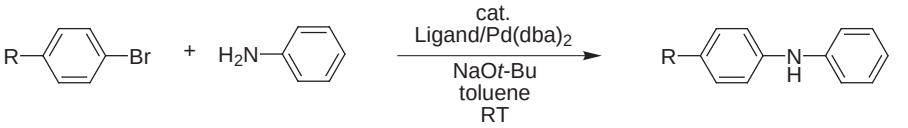
Fig. 18

Guram's phosphine **5** and $Pd_2(dba)_3$ efficiently mediate the arylation of aniline derivatives at elevated temperatures as well, Eq. (90) [47].



(90)

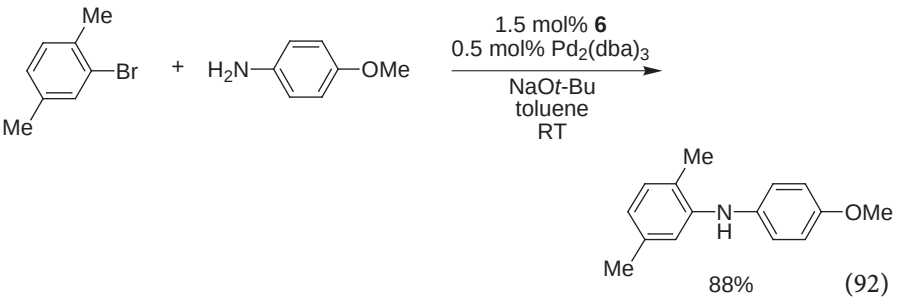
Hartwig reported that ferrocene-based diphosphine **13** catalyzes the arylation of aniline at room temperature, Eq. (91) [72]. Additionally, the $(t\text{-Bu})_3$P/Pd-based system effects the room-temperature condensation of anilines and aryl bromides. However, the $(t\text{-Bu})_3$P/Pd-catalyst is considerably more active [50]. While the reaction with 4-bromotoluene and aniline proceeded in 20 h using 5 mol% **15**/Pd(dba)$_2$, the reaction between bromobenzene and aniline was complete in 1 h using only 1 mol% of the $(t\text{-Bu})_3$P-derived catalyst.



R	Reaction Conditions	Yield, %
Me	5 mol % **15**, 5 mol% Pd(dba)$_2$	94
H	0.8 mol % $(t\text{-Bu})_3$P, 2 mol% Pd(dba)$_2$	87

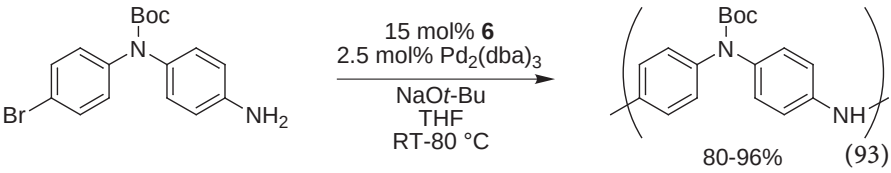
(91)

The **6**/Pd-catalyst is also capable of coupling aryl bromides and arylamines at room temperature and tolerates electron-donating groups and *ortho* substitution on the aryl bromide, Eq. (92) [42a]. Although the transformation can be performed at ambient temperature, the scope of the reaction is much greater at 80–100 °C. In addition, at elevated temperatures, bases such as Cs_2CO_3 and K_3PO_4 may be used.

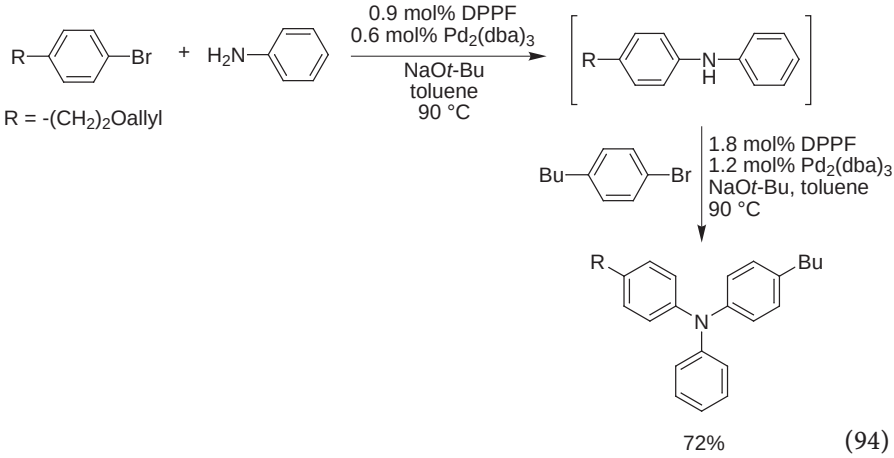


(92)

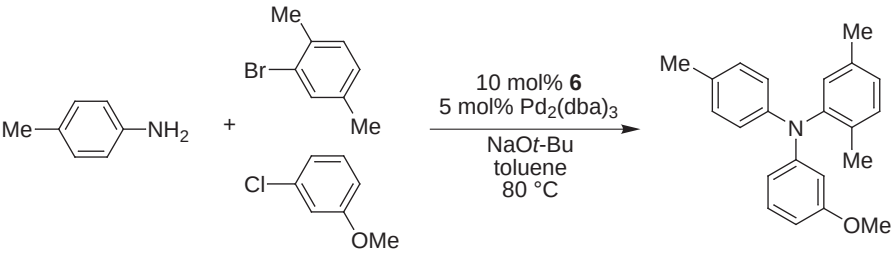
The high reactivity of the **6**/Pd-catalyst was exploited in the preparation of high molecular weight polyaniline, Eq. (93) [99]. After thermolytic deprotection of the Boc protecting groups and air oxidation, emeraldine, the conductive form of polyaniline was obtained.



The arylation of aniline derivatives can be executed such that triarylamine products can be obtained from a one-pot procedure. Marder and co-workers coupled aniline with the first equivalent of aryl bromide using the DPPF/Pd-based catalyst at 90 °C, Eq. (94) [100]. After the reaction was judged complete by TLC, the second aryl bromide was added to the reaction, along with an addition amount of base and catalyst. The resulting mixture was heated to 90 °C. After chromatography, the unsymmetrical triarylamine was obtained in 72 % yield.

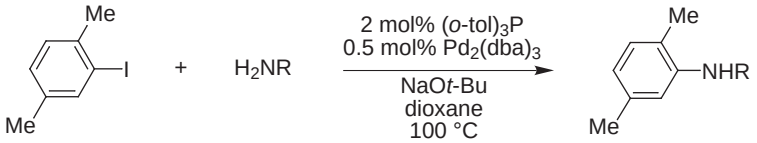


Harris and Buchwald took advantage of the differential reactivity between aryl chlorides and aryl bromides in the Pd-catalyzed C-N bond coupling to design a simple one-pot procedure for the preparation of unsymmetrical triarylamines, Eq. (95) [101]. Reaction of the aniline with an aryl bromide and an aryl chloride in the presence of the **6**/Pd-catalyst resulted in clean production of the desired triarylamine. After complete consumption of the aryl bromide to furnish the corresponding diarylamine, the aryl chloride then reacted to yield the desired unsymmetrical product.



2.3.3
Reaction of Primary Amines with Aryl Iodides

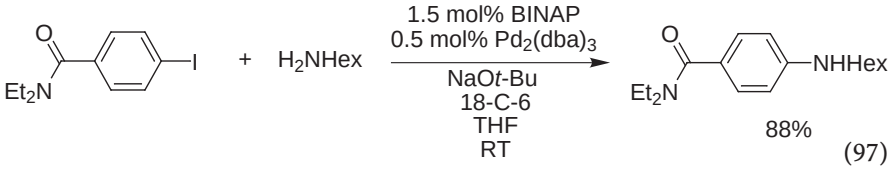
Wolfe and Buchwald first reported the palladium-catalyzed arylation of primary amines with aryl iodides in 1996 [67]. The (*o*-tol)$_3$P/Pd-system effected the reaction in moderate yields. Both aliphatic and arylamines were coupled in moderate yield, Eq. (96).



R	Yield, %
Hex	69
Ph	64

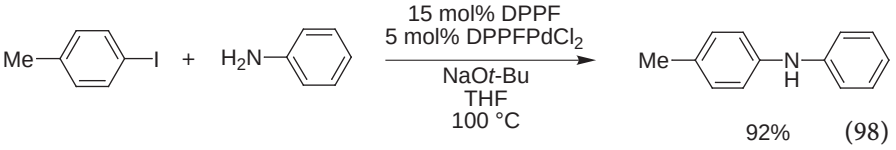
(96)

Subsequently, Wolfe and Buchwald reported a significant improvement in the coupling of aryl iodides and primary amines [68]. The addition of 18-crown-6 to the reaction resulted in a significant improvement in this catalyst system. In addition, BINAP was used as the supporting ligand instead of (*o*-tol)$_3$P. While the coupling of 4-iodo-*N*,*N*-diethylbenzamide and *n*-hexylamine proceeded in only 19% yield using the original procedure, the room-temperature/BINAP/18-crown-6 procedure resulted in an 88% isolated yield of the desired product, Eq. (97).



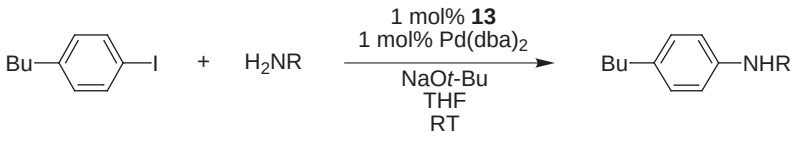
(97)

Hartwig reported the arylation of anilines with aryl iodides using a DPPF/Pd-catalyst, Eq. (98) [29]. This system provided the desired diarylamines in good to excellent yield.



(98)

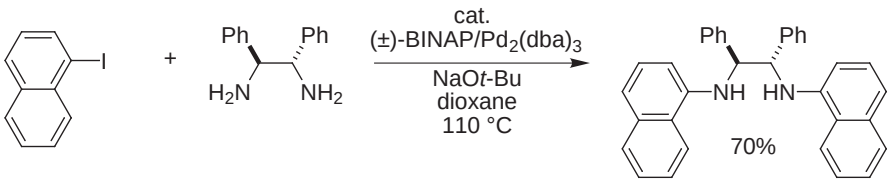
The catalyst derived from **13** and Pd(dba)$_2$ is effective in the arylation of primary amines with aryl iodides as well [72]. The **13**/Pd-system is sufficiently reactive to accomplish this transformation at room temperature, Eq. (99). While aliphatic amines are coupled in moderate yield, the arylation of aniline derivatives proceeds quite efficiently.



R	Yield, %
Bu	47
Ph	95

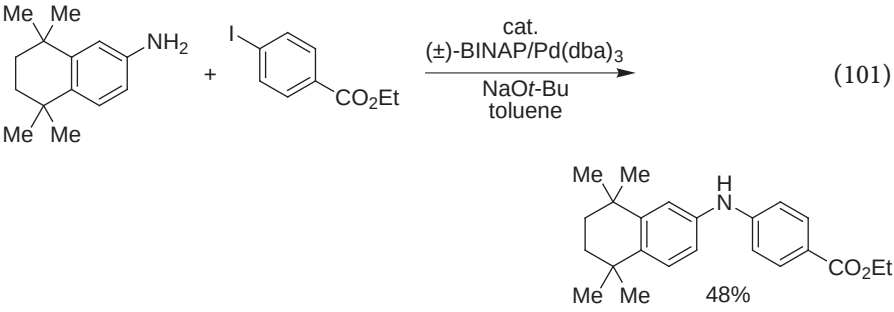
(99)

Denmark utilized the BINAP/Pd-catalyst to doubly arylate 1,2-diphenylethylenediamine with 2-iodonaphthalene, Eq. (100) [102]. The reaction below proceeded in 70% yield, and no epimerization due to β-hydride elimination/reinsertion was observed. The resulting diamine was used to prepare a chiral HMPA derivative.



(100)

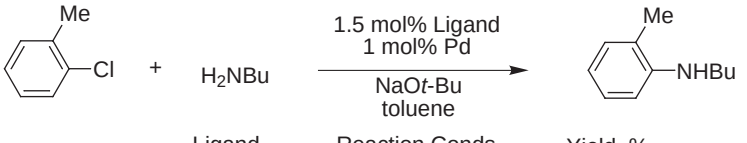
Kagechika et al. reported the preparation of a retinoic nuclear receptor ligand utilizing the BINAP/Pd-catalyzed C-N bond forming reaction [103]. The aniline derivative below was coupled with 4-iodoethylbenzoate in 48% yield, Eq. (101).



(101)

2.3.4
Reaction of Primary Aliphatic Amines with Aryl Chlorides

Hartwig and co-workers reported that several ferrocene-based diphosphines are useful in the arylation of primary amines with aryl chlorides [72]. Known ligands **20** [104] and **21** [105] are particularly effective in the coupling of chloroarenes and primary aliphatic amines, Eq. (102).



Ligand	Reaction Conds.	Yield, %
13	$Pd(dba)_2$, 110 °C	57
20	$Pd(OAc)_2$, 85 °C	89
21	$Pd(OAc)_2$, 85 °C	94

(102)

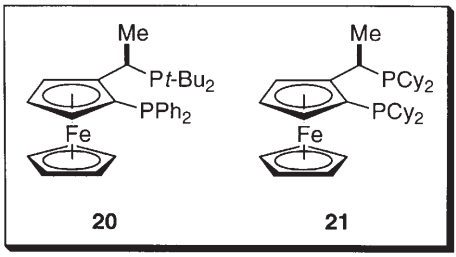
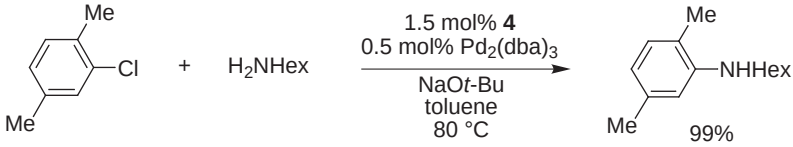


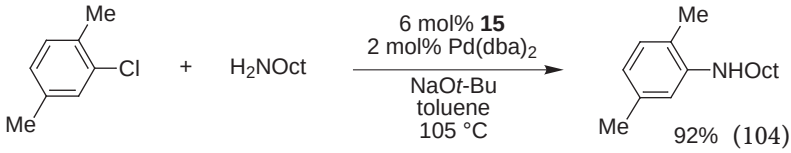
Fig. 19

Concurrently with this report from Hartwig, Buchwald and co-workers reported that the system based on commercially available ligand **4** is an excellent catalyst for the coupling of aryl chlorides and primary aliphatic amines, Eq. (103) [42].



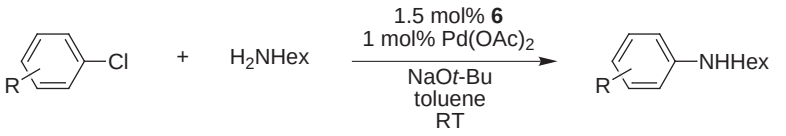
(103)

Phosphine **15**, developed by the Symyx group, can also mediate the C-N bond formation between an aryl chloride and a primary amine, Eq. (104) [47, 75].



(104)

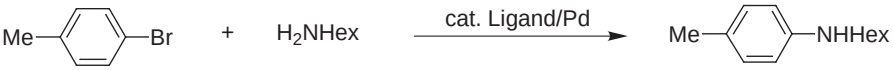
The catalyst formed from **6** and palladium acetate mediates the reaction between a large number primary amines and aryl chlorides as room temperature, Eq. (105) [42a, 48]. This catalyst enjoys an even wider substrate scope, however, when the transformation is performed at elevated temperatures. Additionally, elevated temperatures allow for the use of mild bases in the C-N bond forming reaction.



R	Yield, %
2,5-Me_2	98
o-OMe	99

(105)

Heterocyclic carbene ligands have also proven effective in the coupling of aryl chlorides and primary amines. While Nolan reported that the ligand based on **7** effects the desired reaction at elevated temperatures [52], Hartwig reported that the saturated ligand catalyzes the reaction at room temperature, Eq. (106) [76].

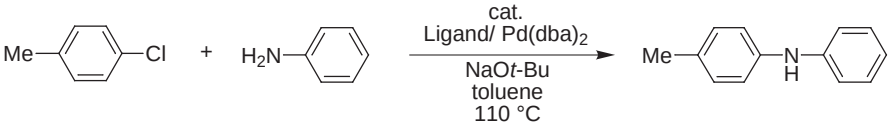


L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
7 (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	86
16 (2)	$Pd(dba)_2$ (2)	NaO*t*-Bu, DME, RT	40

(106)

2.3.5
Reaction of Primary Arylamines with Aryl Chlorides

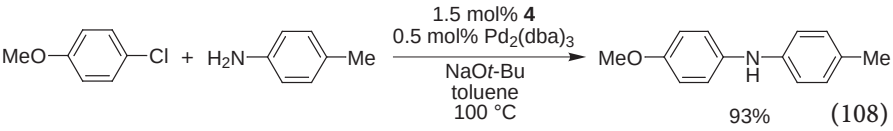
Hartwig reported that the ferrocene-derived phosphines **13**, **20**, and **21** are all effective as supporting ligands in the Pd-catalyzed reaction of aniline derivatives and aryl chlorides, Eq. (107) [72]. These bulky, electron-rich ligands allow for the desired C-N formation to be performed with as little as 1 mol% Pd.



Ligand (mol%)	mol% Pd	Yield, %
13 (4.5)	3	93
20 (1.5)	1	99
21 (3.0)	2	96

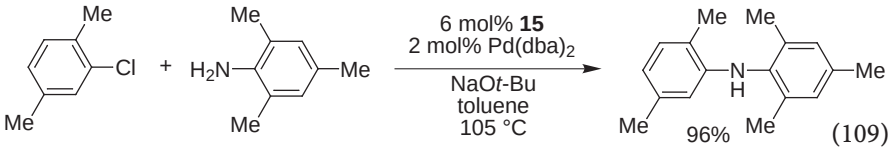
(107)

The catalyst derived from commercially available aminophosphine **4** is also mediates the desired reaction between chloroarenes and aniline derivatives, Eq. (108). Although the **4**/Pd-system is effective for many applications, the **14**/Pd-catalyst enjoys a similar substrate scope in the cross coupling reaction [42].



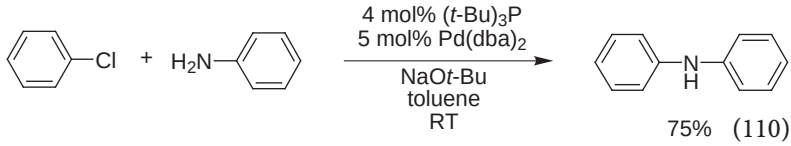
93% (108)

Guram's phosphine **15** proved to be an excellent supporting ligand for Pd in the coupling of arylamines and aryl chlorides [47, 75]. Reaction of the hindered aniline below with a **15**/Pd-catalyst provided the desired product in excellent yield, Eq. (109).



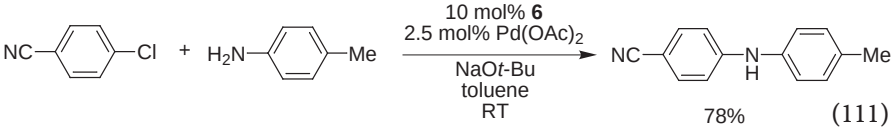
(109)

Hartwig reported that tri-*tert*-butylphosphine/Pd-catalysts mediate the coupling of aniline derivatives and aryl chlorides at room temperature, Eq. (110) [50]. Electron-deficient, electronically neutral, and electron-rich aryl chlorides were tolerated in the coupling reaction.



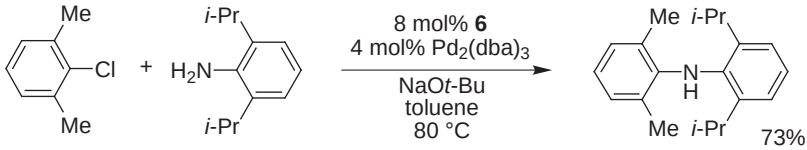
(110)

Bulky phosphine **6** also effects the desired cross coupling at room temperature for a wide variety of aryl bromides and arylamines, and at elevated temperatures, the substrate scope is greatly enhanced [42a,48].



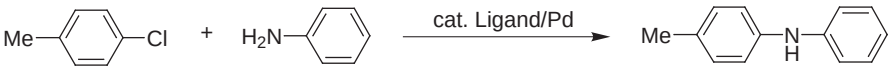
(111)

The high reactivity of the of the **6**/Pd-system is exemplified by the transformation depicted in Eq. 122. Despite the extreme steric demand of these two substrates, the desired product was obtained in 73 % yield [42a].



(112)

As was observed with primary aliphatic amines, the carbene-derived catalysts are able to effect the coupling of aniline derivatives with chloroarenes. The saturated carbene-based system reported by Hartwig provided the desired C-N bond formation product at room temperature, while the system described by Nolan required elevated temperatures [52, 76].

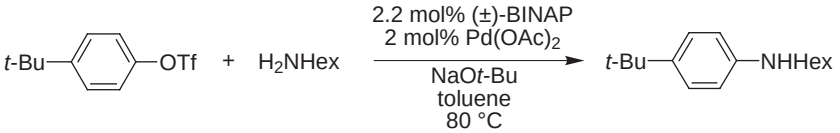


L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
7 (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	96
16 (2)	$Pd(dba)_2$ (2)	NaO*t*-Bu, DME, RT	82

(113)

2.3.6
Reaction of Primary Aliphatic Amines with Aryl Sulfonates

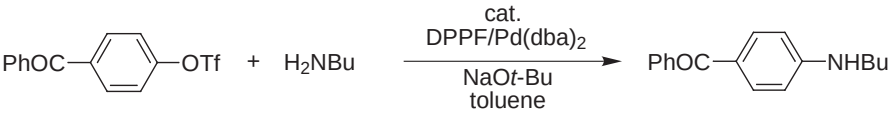
Wolfe and Buchwald reported that the arylation of aliphatic amines with aryl triflates could be effected with the BINAP/Pd-catalyst [80]. Triflate cleavage was a common side reaction, thus, slow addition of the aryl triflate often resulted in improved yields of the desired compound.



Reaction Conds.	Yield, %
Standard Conditions	55
Slow Addition of Triflate	65

(114)

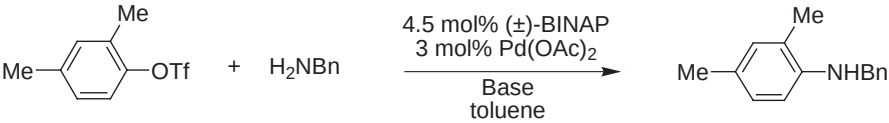
Simultaneously, Hartwig reported that the DPPF-based system also mediates the desired C-N bond formation [81]. The Yale group observed that slow addition of the aryl triflate often improved yield of the desired product, Eq. (115).



Reaction Conds.	Yield, %
Standard Conditions, 5 mol% Pd, 100 °C	57
Slow Addition of Triflate, 1.5 mol% Pd, 85 °C	63

(115)

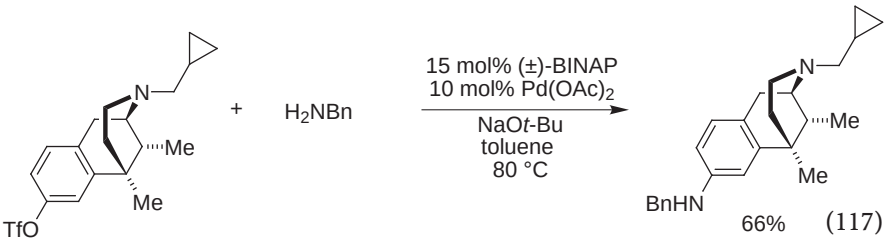
Wolfe and Buchwald susbsequently reported that by use of a milder base such as Cs_2CO_3 resulted in significant improvements in yield, particularly in the cases with electron-poor aryl triflates [82].



Base	Yield, %
NaO*t*-Bu	72
Cs_2CO_3	90

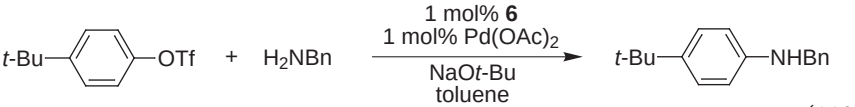
(116)

Wentland et al. utilized the BINAP/Pd-protocol to derivatize the opioid cyclazocine with several amines. For example, the desired aminated alkaloid was obtained in 66 % yield, Eq. (117) [84].



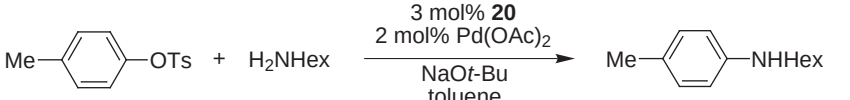
66% (117)

Catalysts based on bulky phosphine **6** effect the arylation of primary aliphatic amines with aryl triflates at room temperature, Eq. (118) [42a]. Substantial improvement in scope is observed when the reactions are performed at elevated temperatures with mild bases such as K_3PO_4; triflate cleavage is often less problematic under these conditions.



81% (118)

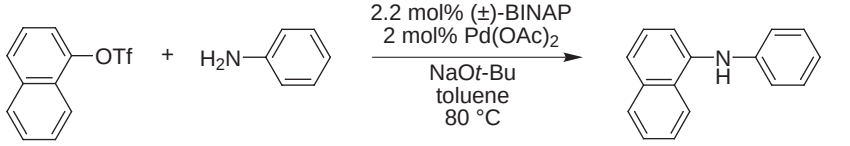
Hartwig reported the first amination of an aryl tosylate with an aliphatic amine. Utilizing electron-rich ferrocene-based ligand **20**, the coupling with hexylamine shown below proceeded in 83 % isolated yield, Eq. (119) [72].



83% (119)

2.3.7
Reaction of Primary Arylamines with Aryl Sulfonates

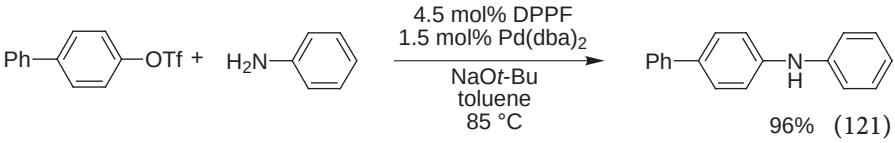
As was observed with aliphatic amines, slow addition of the aryl triflate to the aniline in the presence of the BINAP/Pd-catalyst often improved the yield of the desired product, Eq. (120) [80].



Reaction Conds.	Yield, %
Standard Conditions	61
Slow Addition of Triflate	68

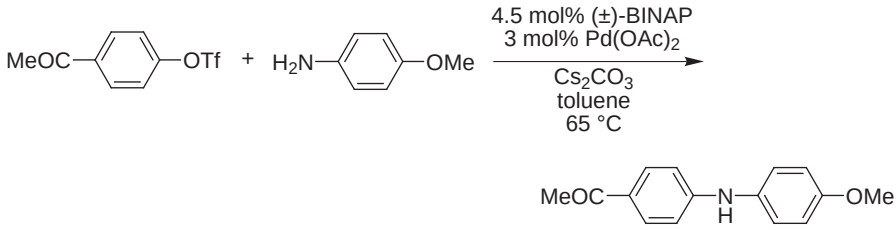
(120)

With the DPPF-based system, better yields of the C-N bond formation products were often obtained in the reaction of aryl triflats and anilines compared to the BINAP-catalysts, Eq. (121), however, triflate cleavage was still a significant side reaction when electron-poor aryl triflates were used [81].



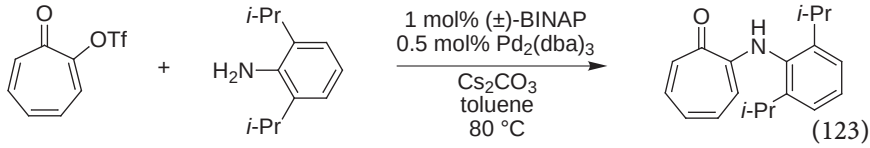
96% (121)

The Buchwald group revealed that the use of mild bases such as Cs_2CO_3 and K_3PO_4 helps minimize the amount of triflate cleavage [82], thus improving the yield of the arylation product, Eq. (122). In addition, functionality that is sensitive to NaO*t*-Bu is better tolerated when bases such as Cs_2CO_3 are used.



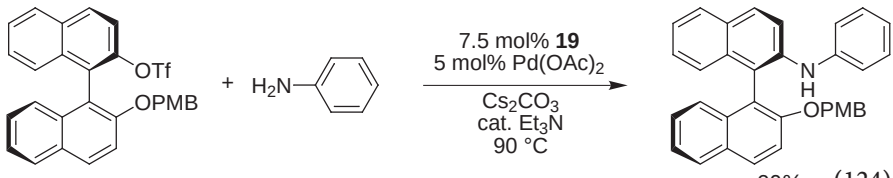
90% (122)

Hicks and Brookhart reported the amination of a tropolone triflate using the BINAP/Pd-catalyst as a strategy to prepare new ligand precursors [106]. For example, the coupling the sterically hindered 2,5-di*iso*-propylaniline proceeded in 86% isolated yield, Eq. (123).



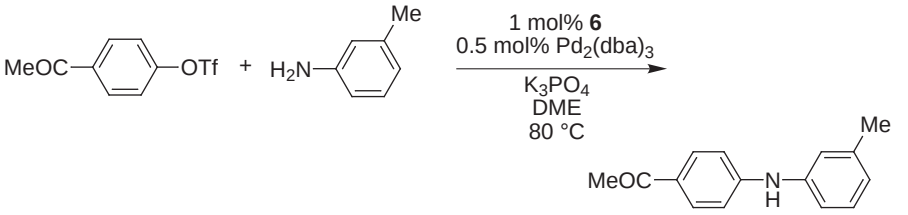
(123)

Singer and Buchwald found that the catalyst derived from DPEphos (**19**) was optimal for the arylation of the triflate derived from BINOL shown below, Eq. (124) [107]. Several useful chiral ligand building blocks were prepared in good to excellent yield.



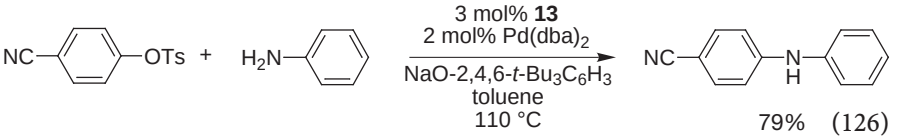
90% (124)

Bulky phosphine **6** affords an extremely active catalyst which is capable of effecting the C-N bond formation reaction between aryl triflates and aniline derivatives at room temperature [42a]. However, better yields, less triflate cleavage, and a wider substrate scope are observed when the reactions are performed with K_3PO_4 at elevated temperatures, Eq. (125).



91% (125)

Hartwig reported the first arylation of aniline using an aryl tosylate. The reaction was catalyzed by a **13**/Pd-catalyst, Eq. (126). Using a bulky base and elevated temperatures, the desired product was obtained in 78% yield [72].

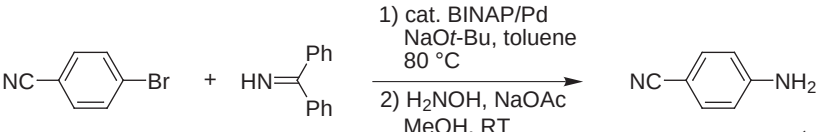


79% (126)

2.4 Arylation of Ammonia Equivalents

Since the use of ammonia in the palladium-catalyzed C-N bond formation reaction is not possible, it was desirable from a synthetic standpoint to develop a practical protocol for the installation of an ammonia equivalent. In 1997, Buchwald et al. reported that commercially available benzophenone imine is useful for such a purpose [108]. This reactant may be coupled with a large variety of aryl halides and triflates to furnish the desired product in good yields. The benzophenone moiety has the advantage that it can be removed via several different methods, allowing the synthetic chemist flexibility in the protecting group removal strategy. Imine removal may be effected by a transamination protocol (with excess hydroxylamine), by hydrogenolysis in the presence of a palladium catalyst, or by acidic hydrolysis.

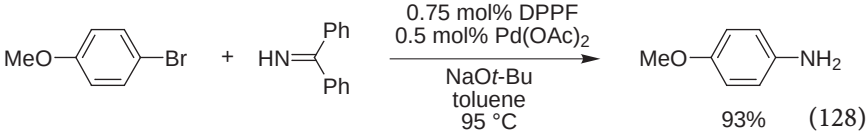
The reaction of benzophenone imine and an aryl bromide usually proceeds in excellent yield. For example, the transformation below is accomplished in 97% yield over both the coupling and deprotection steps, Eq. (127). Good yields are often observed with aryl iodides and triflates with the BINAP/Pd-catalyst as well.



97% (127)

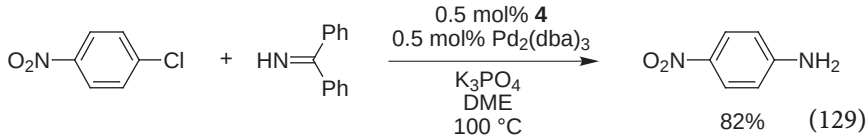
Representative Procedure for the Use of Benzophenone Imine as an Ammonia Equivalent: (Excerpted with permission from [108]. © 1996 Pergamon Press) A Schlenk tube was charged with sodium *tert*-butoxide (1.4 mmol), $Pd_2(dba)_3$ (0.00125 mmol), and BINAP (0.00375 mmol). The Schlenk tube was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (4 ml), 4-*tert*-butylbromobenzene (1.0 mmol), and benzophenone imine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (40 ml), filtered, and concentrated. The crude reaction mixture was then recrystallized from MeOH to furnish the desired product in 90 % yield.

The DPPF-catalyst system is also useful in the arylation of the benzophenone-based ammonia equivalent [109]. The coupling of 4-bromoanisole and benzophenone imine proceeded in excellent yield with only 0.5 mol% palladium, Eq. (128).



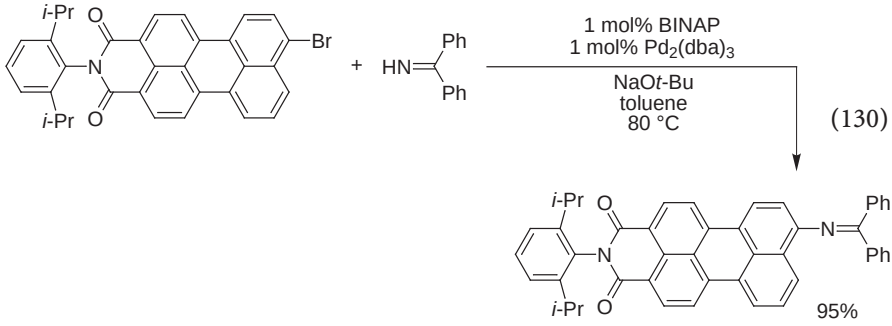
(128)

Aminophosphine **4** has been reported to effect the coupling of benzophenone imine and an electron-poor aryl chloride, Eq. (129) [42a]. Hartwig also reported that the system derived from heterocycle **17** is sufficiently reactive to effect a similar transformation [76].



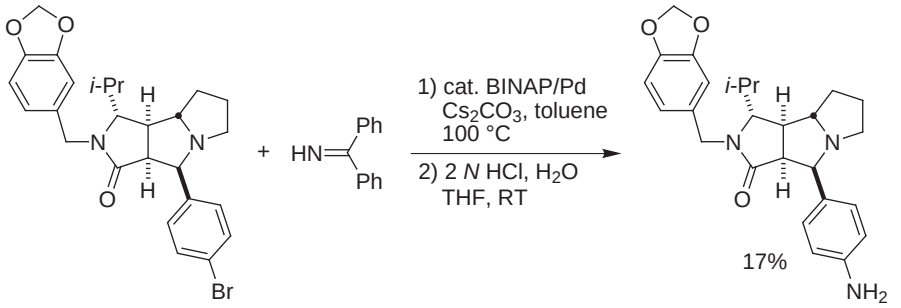
(129)

Several groups have utilized benzophenone imine as an ammonia equivalent in the palladium-catalyzed cross coupling. For example, Müllen and co-workers prepared a new thermotropic dye via the BINAP/Pd-coupling of the corresponding bromide, Eq. (130) [110]. Similarly, Basu reported the amination of a mixture of bromopyrene derivatives [111].



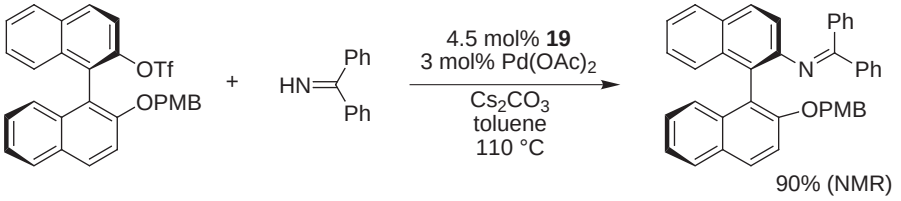
(130)

Diederich et al. prepared the highly functionalized thrombin inhibitor below using the Pd-catalyzed reaction [112]. The desired product was obtained in 17% yield over two steps.



(131)

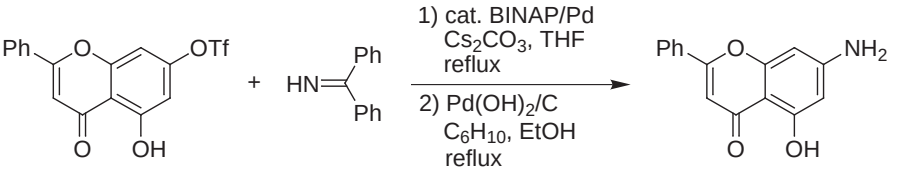
Aryl triflates are also good substrates for the benzophenone imine coupling reaction. For example, Singer and Buchwald prepared the desired amino-BINOL precursor in 87% yield after acidic hydrolysis; the amination itself proceeded in 90% NMR yield when DPEphos (**19**) was used as the supporting ligand, Eq. (132) [107].



90% (NMR)

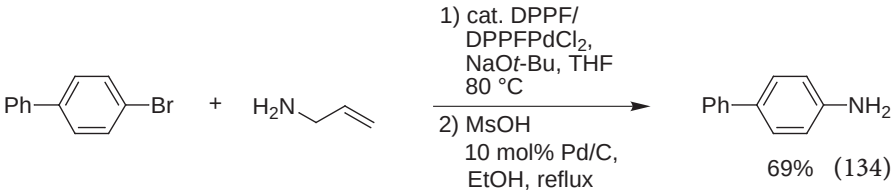
(132)

Similarly, Lemière utilized the Pd/BINAP-protocol to prepare the amino-flavone below in 50% yield over two steps from the corresponding triflate, Eq. (133) [113].



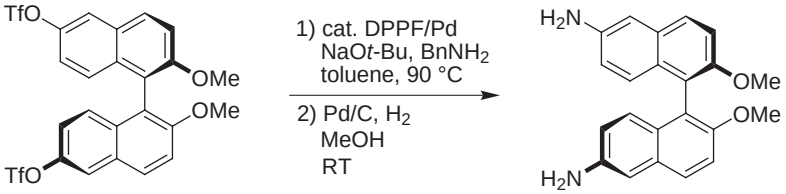
50% (133)

Putnam reported that allylamines may also be used as ammonia equivalents in the Pd-catalyzed coupling reaction [114]. The desired C-N formation was effected with the DPPF/Pd-catalyst; subsequent cleavage of the allyl group was achieved by treatment with methanesulfonic acid in the presence of a Pd/C catalyst, Eq. (134).



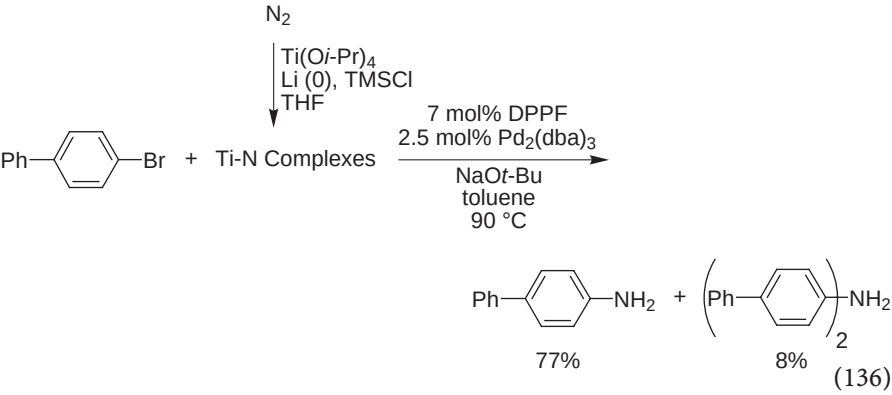
69% (134)

Lee described a strategy where benzylamine could be used as an ammonia equivalent as well [90]. The double reaction of the ditriflate below, followed by hydrogenolysis, furnished the desired ligand precursor in 69% yield over two steps, Eq. (135). The diamine product was also produced by double amination of the corresponding dibromide.



69% (135)

Mori reported that Ti-N complexes obtained from N_2 fixation could be utilized to prepare aniline derivatives via the Pd-catalyzed cross-coupling [115]. The complexes obtained from the reaction of dinitrogen with a mixture of lithium metal, $Ti(O\textit{i}\text{-}Pr)_4$, and TMSCl served as an effective ammonia equivalent to produce the desired aniline derivative after workup, Eq. (136). Thus, with this system, the removal of any nitrogen protecting group was obviated.

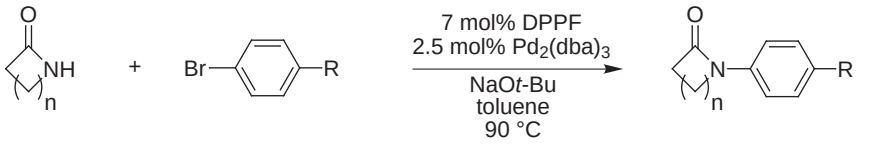


77% 8% (136)

2.5
Arylation of Amides and Carbamates

The coupling of amides and aryl halides or sulfonates is a highly desirable transformation since amides are ubiquitous in biologically active compounds. The arylation of amides however, is considerably different from the analogous reactions of amines since their pKas, and thus their relative reactivities, are considerably different.

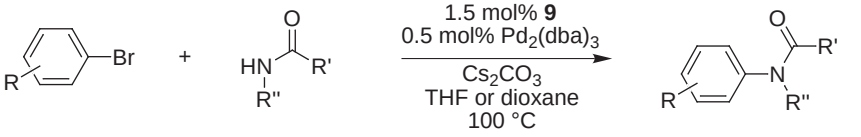
Shakespeare reported the first Pd-catalyzed arylation of an amide [116]. Specifically, he investigated the coupling of lactams and aryl bromides using a DPPF/Pd-protocol, Eq. (137). Significant generality was observed in the coupling of 2-pyrrolidone, however, with both larger and smaller ring sizes, good yields were only observed with electron-poor aryl bromides.



n	R	Yield, %
1	H	20
1	CF_3	52
2	H	82
2	CF_3	90
3	COPh	89

(137)

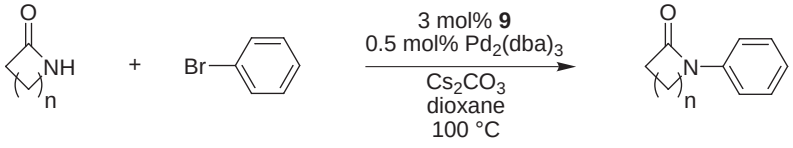
Yin and Buchwald reported that the catalyst based on Xantphos (**9**) as a supporting ligand is an effective and general system for the arylation of amides [117]. Using Cs_2CO_3 as base, aryl bromides possessing electron-withdrawing and electronically neutral groups were effectively coupled, Eq. (138). Both primary and secondary amides cleanly afforded the desired products.



R	R'	R''	Yield, %
p-CN	Ph	H	93
p-CN	Me	Me	97
o-CO_2Me	Ph	H	91
m-CO_2Me	Ph	H	90

(138)

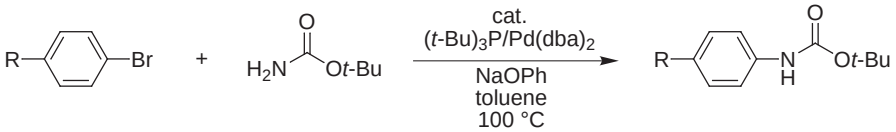
Lactams were also excellent substrates in the arylation reaction using **9**/Pd-catalysts. Notably, the coupling of a β-lactam (n = 1) and bromobenzene afforded the desired product in 93% yield, Eq. (139) [117].



n	Yield, %
1	93
2	96
3	92
4	90

(139)

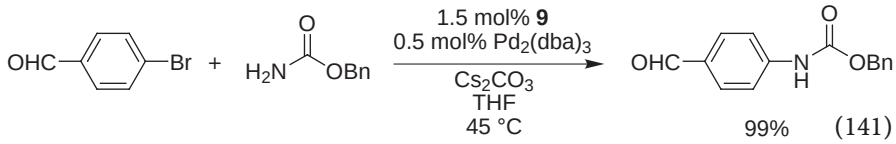
Hartwig reported the first arylation of carbamates utilizing a (*t*-Bu)$_3$P/Pd-catalyst [50]. Aryl bromides bearing electron-withdrawing groups are excellent substrates for the reaction, however, increasing electron density on the aryl bromide results in moderate yields of the desired amide, Eq. (140).



R	Reaction Conds.	Yield, %
Me	5 mol% (*t*-Bu)$_3$P, 2.5 mol% Pd(dba)$_2$	80
CN	5 mol% (*t*-Bu)$_3$P, 2.5 mol% Pd(dba)$_2$	83
OMe	8 mol% (*t*-Bu)$_3$P, 4 mol% Pd(dba)$_2$	62

(140)

The Xantphos (**9**)/Pd-system also mediates the coupling of aryl bromides and carbamates [117]. The coupling of benzyl carbamate below proceeds in quantitative yield when Cs_2CO_3 is used as base, Eq. (141).

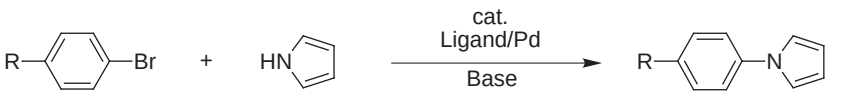


(141)

2.6 Arylation of Nitrogen-Containing Heterocycles

Nitrogen-containing heterocycles are interesting substrates for the amine arylation reaction since many pharmaceuticals possess such functionality. The arylation of such a species is not always straightforward, however, since their pKas are considerably different from simple amines. In addition, some heterocycles, such as indoles, are able to go unwanted side reactions.

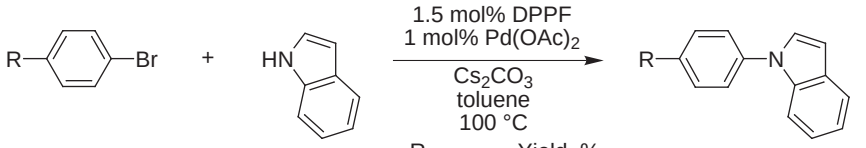
Hartwig first reported the use of the pyrrole in the arylation reaction. Use of a DPPF/Pd-catalyst afforded the desired products in moderate to good yield [109]. Subsequently, the Yale group disclosed that a (*t*-Bu)$_3$P/Pd-catalyst is able to effect the reaction in comparable yields with lower catalyst loadings [50]. Similarly, the Tosoh group reported that Rb_2CO_3 is a more efficient base using the (*t*-Bu)$_3$P/Pd-catalyst under their conditions [118].



R	Reaction Conds.	Yield, %
t-Bu	6 mol% DPPF, 5 mol% $Pd(OAc)_2$, NaO*t*-Bu, 120 °C	87
H	3 mol% $(t\text{-Bu})_3P$, 3 mol% $Pd(dba)_2$, Cs_2CO_3, 100 °C	77
Me	3 mol% $(t\text{-Bu})_3P$, 1 mol% $Pd(OAc)_2$, Rb_2CO_3, 120 °C	70

(142)

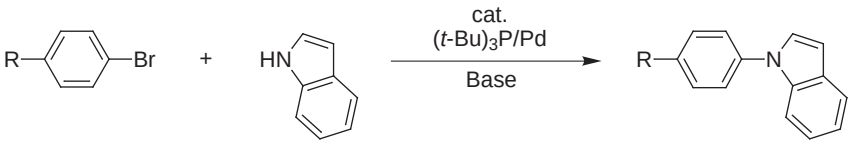
In 1998, Hartwig also described the arylation of indoles using Pd catalysis [109]. With the DPPF/Pd-system, good to excellent yields of the desired product was obtained with electron-deficient aryl bromides.



R	Yield, %
CN	98
Ph	72

(143)

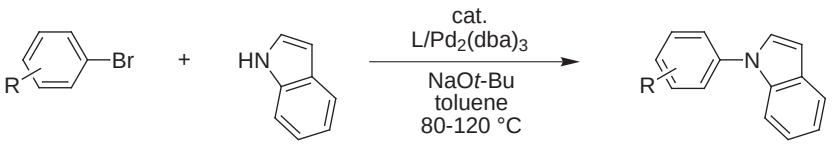
The use of $(t\text{-Bu})_3P$/Pd-catalysts in the arylation of indoles has been reported by both the Hartwig and Watanabe groups [50,118]. Moderate to good yields are observed in the coupling reactions, however, side products resulting from *C*-arylation at the 3-position are commonly isolated as well. Similarly, both groups reported the arylation of carbazoles as well.



R	Reaction Conds.	Yield, %
OMe	3 mol% L, 3 mol% $Pd(dba)_2$, Cs_2CO_3, 100 °C	77
H	3 mol% L, 1 mol% $Pd(OAc)_2$, Rb_2CO_3, 120 °C	70

(144)

Old, Harris, and Buchwald investigated the arylation of indoles and found a very strong dependence of the reaction efficiency on the supporting ligand used [119]. Specifically, it was observed that *C*-arylation was problematic when aryl bromides possessing electron-donating groups or *ortho*-substituents were subjected to the Pd-catalyzed coupling. For example, while aminophosphine **4** was useful in the reaction of 4-bromotoluene, related ligand **22** proved optimal in the coupling of electron-rich aryl bromides such as 4-bromoanisole. Binaphthyl-derived ligand **23** is useful in the coupling of *ortho*-substituted aryl bromides, Eq. (145).



R	Reaction Conds.	Yield, %
p-Me	3.75 mol% **4**, 1.25 mol% $Pd_2(dba)_3$	88
p-OMe	1.5 mol% **22**, 0.5 mol% $Pd_2(dba)_3$	84
3,5-Me_2	7.5 mol% **23**, 2.5 mol% $Pd_2(dba)_3$	87

(145)

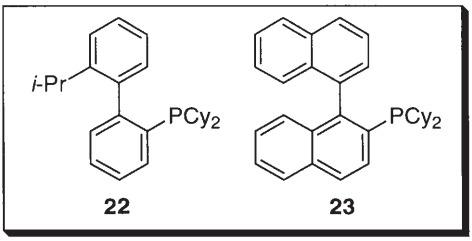
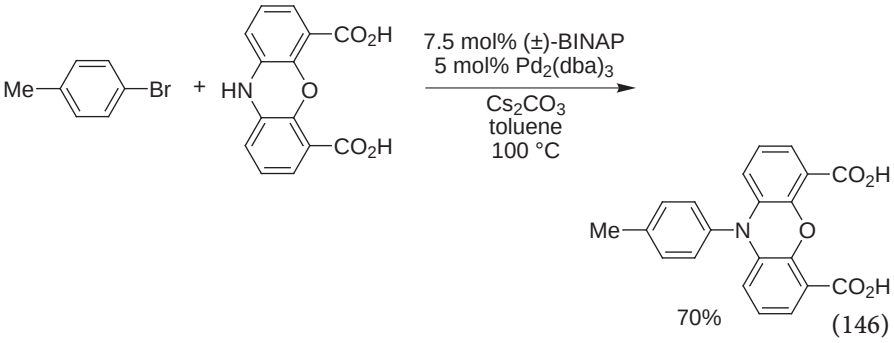


Fig. 20

General Procedure for the N-Arylation of Indoles: (Excerpted with permission from [119]. © 2000 American Chemical Society) A Schlenk tube was charged with sodium *tert*-butoxide (1.4 mmol), $Pd_2(dba)_3$ (0.005 mmol), and **4** (0.015 mmol). The Schlenk tube was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2 ml), aryl bromide (1.0 mmol), and the indole (1.2 mmol) were added. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 – 100 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (20 ml), filtered, and concentrated. The crude reaction mixture was then purified by flash chromatography on silica gel.

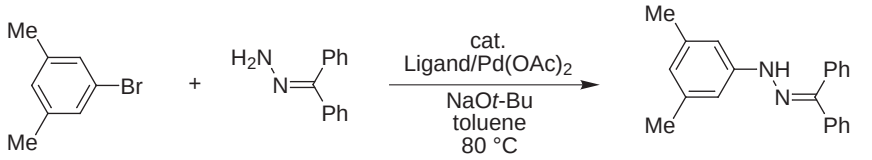
Kelly reported the preparation of several transthyretin amyloid fibril inhibitors using the BINAP/Pd-catalyzed coupling [120]. For example, the coupling below furnished the desired phenoxazine derivative in 70 % isolated yield, Eq. (146).



(146)

2.7
Arylation of Other Nitrogen Substrates

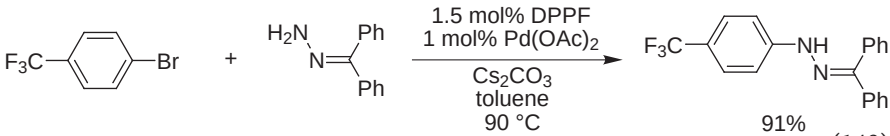
In 1998, the Buchwald group reported the arylation of benzophenone hydrazone with several aryl bromides [121]. The desired reaction could be effected with the BINAP/Pd-catalyst, however, the Xantphos/Pd-system proved particularly well-suited for this transformation, Eq. (147).



Catalyst (mol%)	Yield, %
(*S*)-BINAP/Pd(OAc)$_2$ (1)	87
9/Pd(OAc)$_2$ (0.1)	98

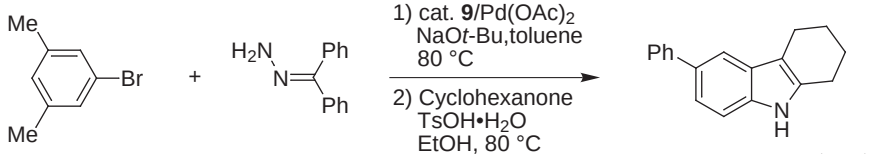
(147)

Concurrently with the report by Buchwald, Hartwig described a similar reaction using the DPPF/Pd-based protocol [122]. The C-N bond coupling proceeded in good to excellent yield with 1 mol% Pd, Eq. (148).



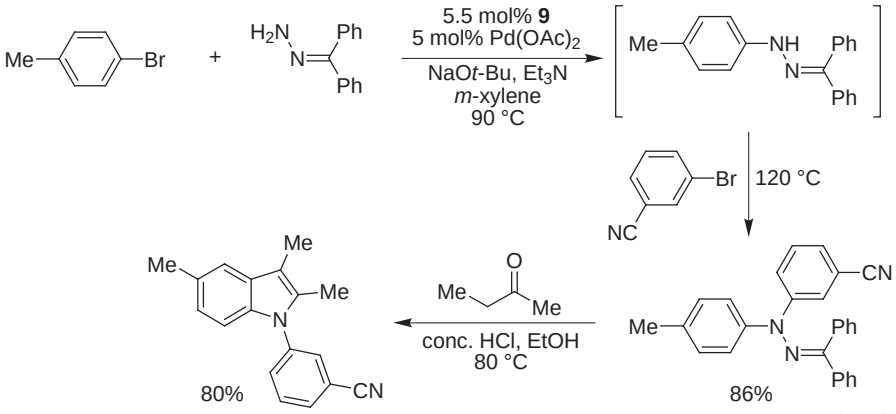
91% (148)

The Buchwald group exploited the Pd-catalyzed hydrazone synthesis for the efficient preparation of indoles. While removal of the benzophenone moiety and isolation of the free hydrazine did not proceed cleanly, the MIT workers found that Fischer indole synthesis could be effected by *in situ* exchange of the ketone group. The desired indoles could thus be isolated in good to excellent yield over two steps, Eq. (149) [121].



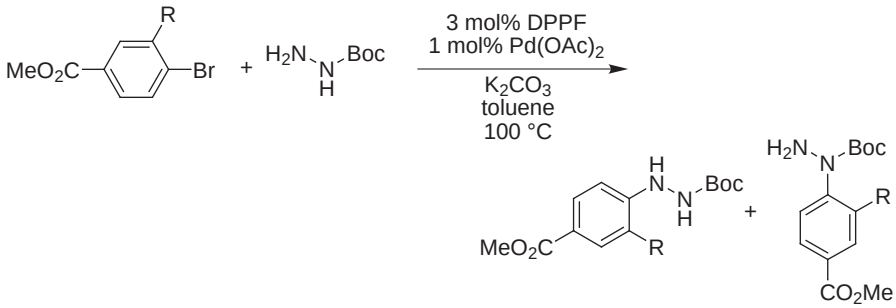
92% (149)

N-Arylindoles could be prepared via a one-pot sequential arylation of benzophenone hydrazone. For example, after the first C-N bond coupling with the less reactive aryl bromide was performed with the **9**/Pd-catalyst; after complete reaction, the second aryl bromide was then introduced to the reaction mixture, Eq. (150) [121]. The doubly arylated product could be cyclized to yield the desired *N*-arylindole in moderate to good yield.



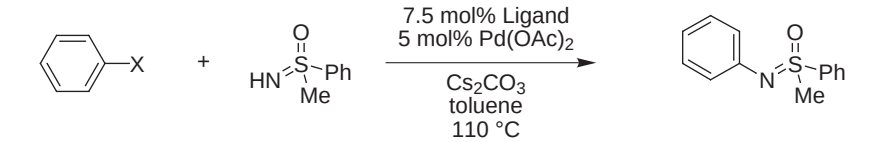
(150)

Skerjl reported that *tert*-butylcarbazate could be regioselectively arylated with the DPPF/Pd-catalyst [123]. When aryl bromides possessing *ortho*-substituents were used, reaction at the less hindered nitrogen was observed, Eq. (151). However, in the absence of *ortho* substitution, the arylation proceeded on the Boc-protected nitrogen.



(151)

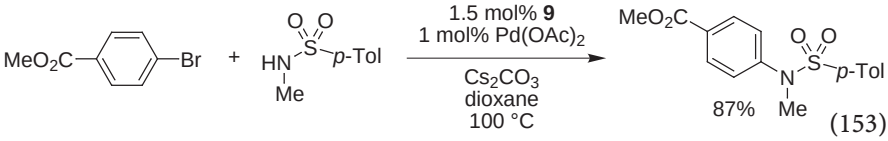
Bolm and co-workers have described the arylation of sulfoximes with aryl bromides, iodides, triflates, and nonaflates [124]. The BINAP/Pd-catalyzed transformation proceeds in moderate to excellent yields, Eq. (152). The resulting *N*-arylsulfoximines were used to prepare new chiral ligands. Harmata and Pavri have used similar transformations to prepare several benzothiazines [125].



X	Ligand	Yield, %
Br	tolBINAP	83
OTf	BINAP	51

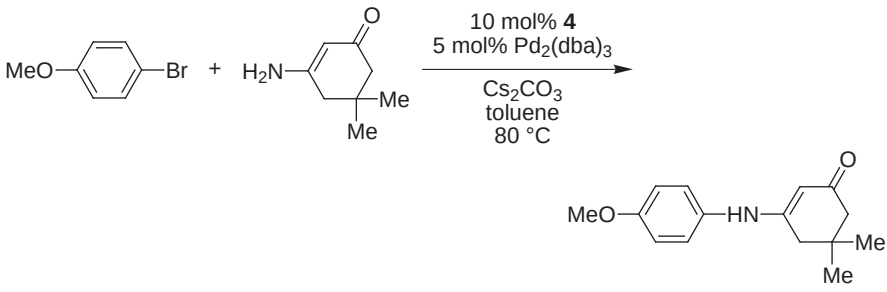
(152)

Yin and Buchwald found that Xantphos (**9**) was the most effective supporting ligand for the arylation of sulfonamides, Eq. (153). Primary and secondary sulfonamides were efficiently reacted under these conditions [117].



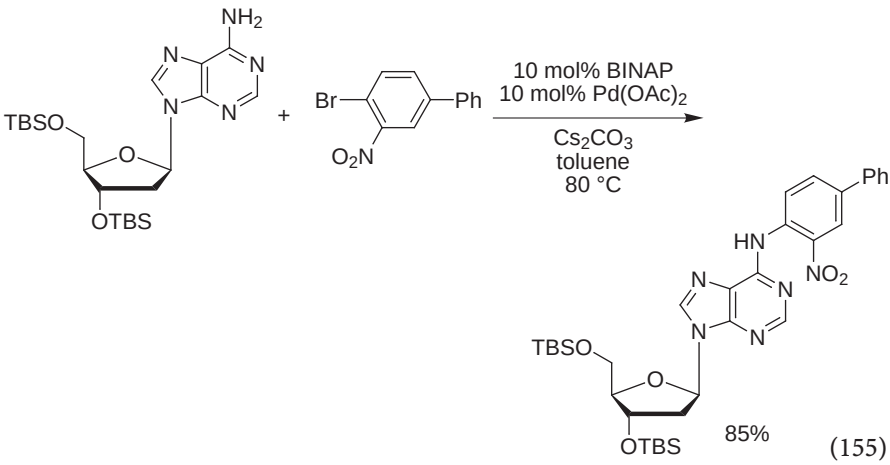
(153)

Several aryl bromides were coupled with the vinylogous amide below in moderate to excellent yields by Edmonson et al., Eq. (154) [126]. The Merck investigators also reported that this C-N bond forming reaction could be exploited to prepare quinoline and indole derivatives.



(154)

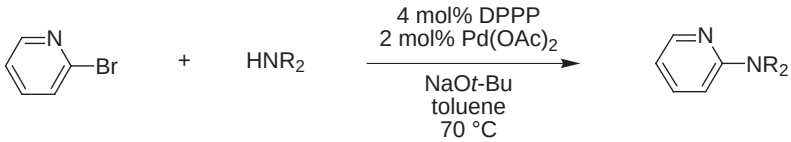
Johnson described the preparation of several 2′-deoxyadenosine and guanosine amine adducts that have been implicated in carcinogenesis via the Pd-catalyzed coupling [127]. The TBS-protected purine derivatives were reacted with several aryl bromides and triflates in good yield using a BINAP/Pd-catalyst and Cs_2CO_3 as base, Eq. (155).



(155)

2.8
Heteroaryl Halides in the Pd-Catalyzed Amine Arylation

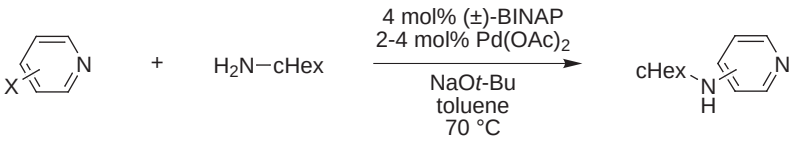
The use of heteroaryl halides in the Pd-catalyzed C-N coupling would be useful to the pharmaceutical chemist since heterocycles are commonly found in biologically active agents. Wagaw and Buchwald first investigated the amination of halopyridines and found that the original $(o\text{-tol})_3P$/Pd-protocols were ineffective [128]. By using bis(1,3-diphenylphosphino)propane (dppp) as a supporting ligand, however, the coupling of bromopyridine with several amines could be effected in good yield, Eq. (156).



Amine	Yield, %
H-N(Me)Bn	85
Morpholine	87

(156)

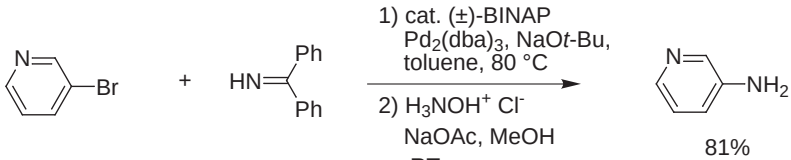
BINAP also proved useful in the C-N bond coupling reactions involving halopyridines [128]. For example, the coupling of primary amines with chloro- and bromopyridines could be performed with the (±)-BINAP/Pd-catalyst in good yield, Eq. (157).



X	Yield, %
2-Cl	73
3-Br	82

(157)

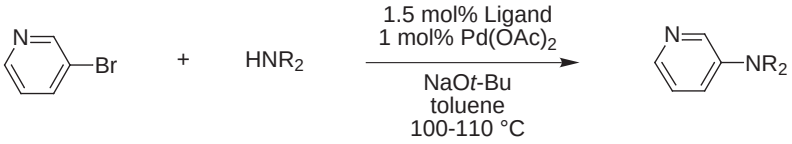
Benzophenone imine may be used as an ammonia equivalent with halopyridines as well. The coupling of the bromopyridine below, followed by deprotection via transamination with hydroxylamine, proceeded in 81% yield over the two steps, Eq. (158) [128]. Analogously, Puttman found that allylamine could also be used as an ammonia equivalent in the C-N coupling reactions of halopyridines [114].



81%

(158)

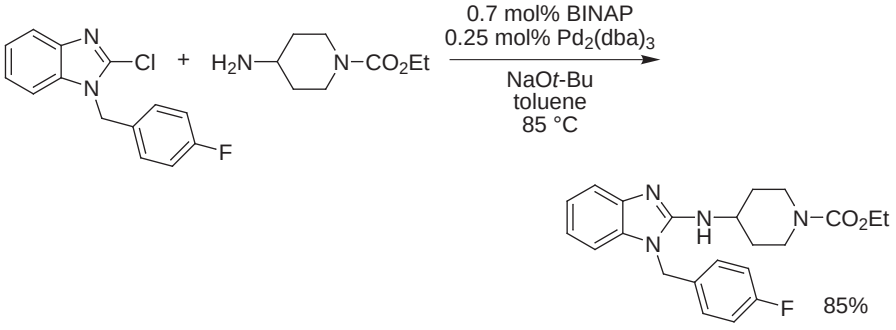
Sterically hindered monophosphines may also be used as supporting ligands in the amination of halopyridines. Commercially available ligands **4** and **6** allow for the desired reaction to proceed in good to excellent yield, Eq. (159) [42].



Amine	Ligand	Yield, %
H-N(Me)Ph	**4**	94
H_2NBn	**6**	86

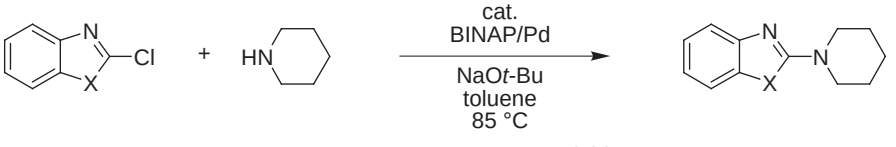
(159)

Other heteroaryl halides may be used in the Pd-catalyzed cross coupling reaction. Senanayake and co-workers reported the reaction of a chlorobenzimidazole and a primary amine to synthesize the antihistamine norastemizol [34, 87]. The key Pd-catalyzed coupling reaction proceeded in 85% isolated yield using 0.5 mol% Pd, Eq. (160). During these investigations, the Sepracor group also noted that primary amines reacted preferentially over secondary amines.



(160)

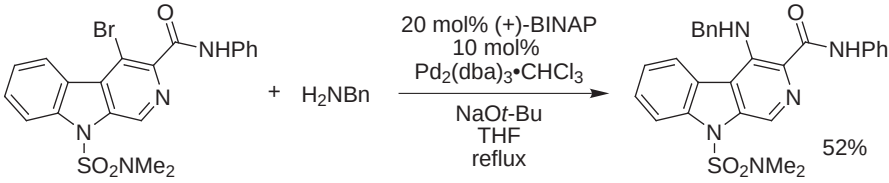
Senanayake also demonstrated that the amination reaction could be effected with several related heteroaryl chlorides [34, 87]. The coupling of piperidine with several heteroarene substrates proceeded in good yield, Eq. (161).



X	Yield, %
O	66
S	78
$NCH_2(4\text{-}F\text{-}C_6H_4)$	71

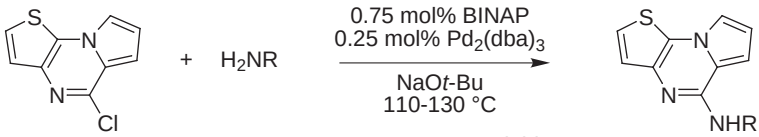
(161)

In 1998, Dodd reported the amination of the β-carboline-carboxylic amide below using the BINAP/Pd-protocol, Eq. (162) [129]. The desired product was obtained in 52 % yield.



(162)

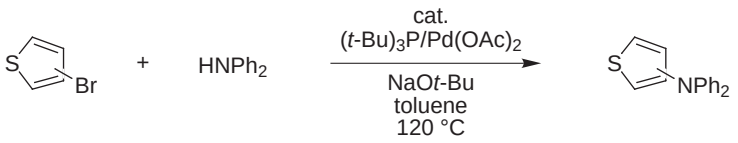
Rouden described the amination of the heteroaryl chloride below with several primary amines using the BINAP/Pd-catalyst, Eq. (163) [130]. The resulting products were new ligands for serotoninergic receptors.



R	Yield, %
n-Hexyl	94
tert-Butyl	65

(163)

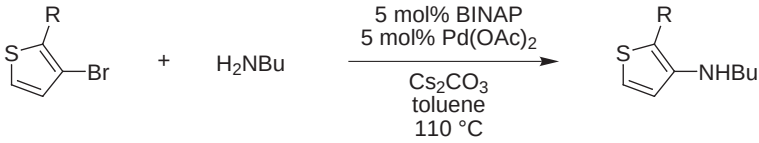
The Tosoh group described the first amination of bromothiophenes with a (t-Bu)$_3$P/Pd-based system [131]. The reactions between several bromothiophenes and diphenylamine proceeded with moderate yields, Eq. (164).



Substitution	Yield, %
3	69
2	36

(164)

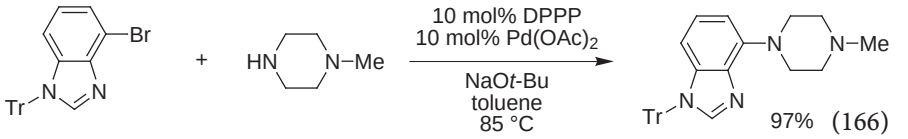
Luker et al. subsequently investigated the use of electron-deficient thiophenes in the C-N bond forming reaction [132]. Using a BINAP/Pd-catalyst, the Nottingham group reported that the desired transformations proceed in good to excellent yield with several primary and secondary amines, Eq. (165).



R	Yield, %
CO_2Me	94
CN	89

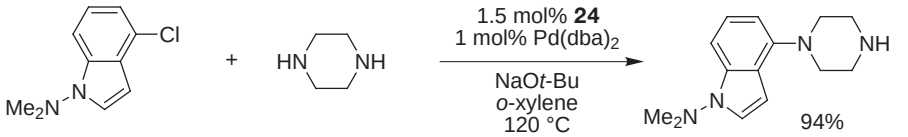
(165)

López-Rodriguez and co-workers prepared a number of serotonin 5-HT_{1A} receptor ligands using palladium catalysis [133]. The Spanish group used both DPPP- and BINAP-based systems to couple bromine-substituted benzimidazoles with piperazines. For example, the reaction of the protected heterocycle below with *N*-methylpiperazine proceeds in excellent yield, Eq. (166).



(166)

Watanabe's group at Tosoh Corporation reported the coupling of a chlorine-substituted indole and piperazine using a **24**/Pd-based catalyst, Eq. (167) [134]. The indole substrate, which was prepare via a novel palladium-catalyzed cyclization, was aminated in 94% yield.



(167)

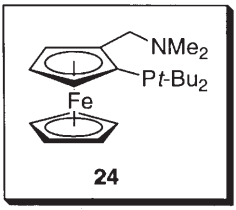
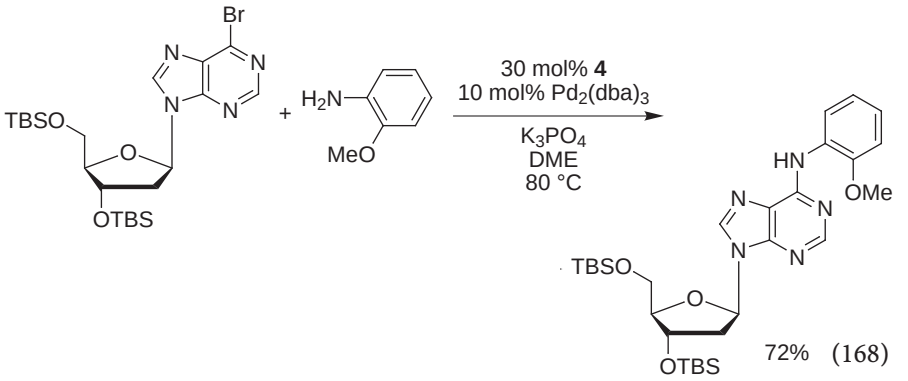


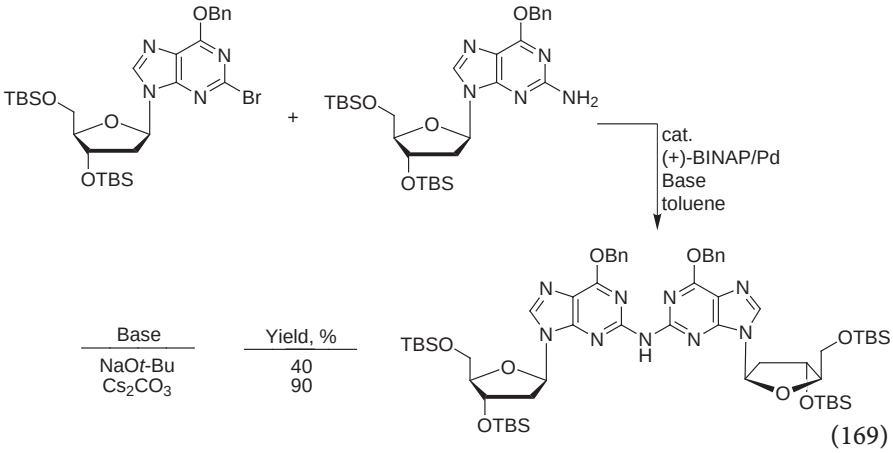
Fig. 21

Several 2′-deoxyadenosine-amine adducts that have been implicated in carcinogenesis were prepared via the Pd-catalyzed amine arylation reaction as reported by Lakshman and co-coworkers [135]. For example, the coupling of the protected 6-bromoadenosine derivative below was achieved in good yield using the **4**/Pd-catalyst, Eq. (168).



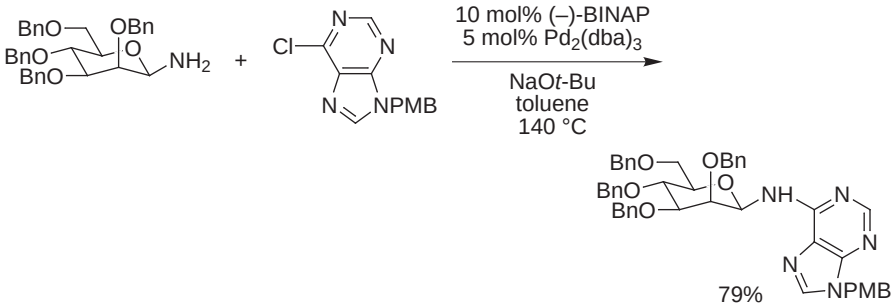
(168)

Crosslinked nucleosides have been similarly prepared by two different groups. While Sigurdsson and Hopkins performed the dimerization below with the BINAP/Pd-catalyst, in the presence of NaO*t*-Bu to isolate the desired product in 40% yield, Johnson found that when Cs_2CO_3 was used as base, the dimer was obtained in 90% yield, Eq. (169) [136].



(169)

Glycosylamines have been coupled to 6-halopurines using the BINAP/Pd-system. Chida and co-workers performed these reaction as a model study towards the synthesis of spicamycin and septacidin antitumor agents [137]. The coupling of the mannose derivative below was achieved at elevated temperatures in a sealed tube to furnish the desired C-N bond formation product in 79% yield, Eq. (170).



(170)

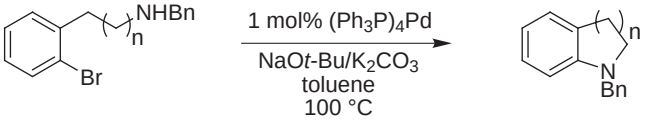
2.9
Intramolecular Arylation of Amines and Amides

2.9.1
Intramolecular Arylation of Amines

More than 15 years ago, Boger reported an intramolecular amine arylation using stoichiometric quantities of palladium. In 1997, the Buchwald group investigated catalytic variants of the cyclization [138]. Initial studies involved the *in situ*

generation of the aminostannane previously described for intermolecular reactions, however, tin-free methods were soon discovered.

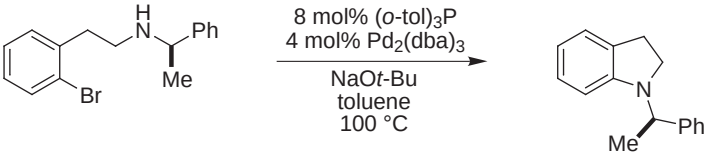
The intramolecular C-N bond forming reactions proved to be more straightforward than their intermolecular counterparts [138]. The desired couplings often could be achieved using $(Ph_3P)_4Pd$ as catalyst to form 5-, 6-, and 7-membered nitrogen heterocycles, Eq. (171).



n	Yield, %
1	87
2	72
3	61

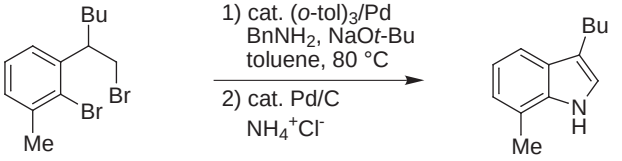
(171)

Unlike the intermolecular variants, the intramolecular amine arylation of α-chiral substrates proceeded without racemization when the reaction was performed with the $(o\text{-tol})_3P$/Pd-catalyst, Eq. (172) [54].



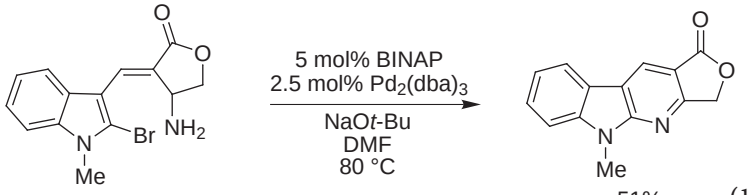
96% ee — 80% y, 96% ee (172)

An alternative indole synthesis was reported by the Buchwald group where initial displacement of the primary bromide by benzylamine is followed by a Pd-catalyzed cyclization, Eq. (173) [139]. After deprotection, the desired indole was obtained in 54% yield over two steps.



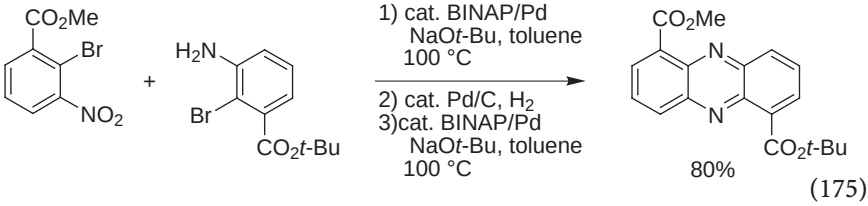
54% (173)

Dodd and Abouabdellah performed the cyclization below with a BINAP/Pd-catalyst to furnish, after air oxidation, the pyrido[2,3-b]indole in 51% yield, Eq. (174) [140].



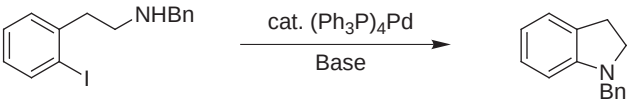
51% (174)

Kamikawa used two different Pd-catalyzed C-N bond-forming reactions for the convergent preparation of several phenazines [93]. After intermolecular coupling was achieved, the nitro group was reduced. Subsequent Pd-catalyzed cyclization afforded the desired product in 80% yield over three steps, Eq. (175).



(175)

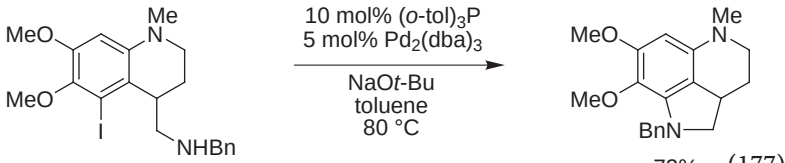
Aryl iodides could also be used in the intramolecular C-N bond coupling. Notably, cyclization could be achieved using triethylamine as base and solvent at room temperature in good yield with the iodide substrate, Eq. (176) [138].



Reaction Conds.	Yield, %
1 mol% cat., NaO*t*-Bu/K_2CO_3, toluene, 65 °C	96
5 mol% cat., Et_3N, RT	87

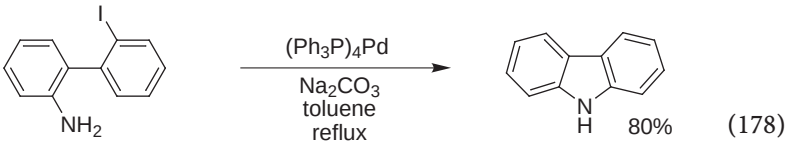
(176)

Exploiting the utility of this type of cylization, Peat and Buchwald described the formal synthesis of several alkaloids. Reaction of the aminoiodide below proceeded in 72% yield, Eq. (177) [141].



72% (177)

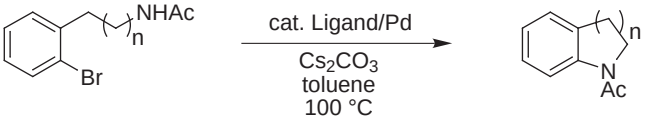
The cyclization below proceeded in 80% yield using stoichiometric quantities of palladium, similar to the report by Boger, Eq. (178) [15, 142]. Wood reported that efforts to render this reaction catalytic in Pd (5 mol%) resulted in only 60% conversion after 5 days.



(178)

2.9.2
Intramolecular Arylation of Amides

Initial studies on the intramolecular arylation of amides revealed that tri(2-furyl)-phosphine was an effective supporting ligand for the cyclization of substrates that furnish five-membered rings, Eq. (179) [138]. The analogous reaction to prepare the six-membered ring product was considerably less efficient, however, providing the quinoline derivative in 44% yield. Subsequent studies by Yang and Buchwald found that several different catalyst systems were more efficient than the original one reported [143]. Specifically, the catalyst derived from MOP (**25**) and $Pd(OAc)_2$ proved particularly effective and formed the same six-membered ring in 87% yield using only 3.3 mol% Pd. Cyclization to the seven-membered ring could best be effected using Xantphos (**9**) as ligand.



n	Reaction Conds.	Yield, %
1	20 mol% (2-furyl)$_3$P, 10% $Pd_2(dba)_3$	99
2	20 mol% (2-furyl)$_3$P, 10% $Pd_2(dba)_3$	44
2	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$	87
3	5 mol% **9**, 3.3 mol% $Pd(OAc)_2$	90

(179)

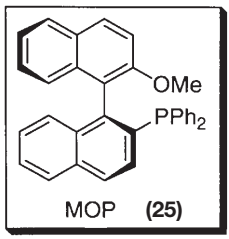
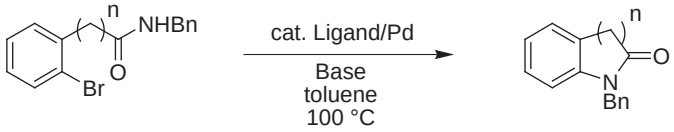


Fig. 22

The synthesis of lactams could also be performed by the (*o*-tol)$_3$P/Pd-system, however, high catalyst loadings were required, Eq. (180) [138]. Yang and

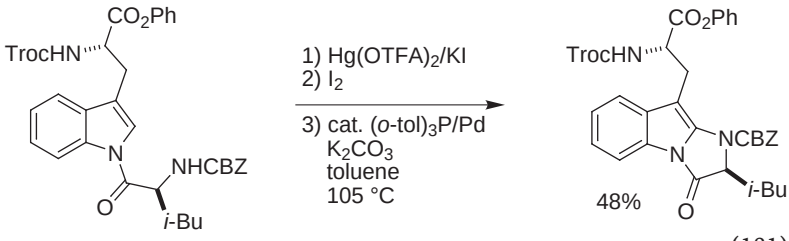


(180)

n	Reaction conds.	Yield, %
1	20 mol% (*o*-tol)$_3$P, 10% $Pd_2(dba)_3$, K_2CO_3	59
2	20 mol% (*o*-tol)$_3$P, 10% $Pd_2(dba)_3$, K_2CO_3	82
1	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	82
2	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	94
3	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	88

Buchwald later showed that the same reaction could be more efficiently accomplished using a MOP (**25**)/Pd-catalyst [143]. In addition, the **25**/Pd-protocol allowed for the analogous cyclizations to be conducted with carbamate substrates.

Snider and co-workers executed a palladium-catalyzed carbamate cyclization as a key step in the synthesis of (–)-asperlicin [144]. The dipeptide below was converted to the desired intermediate in 48% yield over 3 steps without epimerization of the two stereocenters, Eq. (181).



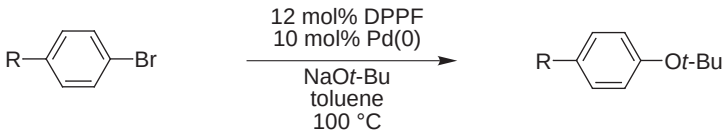
(181)

3
Palladium-Catalyzed Alcohol Arylation

3.1
Reaction of Aliphatic Alcohols

The arylation of aliphatic alcohols is particularly challenging because the competitive β-hydride elimination side reaction that was problematic in the amine arylation is even more prevalent in the analogous C-O bond forming reactions. Thus, the coupling of tertiary alcohols such as *tert*-butanol and aryl halides has seen considerable success, while general methods for the arylation of primary and secondary alcohols have been more elusive.

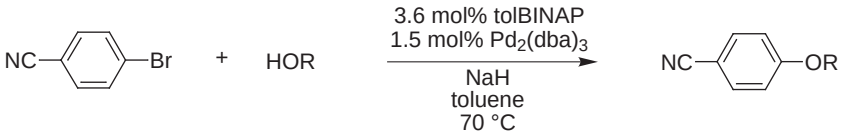
Hartwig first reported the arylation of *tert*-butanol in 1996 [145]. Using a DPPF/Pd-catalyst and NaO*t*-Bu as the *tert*-butoxy source, several electron-deficient aryl bromides were coupled in moderate yield, Eq. (182).



R	Yield, %
CHO	66
CN	58
COPh	69

(182)

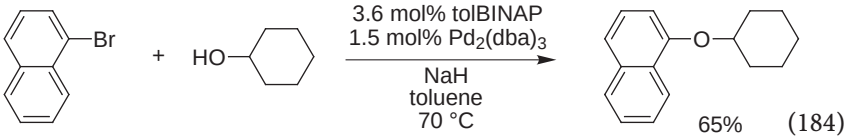
The reaction between aryl bromides and aliphatic alcohols bearing α-hydrogens was first described by Buchwald et al. using a tolBINAP/Pd-system [146]. Several primary and secondary alcohols were coupled with electron-deficient aryl bromides in moderate to good yield, Eq. (183).



R	Yield, %
Bn	71
Me	81

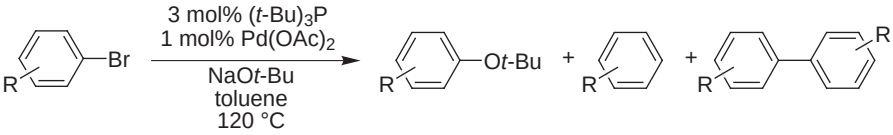
(183)

In limited cases, electronically neutral aryl bromides also served as good substrates in the Pd-catalyzed C-O bond formation with the tolBINAP/Pd-system. For example, 1-bromonaphthalene was coupled with cyclohexanol in 65% yield, Eq. (184).



(184)

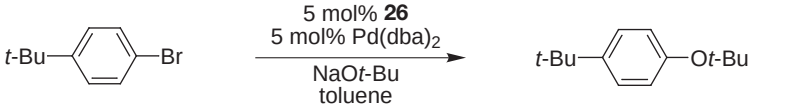
The Tosoh group reported that a $(t\text{-Bu})_3$P/Pd-catalyst allowed the preparation of *tert*-butyl ethers from the corresponding aryl bromides and NaO*t*-Bu [147]. Electron-withdrawing as well as electron-donating substituents were tolerated on the aryl bromide, although increased electron density on the aryl bromide results in greater amounts of reduced arene and biaryl side products, Eq. (185).



R	Ratio	Yield, %
4-CHO	99.5:0.5:0	91
4-*t*-Bu	94:4:2	85
3-OMe	70:26:4	82

(185)

Di-*tert*-butylferrocenylphosphine (**26**) is an excellent supporting ligand for the coupling of NaO*t*-Bu and aryl bromides (eq 186) [148]. During kinetic studies of this reaction, Hartwig and co-workers noted that a portion of the aryl halide was consumed prior to formation of the aryl ether product [149]. It was subsequently determined that ligand **26** was being arylated during the course of the reaction to yield a much more active catalyst system. Pentaphenylated ligand **27** could in fact be prepared from **26** and chlorobenzene via palladium catalysis in 85% yield.



(186)

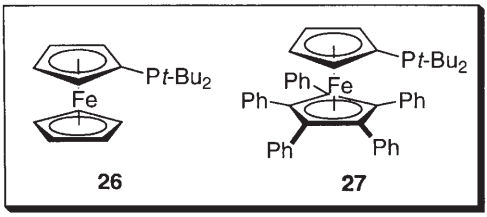
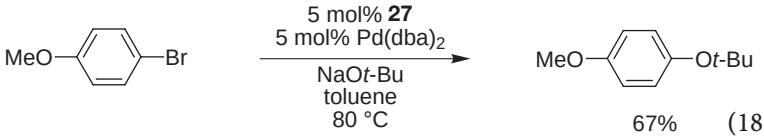


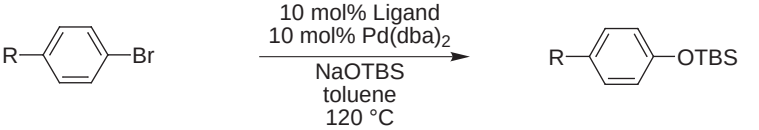
Fig. 23

The **27**/Pd-catalyst is considerably more reactive that the **26**-based system. The new, more reactive catalyst was reported to allow the coupling of electron-rich aryl bromides with NaO*t*-Bu in moderate yields, Eq. (187) [149].



(187)

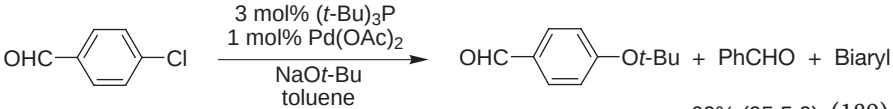
Mann and Hartwig have also investigated the use of sodium *tert*-butyldimethylsilanoate (NaOTBS) in the C-O bond forming reaction with aryl bromides [150]. The efficacy of DPPF- and tolBINAP-based catalysts, as well as nickel-based systems, were compared, Eq. (188).



Ligand	GC Yield, %
DPPF	49
tolBINAP	75

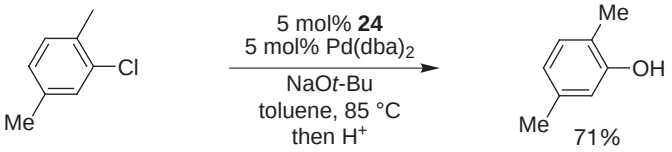
(188)

Watanabe et al. have reported that electron-deficient aryl chlorides may be coupled with NaO*t*-Bu in the presence of the (*t*-Bu)$_3$P/Pd-catalyst, Eq. (189) [147].



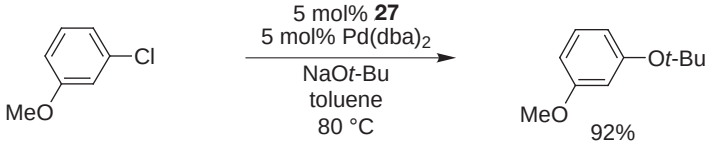
(189)

Ferrocene-based phosphine **24** is also an effective supporting ligand for the Pd-catalyzed condensation of chloroarenes and sodium *tert*-butoxide [148]. The coupling of 2-chloro-*para*-xylene, followed by acid mediated cleavage of the *tert*-butyl group, yielded the desired phenol in 71% yield, Eq. (190).



(190)

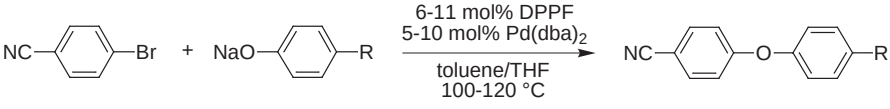
Pentaphenylated ligand **27** forms a catalyst that is considerably more reactive than **26**. This system mediates the efficient coupling of electron-rich aryl chlorides with NaO*t*-Bu; *meta*-chloroanisole was reacted in 92% yield, Eq. (191) [149].



(191)

3.2 Reaction of Phenol Derivatives

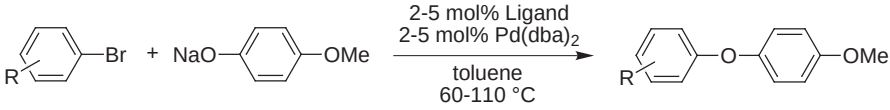
Methods for the arylation of phenols have been more successful than analogous reactions of aliphatic alcohols since the Pd (II) phenoxide intermediate is unable to undergo unwanted β-hydride elimination. Hartwig and co-workers first reported the use of a DPPF/Pd-catalyst to prepare diaryl ethers in 1997 [151]. The system was particularly effective with electron-deficient aryl bromides and electron-rich phenols, Eq. (192).



R	Yield, %
OMe	92
H	51

(192)

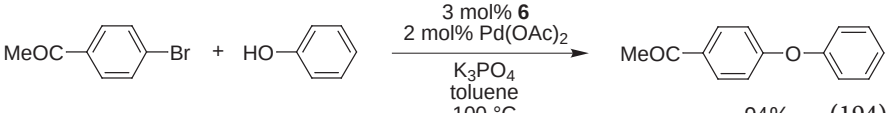
The use of ferrocene-based ligands **26** and **27** also effected the Pd-catalyzed formation of diaryl ethers, Eq. (193) [148, 149]. The **27**/Pd-catalyst is more reactive and mediates the transformation in better yield and at lower temperatures.



Ligand	R	Yield, %
26	2-Me	85
27	2-Me	99
26	4-*t*-Bu	74

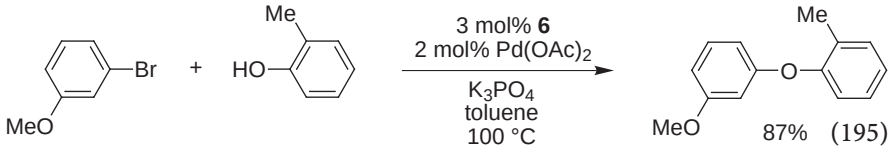
(193)

Buchwald and co-workers disclosed that the palladium-catalyzed diaryl ether formation can be performed with a **6**/Pd-based system [152]. These reactions are accomplished using a mild base such as K_3PO_4, and with electron-poor aryl bromides, the reactions proceed in good to excellent yield, Eq. (194).



94% (194)

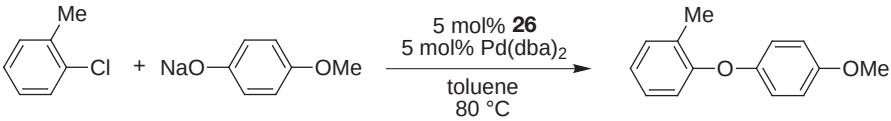
In some cases, the **6**/Pd-catalyst is capable of mediating the coupling of electron-rich aryl bromides and phenols as well [152]. For example, the reaction of 3-bromoanisole shown below proceeded in 87% yield, Eq. (195). With more challenging electron-rich substrates, other bulky ligands are better suited.



87% (195)

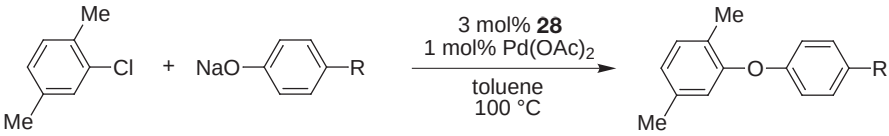
General Procedure for the Preparation of Diaryl Ethers using 6/Pd: (Excerpted with permission from [152]. © 1999 American Chemical Society). An oven-dried resealable Schlenk tube was fitted with a rubber septum and was cooled to room temperature under an argon purge. The septum was removed, and the tube was charged with palladium acetate (4.5 mg, 0.02 mmol, 2.0 mol%), ligand **6** (13.6 mg, 0.03 mmol, 3.0 mol%) potassium phosphate (424 mg, 2.0 mmol), the phenol (1.2 mmol) and the aryl halide (1.0 mmol). The tube was capped with a septum and purged with argon, and then toluene (3 ml) ws added through the septum. The tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 100 °C for 14–26 h. The reaction was then allowed to cool to room temperature and was then diluted with ether (40 ml), filtered and concentrated. The crude material was purified by flash chromatography on silica gel.

The catalyst based on ligand **26** has also been reported to mediate the formation of diaryl ethers from aryl chlorides. The reaction below proceeded in 82% yield, Eq. (196) [148].



82% (196)

The Buchwald group has reported that hindered binaphthyl-derived phosphine **28** is an effective supporting ligand for the coupling of aryl chlorides and phenols [152]. This catalyst system provided the desired ethers in good to excellent yield, Eq. (197).



R	Yield, %
OMe	79
H	92

(197)

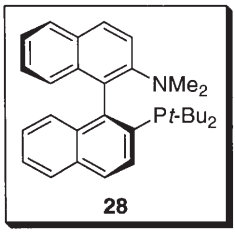
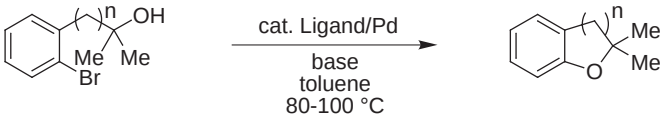


Fig. 24

3.3 Intramolecular Arylation of Alcohols

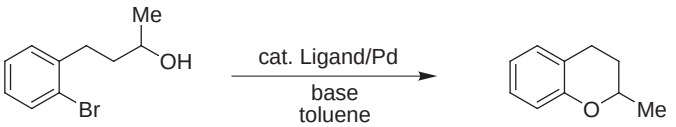
Similar to the development of the palladium-catalyzed C-N bond forming reactions, investigations into the intramolecular alcohol arylation were first conducted. The Buchwald group first reported the intramolecular variant of this reaction in 1996 utilizing both tolBINAP- and DPPF-based catalysts [153]. Five- and six- and seven-membered rings were formed in the cyclizations in moderate to excellent yield, Eq. (198). Yields were greatly diminished when the alcohol substrates contained hydrogens α- to the oxygen due to competitive β-hydride elimination of the palladium (II) alkoxide intermediate. Similarly, Hartwig subsequently reported that the **26**/Pd-catalyst could effect the cyclization below [148].



(198)

n	Reaction Conds.	Yield, %
1	6 mol% tolBINAP, 5 mol% $Pd(OAc)_2$, K_2CO_3	89
1	2 mol% **26**, 2 mol% $Pd(dba)_2$, NaO*t*-Bu	78
2	3.6 mol% DPPF, 3 mol% $Pd(OAc)_2$, NaO*t*-Bu	69
3	3.6 mol% DPPF, 3 mol% $Pd(OAc)_2$, NaO*t*-Bu	64

Recently, Buchwald and co-workers reported improved procedures for intramolecular Pd-catalyzed C-O bond forming reactions with primary and secondary alcohol-containing substrates based on hindered ligands **6, 29**, and **30** [154]. While the DPPF/Pd-system accomplished the cyclization below in only 32% yield, the catalyst based on commercially available phosphine **6** furnished the heterocycle in 83% yield, Eq. (199). Hindered ligand **29** also provided the desired product in good yield.



(199)

Reaction Conds.	Yield, %
10 mol% DPPF, 5 mol% $Pd(OAc)_2$, NaO*t*-Bu	32
5 mol% **27**, 5 mol% $Pd(dba)_2$, NaO*t*-Bu	64
3.5 mol% **6**, 3 mol% $Pd(OAc)_2$, Cs_2CO_3	83
3.5 mol% **29**, 3 mol% $Pd(OAc)_2$, Cs_2CO_3	79

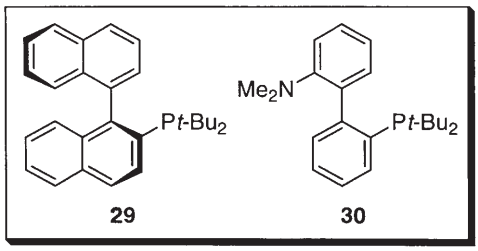
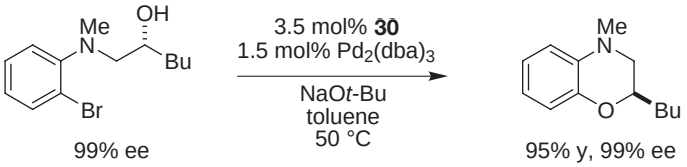


Fig. 25

The **29** and **30**/Pd-catalysts allowed for the efficient cyclization of substrates bearing primary and secondary alcohol substituents [154]. Reaction of both aryl chlorides and bromides was possible, providing five-, six- and seven-membered heterocycles in moderate to good yield. Additionally, enantiomerically enriched heterocycles could be prepared without epimerization of the carbinol-bearing stereocenter, Eq. (200).



(200)

4 Conclusions

Palladium-catalyzed C-N bond and C-O bond forming reactions are useful methods for organic synthesis. The iterative development of new catalyst systems has revealed profound ligand effects, both electronic and steric, on the selectivity and efficiency of these transformations. Mechanistic studies have been instrumental to the progress of both our research program as well as that of the Hartwig group. Based on empirical observations, it seems that designing a "silver bullet" ligand that effects all desired cross couplings is unlikely. Thus, our group, and others, have sought to develop a toolbox of ligands that allow the synthetic chemist to effect the desired transformation as efficiently and practically as possible. Continued efforts will improve the scope of these methods and the mechanistic understanding of these processes.

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