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Review

Palladium-catalyzed amination of aryl halides and sulfonates☆

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Abstract

In this review, the progress made in the palladium-catalyzed amination of aryl halides and sulfonates is described with particular attention given to applications in synthetic organic chemistry. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Anilines; *N*-Aryl amines; Palladium catalysts; Phosphine ligands

1. Introduction

The synthesis of compounds containing the *N*-aryl moiety has attracted a great deal of interest recently due to the importance of such compounds in fields as diverse as natural products [1], photography [2], and materials [3]. Although a number of traditional methods exist for aryl C–N bond construction [4–16], they typically suffer from problems such as limited generality, harsh conditions, the need to employ stoichiometric quantities of valuable reagents, numerous synthetic steps, or regiochemical ambiguities.

From the standpoint of directness and atom-economy, a transition metal-catalyzed approach to C–N bond construction is appealing because it entails simply the cross-coupling of an amine with an aryl halide. In the past four years, our group at MIT [17–33] and John Hartwig's group at Yale [34–40] have progressively and independently contributed to the development of a general, reliable, and practical methodology for the formation of aromatic carbon–nitrogen bonds. It is the purpose of this report to review the types of products that are now accessible using palladium-catalyzed C–N bond forming methodology. We will describe the optimal conditions now used in the preparation of tertiary amines, secondary amines, primary amines (anilines), as well as the special cases of intramolecular cyclizations. These procedures are built upon many ground-breaking studies of others which, for reasons of space, cannot be covered thoroughly in this review[1].

The reader is therefore referred to the original literature for the mechanistic insights that were gleaned from these earlier reports, and to narrative account articles from both the Buchwald [44] and Hartwig [45] groups that chronicle the progression of exciting developments that ultimately brought C–N bond forming technology to its present state.

☆ Dedicated to Professors Richard Heck and Jiro Tsuji in recognition of their manifold pioneering contributions to the field of organopalladium chemistry.

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[1] For examples of breakthroughs in Pd-catalyzed cross-coupling reactions, see references [41–43].

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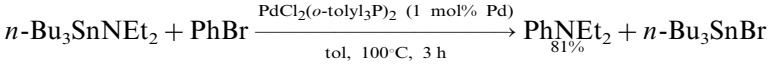
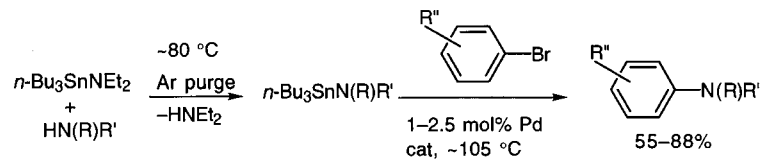
2. Background and outline

The first procedure for the Pd-catalyzed *N*-arylation reaction was provided by Migita and co-workers in 1983 [46]. In this report, they showed that aryl bromides reacted with *N*,*N*-diethylaminotributyltin to afford the corresponding *N*,*N*-diethylanilines, as well as tri-*n*-butyltin bromide as the stoichiometric by-product. A severe limitation of this protocol was that it was not readily extendable to other amine types since amino stannanes are typically not commercially available, and are both thermally and moisture-sensitive.

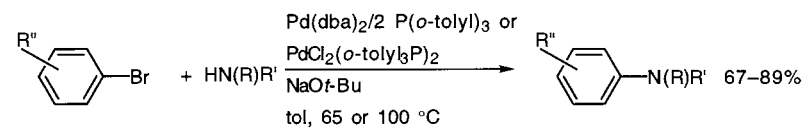


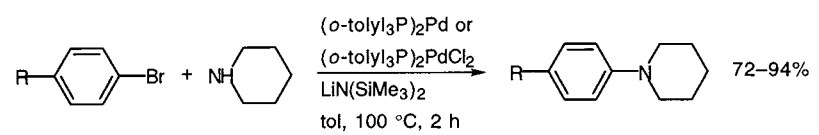
This problem was solved by Buchwald and Guram in 1994 [17], who exploited the ability of *N*,*N*-diethylaminostannane to undergo transamination reactions [47]. Aminotin compounds which they were able to prepare in situ were found to undergo cross-coupling reactions with a variety of aryl bromides.



Despite the increased generality of this protocol relative to the Migita procedure, it was still undesirable that stoichiometric amounts of tin were required.

Amination of aryl bromides under tin-free conditions was achieved nearly simultaneously by both the Buchwald [18] and Hartwig [35] groups. Using P(*o*-tolyl)$_3$ as ligand, a palladium catalyst, and an appropriate base, most commonly NaO*t*-Bu, they were able to cross-couple a variety of different amines and aryl bromides. Although this methodology has expanded greatly over the past three years, now encompassing a variety of other nitrogen-containing species and other aryl 'halides' (bromides, iodides, chlorides, and sulfonates), the basic features of this catalytic cycle are operative in all of these transformations.



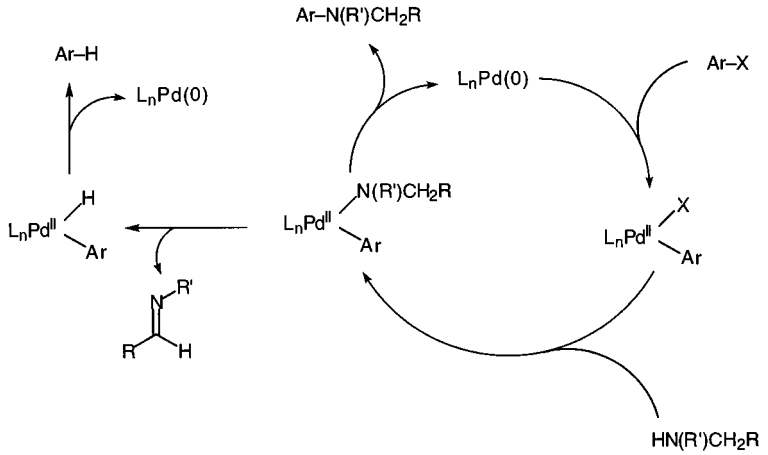


A reasonable mechanism for the catalytic cycle of this transformation is shown in Scheme 1[2]. A Pd(0) species is thought to be the active catalyst, and the catalytic cycle is believed to involve oxidative addition [49] of the aryl halide, coordination and deprotonation of the amine, followed by reductive elimination [51,52] of the *N*-aryl product[3]. Also worth noting is that instead of reductively eliminating the *N*-aryl product, the putative palladium amide can undergo a β-hydride elimination leading ultimately to a reduced arene by-product (Ar–H)[4]. In general, this side-reaction becomes more important when electron-donating aryl halides/sulfonates are employed, since electron-deficient palladium species more readily undergo reductive elimination. It was the attempts to solve this particular problem, as well as issues of functional group compatibility, that spawned many of the refinements and improvements in C–N bond forming methodology.

[2] For the similarity to other cross-coupling procedures, see reference [48].

[3] Hartwig has shown that a palladium-*t*-butoxide species is catalytically active and is thus a viable intermediate in the catalytic cycle. See reference [53].

[4] Hartwig has shown that the arene by-product can arise via other pathways as well. See reference [54].



Scheme 1.

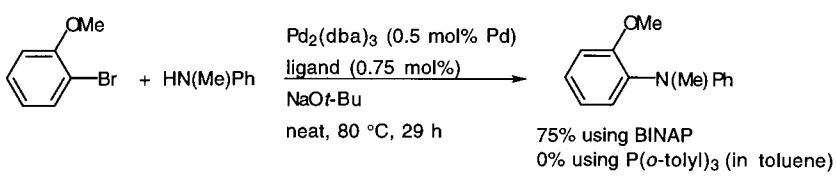
We will attempt to provide an overview of the achievements in this field from the vantage point of the types of products that are now accessible, and the starting materials that can be employed. The use of aryl iodides as starting materials will be discussed in the context of the use of aryl bromides. Aryl bromides are still the most widely used aryl halides, and the results seen with aryl iodides must be presented in light of what is possible with aryl bromides, since aryl iodides are often more expensive and less readily available than their aryl bromide counterparts. Aryl chlorides are less reactive than aryl bromides in Pd-catalyzed aminations, but this liability must be weighed against the greater availability and lower cost of aryl chlorides. Similarly, though aryl sulfonates require preparation and can be more base-labile, the phenol precursors are often inexpensive and/or readily available.

This review is organized by the types of products that are produced. Intermolecular reactions will be covered first, beginning with the *N*-arylation of secondary amines, followed by the *N*-arylation of primary amines. Within each of these sections, we will deal with the use of different halides and sulfonates. We then describe intramolecular reactions, which will be seen to exhibit markedly different reactivity patterns than intermolecular reactions. Within each section, we will describe relevant chronological developments and attempt to provide examples which illustrate the current state-of-the-art (ca. July, 1998) so as provide guidelines on how to best achieve the desired transformation. While this organization necessarily results in some redundancy, we feel that it provides information in the manner most useful to the synthetic chemist.

3. *N*-Arylation of secondary amines

3.1. Cross-coupling of acyclic amines with aryl bromides

Although in some cases monodentate ligands such as P(*o*-tol)$_3$ were suitable ligands for the cross-coupling of *N*-methyl(aryl) or *N*-methyl(alkyl) amines with aryl bromides [18], chelating bidentate phosphine ligands were more often preferable [20], typically providing less of the reduced arene side-product[5]. For instance, *N*-methylaniline was *N*-arylated with 2-bromoanisole in the absence of solvent in 75% yield using $Pd_2(dba)_3$ and the bisphosphine BINAP [56,57] as ligand[6], while the same reaction with P(*o*-tolyl)$_3$ in toluene did not afford any of the desired product.

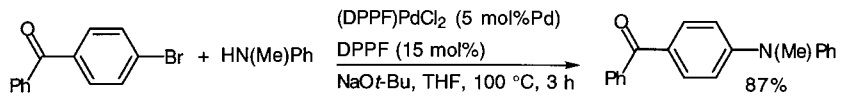


[5] Whitesides has shown that β-hydride elimination occurs following ligand dissociation in L_2PtR_2 complexes. Complexes where L_2 is a chelating phosphine do not undergo β-hydride elimination. See reference [55].

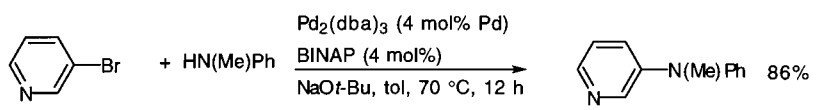
[6] Racemic BINAP is available from Strem Chemical. In conjunction with $Pd_2(dba)_3$, we encountered no differences between use of the optically active material and use of the racemic material. With $Pd(OAc)_2$, no difference in yield or reaction time is observed provided the ligand is dissolved completely and combined with the $Pd(OAc)_2$ prior to addition of the remaining reagents: J.P. Wolfe, S.L. Buchwald, unpublished results.

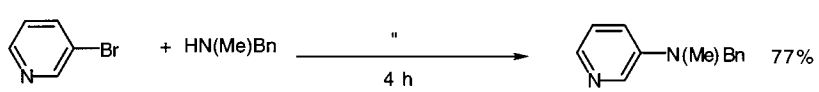
Similarly, *N*-arylation of *N*-methylaniline with 2-bromo-*p*-xylene using BINAP as ligand afforded the corresponding tertiary amine in 79% yield, whereas the same reaction with P(*o*-tolyl)$_3$ as ligand proceeded in only 5% yield.

Concurrent with our group's investigations into the uses of BINAP as ligand, Hartwig and co-workers found that (DPPF)PdCl$_2$ also constitutes an effective catalyst system for the amination of a secondary amine [36], although its utility in this context was demonstrated only in a cross-coupling reaction with a *p*-substituted electron-deficient aryl bromide.

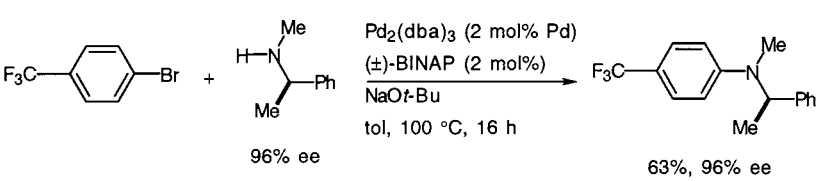


In addition to minimizing the production of reduced arene side-products, the use of bisphosphine ligands in lieu of P(*o*-tolyl)$_3$ was beneficial in other applications. In palladium-catalyzed cross-coupling reactions with bromopyridines, essentially no turnover was observed when P(*o*-tolyl)$_3$ was used as ligand. When BINAP was employed as ligand, however, *N*-methylaniline was *N*-arylated with 3-bromopyridine in 86% yield, and the analogous reaction with *N*-methylbenzylamine occurred in 77% yield [22]. A plausible rationale for the improved yield with BINAP is that the use of chelating ligands prevents formation of catalytically inactive bis-pyridyl Pd-species [50].





Another advantage of bisphosphine ligands 'vis-à-vis' P(*o*-tolyl)$_3$ was uncovered in attempts to *N*-arylate enantiomerically enriched α-substituted amines. Whereas use of P(*o*-tolyl)$_3$ led to products of greatly diminished enantiomeric excess (ee) , the use of BINAP as ligand resulted in essentially complete preservation of stereochemical integrity [25].

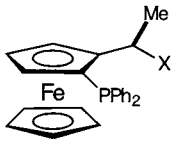


It is nevertheless worth noting that although BINAP was found to be superior to P(*o*-tolyl)$_3$ in these instances, in some cases cross-coupling reactions with BINAP as ligand still formed significant quantities of reduced arene side products. This was particularly problematic when acyclic (alkyl) aryl secondary amines (with groups larger than methyl) and/or electron-rich aryl bromides are employed, as well as in the cross-coupling reactions of acyclic dialkylamines.

For these two classes of reactions, ferrocenyl-derived ligands (±)-PPF–OMe (**1a**) and (±)-PPFA (**1b**) [58] were found to give much improved results [31]. These ligands[7] appear both from empirical results and electronic considerations to confer the same benefits as other chelating ligands (e.g. BINAP) when used in lieu of P(*o*-tolyl)$_3$.

[7] Both PPF–OMe and PPFA are available in optically active form from Aldrich Chemical.

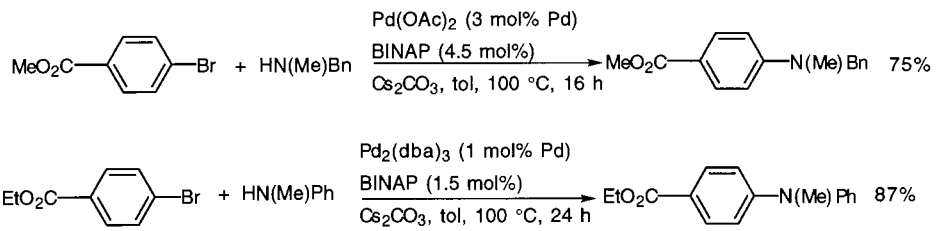
For instance, the Pd-catalyzed cross-coupling reaction of di-*n*-butylamine with 4-*t*-butyl-bromobenzene (0.5 mol% Pd, 0.75 mol% ligand) afforded a 5.2:1 ratio of reduced arene to product (8% GC yield) using BINAP as ligand, and a 4.9:1 ratio and 9% GC yield using DPPF as ligand[8].



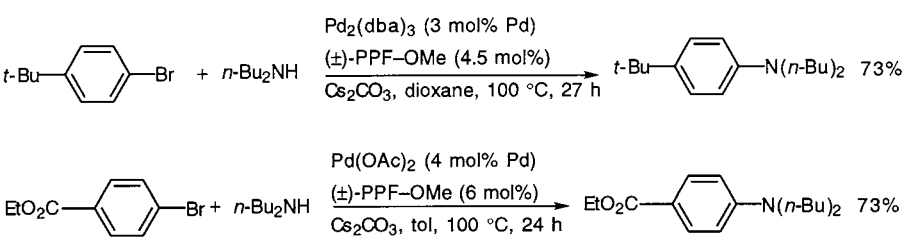
(±)-PPF–OMe (**1a**, X = OMe)
(±)-PPFA (**1b**, X = NMe_2)

The same reaction using ligand **1a** (0.75 mol%, 0.5 mol% Pd) afforded a 39:1 ratio of product to reduced arene (97% GC yield, 93% isolated yield) and an 89% isolated yield with **1b**. Whereas low yields were obtained in attempted cross-couplings of di-*n*-butylamine with 2-bromopyridine using BINAP as ligand, an 84% isolated yield was realized when ligand **1a** was employed.

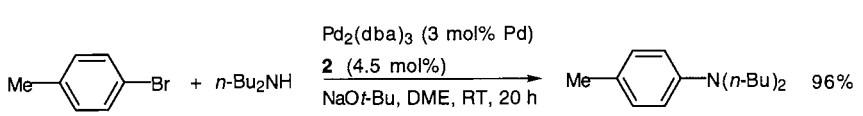
While a solution to the secondary acyclic amine problem greatly increased the generality of the amination protocol, the requirement that NaO*t*-Bu be used as base posed problems with respect to functional group tolerance. Because many base-sensitive functionalities are themselves electron withdrawing groups, many cross-coupling reactions with base-sensitive aryl bromides proceed even with the use of the milder base Cs_2CO_3 [28].



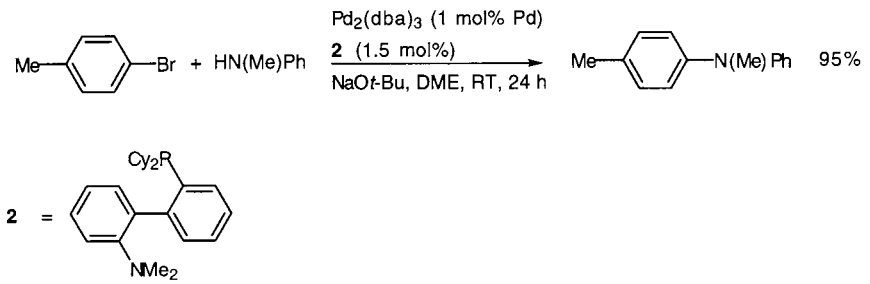
Attempts to extend this protocol to include the coupling of electronically neutral aryl bromides using BINAP as ligand resulted instead in significant quantities of the reduced arene side-product. However, the less electron-rich nature of PPF–OMe did allow this and other transformations to take place [28].



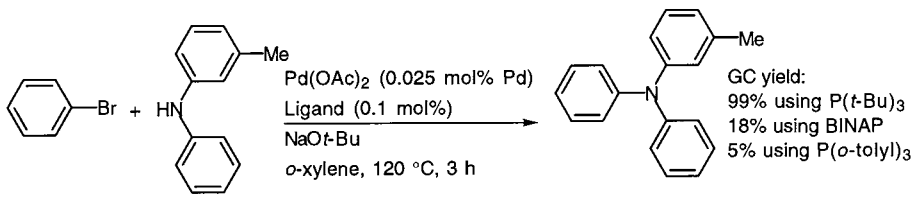
Another ligand which we have found to address the problematic cross-coupling of secondary acyclic amines is the chelating aminophosphine ligand **2** [59]. Though not commercially available, ligand **2** was found to give superior results relative to PPF–OMe. For example, using **2**/Pd(0), 4-bromotoluene was cross-coupled with di-*n*-butylamine in 96% yield, and with *N*-methylaniline in 95% yield. What is notable about this ligand system is that the amination reactions proceed at room temperature, as opposed to 80 or 100°C which is typically required when P(*o*-tolyl)$_3$, BINAP, or PPF–OMe are used as ligand. Similar rate accelerations have also been observed by Hartwig in coupling reactions used to prepare other classes of substrates and which are described later in this review. Not only do lower reaction temperatures expand the substrate scope and functional group tolerance of the *N*-arylation methodology, a room temperature protocol is much more amenable to rapid throughput screening methods and/or combinatorial applications.



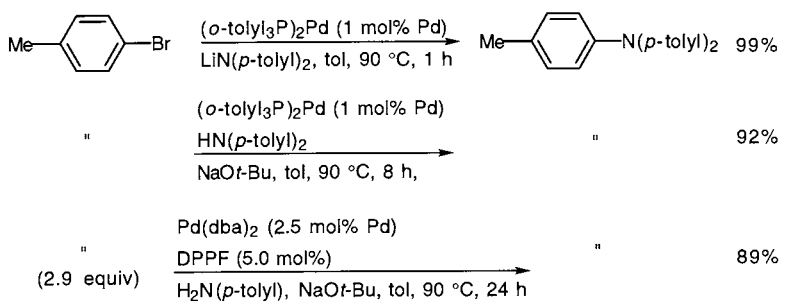
[8] Using 5 mol% of (DPPF)$PdCl_2$ and 15 mol% of DPPF resulted in a 43% GC yield.



The benefits associated with the use of chelating ligands should not detract from the role of monodentate phosphine ligands in synthetic applications of C–N bond-forming methodology. In particular, bulky, electron-rich monophosphine ligands have not only found considerable application in synthetic organic chemistry, they are in some instances the most efficient and active ligands. Yamamoto, Nishiyama, and Koie have disclosed an efficient method for the preparation of triarylamines from the Pd-catalyzed *N*-arylation of diarylamines [60]. Using P(*t*-Bu)$_3$ as ligand for the Pd-catalyst, they report that *N*-(3-methylphenyl)diphenylamine is prepared in 99% yield from bromobenzene and *N*-(3-methylphenyl)aniline, whereas the use of BINAP as ligand resulted in an 18% yield, and employing P(*o*-tolyl)$_3$ furnished only a 5% yield of product.



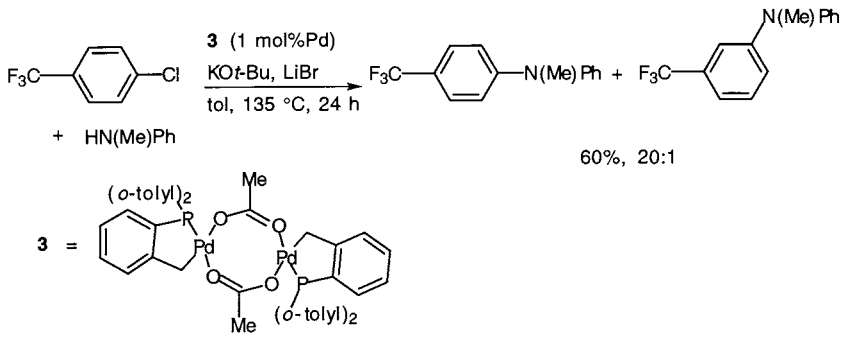
In other instances, Hartwig and co-workers have found that P(*o*-tolyl)$_3$ is an effective ligand for the preparation of triarylamines [38]. In studies of methods to prepare triarylamine dendrimers, they reported that lithiated diarylamines can be *N*-arylated using a [P(*o*-tolyl)$_3$]$_2$Pd catalyst system, or alternatively the free diarylamine can be *N*-arylated using NaO*t*-Bu as base. In each case, the product yields exceeded 90%. By using two molar equivalents of aryl bromide, anilines could also be converted to triarylamines using a catalyst system based on Pd(dba)$_2$/DPPF[9].



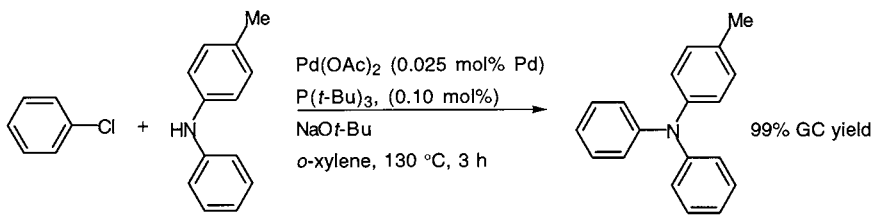
3.2. Cross-coupling of acyclic amines with aryl chlorides

Using a protocol resembling that developed for the amination of aryl bromides, we found that aryl chlorides were less reactive than aryl bromides in Pd-catalyzed aminations, thus neither P(*o*-tolyl)$_3$ nor BINAP were effective ligands for the amination of aryl chlorides. While we initially explored nickel-based alternatives with some success [62], Beller and co-workers found that they could aminate electron-poor aryl chlorides when the original protocol [17–40] was modified by performing the reaction at higher temperatures (135°C), in the presence of LiBr, and when KO*t*-Bu was used as base and palladacycle **3** was employed as catalyst [63].

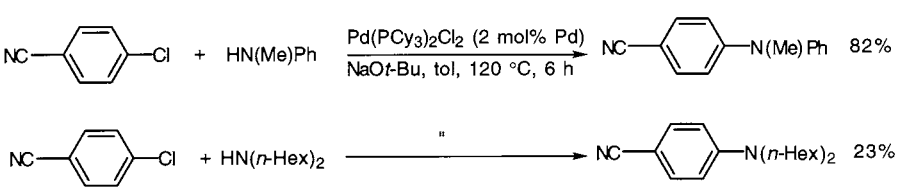
[9] For another Pd-catalyzed approach to triarylamine synthesis. See reference [61].



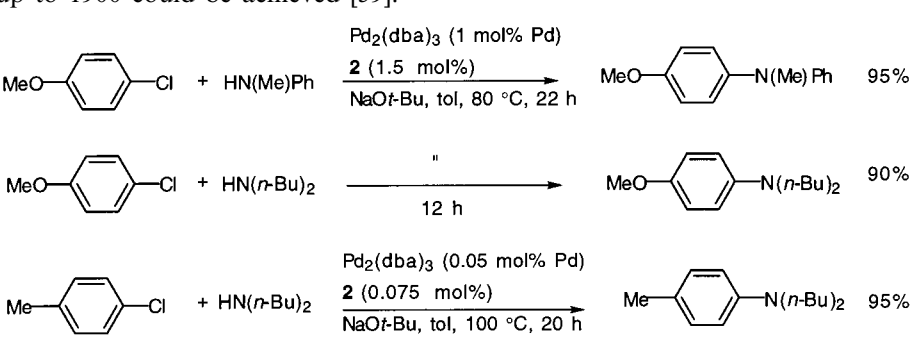
The formation of regioisomers does suggest, however, that the amination proceeded at least to some degree via a benzyne intermediate. Using P(*t*-Bu)$_3$ as ligand, Yamamoto, Nishiyama, and Koie have prepared triarylamines via a Pd-catalyzed coupling of a diarylamine with chlorobenzene using NaO*t*-Bu as base, without any other additives [60].



It should be noted that compared to the analogous reaction using bromobenzene, this reaction did require higher temperatures, higher concentration of halide, and more halide (130°C, 8.0 M, two equivalents vs. 100°C, 0.7 M, one equivalent). With the electron-rich ligand tricyclohexylphosphine, Reddy and Tanaka noted that the cross-couplings of *N*-methylaniline with 4-chlorobenzonitrile proceed in good yield at 120°C without additives (e.g. LiBr), using NaO*t*-Bu as base [64].



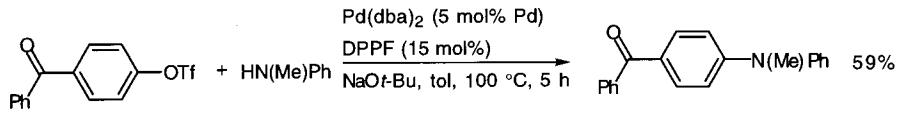
However, cross-coupling reactions of dialkylamines proceeded in poor yield, even with electron-deficient aryl chlorides. The high activity of the aminophosphine ligand **2** is clearly evident in Pd-catalyzed cross couplings of 4-chloroanisole with *N*-methylaniline, which proceeded in 95% yield at 80°C, and with di-*n*-butylamine, which proceeded in 90% under those reaction conditions (1 mol% Pd was used in both of these cases). At lower catalyst loadings, turnover numbers up to 1900 could be achieved [59].



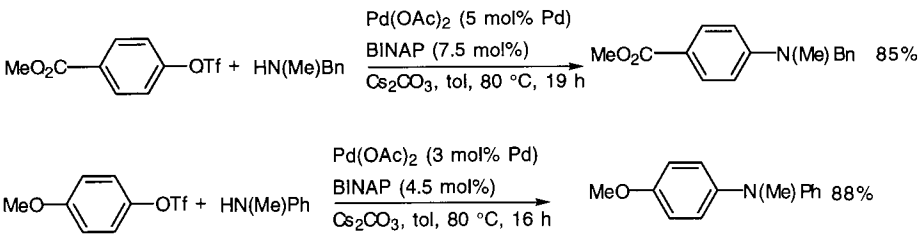
3.3. Cross-couplings of acyclic amines with aryl triflates

Using conditions similar to those developed for the amination of aryl bromides, our group and Hartwig's group found that good yields could be obtained utilizing electronically neutral or electron-rich aryl triflates [26,37].

Electron-deficient aryl triflates in general gave low product yields, due to NaO*t*-Bu-induced cleavage of the aryl triflate, with subsequent liberation of the corresponding sodium phenoxide.

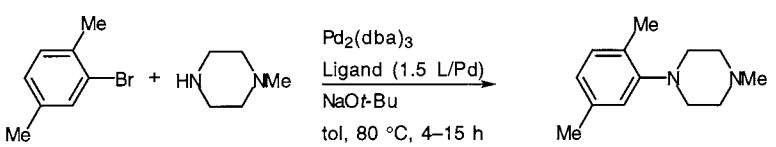


Although this problem could be partially remedied by employing higher catalyst loadings and by adding the aryl triflate slowly to the reaction mixture [37], a more general solution was to employ Cs_2CO_3 as base in lieu of NaO*t*-Bu [29]. Electron-deficient aryl triflates, including those that were base-sensitive, were aminated in high yields. Unlike the case with electron-rich aryl bromides where the use of BINAP/Cs_2CO_3 afforded large amounts of the reduced arene side-product [31], use of BINAP/Cs_2CO_3 with electron-rich aryl triflates afforded cross-coupled products in high yields.



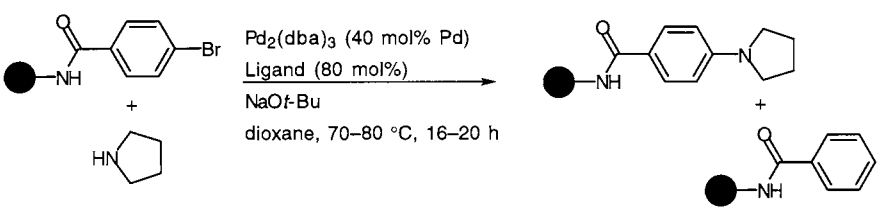
3.4. Cross-coupling of cyclic amines with aryl bromides

Compared with acyclic amines, the Pd-catalyzed cross-coupling reaction of cyclic amines with aryl bromides tended to provide less of the reduced arene side-product. Nevertheless, we found that while monodentate ligands such as P(*o*-tol)$_3$ were suitable ligands for these reactions [18], bidentate phosphine ligands were more frequently preferred, typically providing less of the reduced arene side-product [20]. For instance, the cross-coupling of 2-bromo-*p*-xylene with *N*-methylpiperazine proceeded in 98% yield using BINAP as ligand, even at catalyst loadings as low as 0.05 mol% Pd, whereas a 47% yield was realized when P(*o*-tolyl)$_3$ (2 mol% Pd) was substituted for BINAP.



98% using BINAP (2 mol% Pd)
98% using BINAP (0.05 mol% Pd), neat
47% using P(*o*-tolyl)$_3$ (2 mol% Pd)

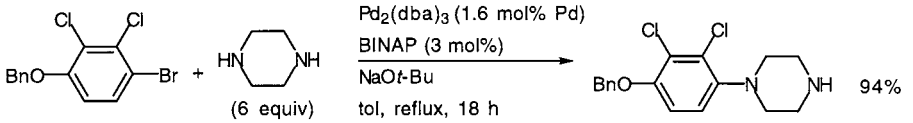
Similar findings have also been reported in solid-phase applications of this methodology. Willoughby and Chapman have found that using a 4-bromobenzamide resin, attempted Pd-catalyzed cross-coupling with pyrrolidine proceeded to 75% completion when P(*o*-tolyl)$_3$ was ligand, but the ratio of desired product to reduced arene side-product was ca. 2:1 [65]. When the process was conducted using BINAP as ligand, the reaction proceeded to 84% completion, and a 97:3 ratio of product to reduced arene was found.



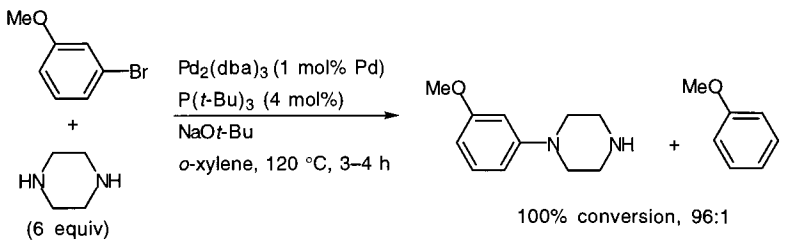
75% conversion, 66:34 using P(*o*-tolyl)$_3$
84% conversion, 97:3 using BINAP

The ratio of *N*-arylated product to reduced arene side-product is sensitive to the nature of the phosphine ligand, and while we found that BINAP is generally superior to the monodentate P(*o*-tolyl)$_3$, both monodentate and

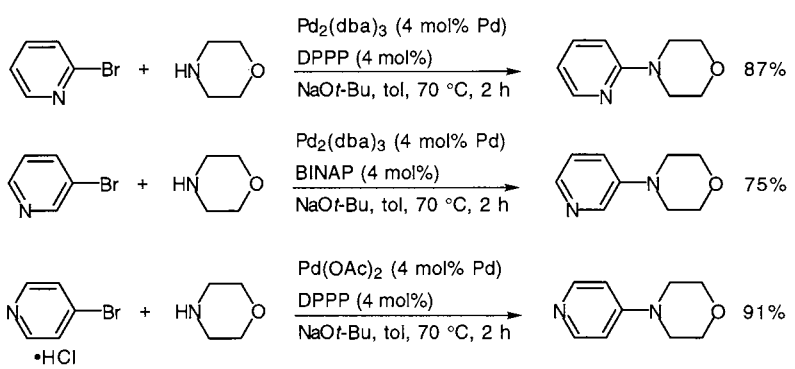
bidentate phosphines have found uses in synthetic applications. For instance, Morita and co-workers used a $Pd_2(dba)_3$/BINAP system to prepare a key intermediate in the synthesis of a metabolite of the antipsychotic agent Aripiprazole [66].



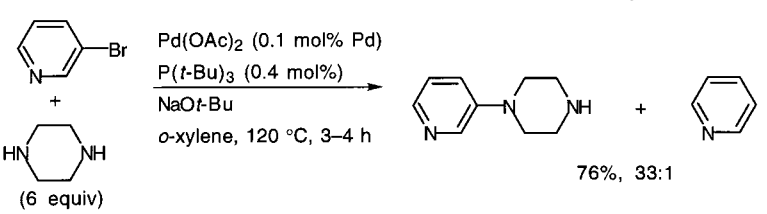
Nishiyama, Yamamoto, and Koie found that a catalyst system prepared from $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ (0.5 mol% catalyst) displayed high activity (100% conversion) and selectivity (> 96:1 ratio of product to reduced arene) in the cross-coupling of piperazine with *m*-bromoanisole [67][10].



Whereas the use of bisphosphine ligands was ineffective in Pd-catalyzed cross-coupling reactions of acyclic dialkylamines with bromopyridines, they proceeded smoothly with cyclic secondary amines. For instance, morpholine could be *N*-arylated by 2-bromopyridine using $Pd_2(dba)_3$ and 1,3-bis(diphenylphosphino)propane (DPPP), by 3-bromopyridine using $Pd_2(dba)_3$ and BINAP, and by 4-bromopyridyl hydrochloride using $Pd(OAc)_2$ and DPPP [22]. Although we obtained only trace products using P(*o*-tolyl)$_3$ as ligand, other workers have found that monophosphine ligands can be effectively employed.



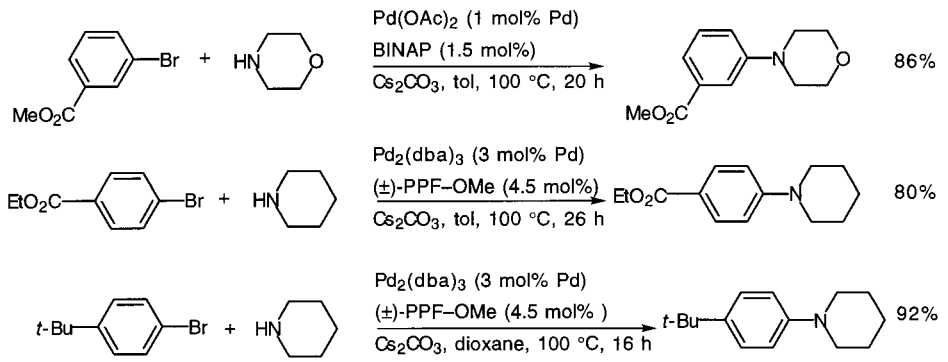
For example, Nishiyama, Yamamoto, and Koie used a $Pd_2(dba)_3$/P(*t*-Bu)$_3$ system to cross-couple 3-bromopyridine with piperazine in 76% yield [67]. In this case, P(*t*-Bu)$_3$ is presumably a better ligand than a 3-substituted pyridine.



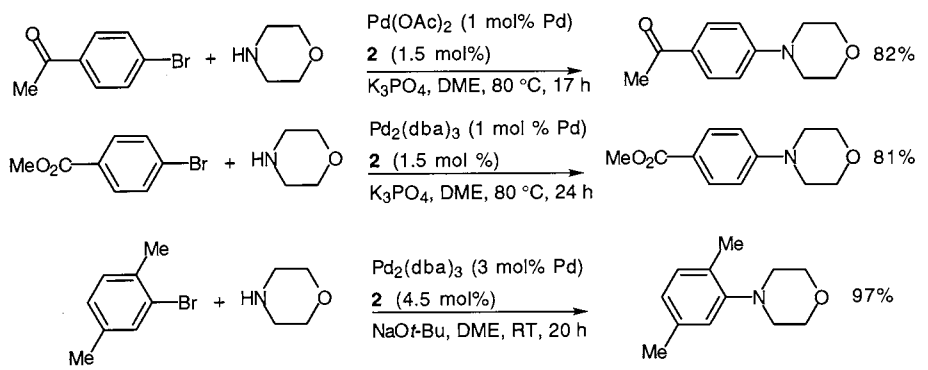
With regard to functional group tolerance, the substitution of Cs_2CO_3 for NaO*t*-Bu in Pd-catalyzed arylations of cyclic secondary amines allows for the inclusion of substrates incompatible with the NaO*t*-Bu conditions such as methyl and ethyl esters. Though this protocol was not generally effective in the cross-coupling of cyclic secondary amines with electron-donating aryl bromides using BINAP[11], these cross-coupling reactions proceeded efficiently using PPF–OMe (**1**) as ligand [31].

[10] For other Pd-catalyzed *N*-arylation reactions of piperazine and its protected derivatives. See references [68,69].

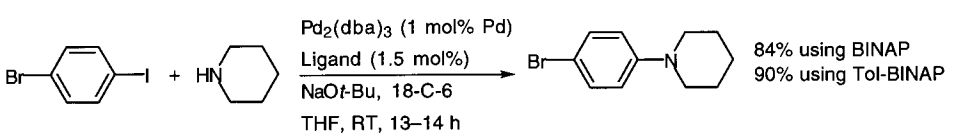
[11] Despite this trend, the cross-coupling of 2-bromo-*p*-xylene with pyrrolidine was most efficient using BINAP as ligand.



Greater functional group compatibility was also possible using the more active aminophosphine ligand **2**, wherein potassium phosphate was found to have adequate basicity to promote the Pd-catalyzed amination reaction at 80°C [59]. Under these conditions, enolizable ketones and methyl esters were tolerated. For electron-rich bromides, the reaction could be run at room temperature in DME as solvent, all be it the stronger base, NaO*t*-Bu was needed.

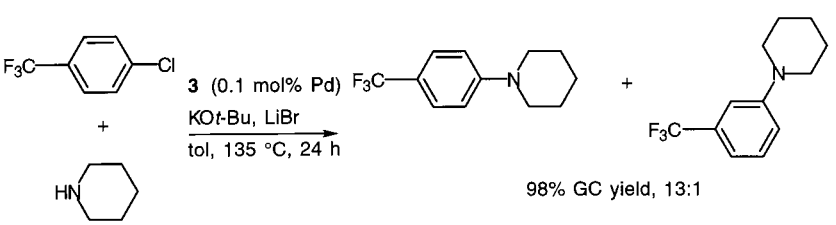


Amination reactions which proceed at room temperature not only allow for greater functional group tolerance, but allow the preferential amination of an aryl C–I bond in the presence of an aryl C–Br bond. We have noted that when the Pd-catalyzed amination reaction is conducted in the presence of 18-crown-6, aryl iodides can be aminated in THF at room temperature [27]. Since aryl bromides are nearly inert under those conditions, amination at the aryl C–I bond in *o*-, *m*-, or *p*-bromo(iodo)benzene can be achieved.

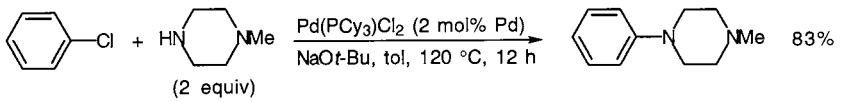


3.5. Cross-couplings of cyclic amines with aryl chlorides

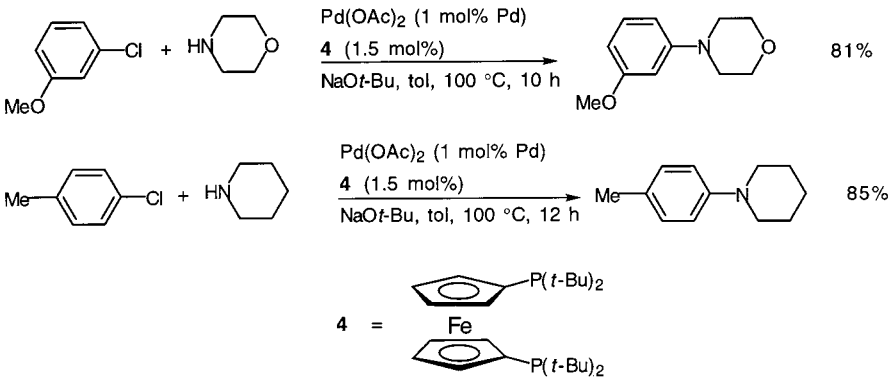
As with aryl bromides, the cross-coupling reactions generally proceed in higher yields with cyclic amines than with acyclic amines. For instance, the palladacycle **3**-catalyzed amination of 4-chlorobenzotrifluoride proceeded in fair yield with an acyclic dialkyl amine (60% GC yield with di-*n*-butylamine), but the analogous cross-coupling of piperidine proceeded in better yield (98% GC yield) [63].



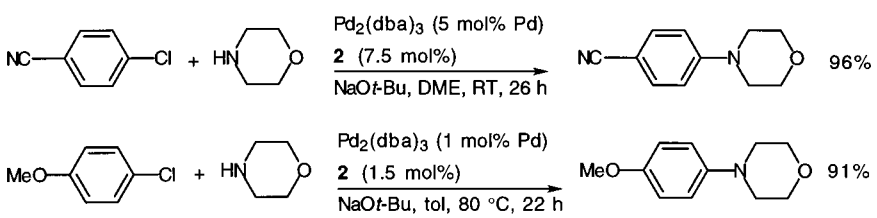
By using the more electron-rich ligand PCy_3, Reddy and Tanaka noted that secondary amines can be cross-coupled with aryl chlorides in good yield, provided NaO*t*-Bu is used as base, and a two-fold excess of the chloride is employed [64].



Finally, using the known chelating ferrocenyl-derived alkyl phosphine ligand **4** [70,71], Hartwig and Hamann have similarly shown that cyclic secondary amines can be *N*-arylated in high yields by a number of unactivated aryl chlorides under relatively mild conditions [72].

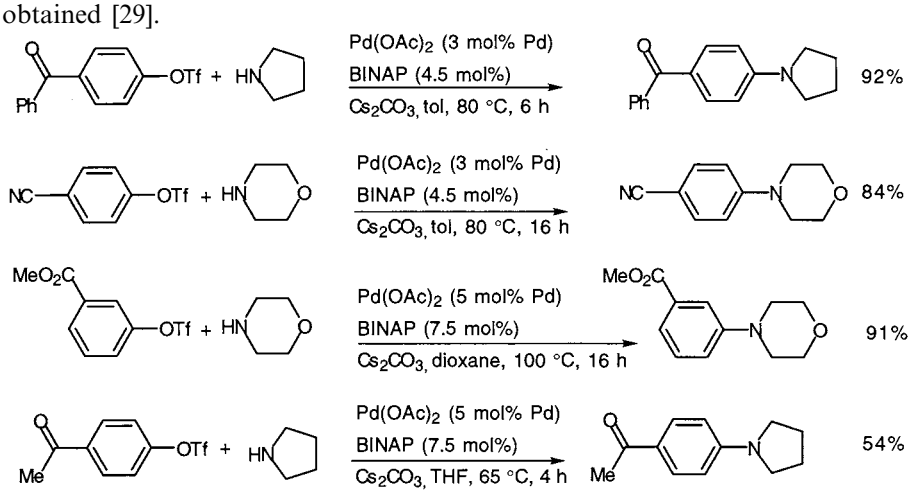


The utility of **4** in Pd-catalyzed cross-coupling reactions is complemented by the aminophosphine ligand **2** in palladium-catalyzed amination reactions. When used with $Pd_2(dba)_3$, we have recently shown that the **2**/Pd(0) catalyst system catalyzes the *N*-arylation of morpholine with 4-chlorobenzonitrile at room temperature in 96% yield. Even highly electron-rich aryl chlorides (*p*-MeO substituted) are found to react, though in these cases, heating to 80°C is necessary [59].

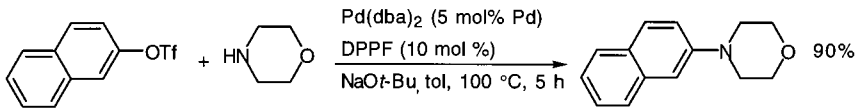


3.6. Cross-couplings of cyclic amines with aryl triflates

Using a Pd/BINAP catalyst system and Cs_2CO_3 as base, we found that the amination of both electron-rich and electron-deficient aryl triflates proceeded in high yields. Only in the case of an enolizable ketone were fair yields obtained [29].



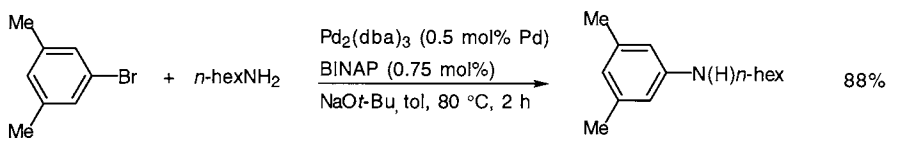
Hartwig and co-workers have also demonstrated that the use of NaO*t*-Bu in conjunction with $Pd(dba)_2$/DPPF is suitable in many instances as well [37], although as seen previously somewhat lower yields are obtained when electron-deficient aryl triflates are employed.

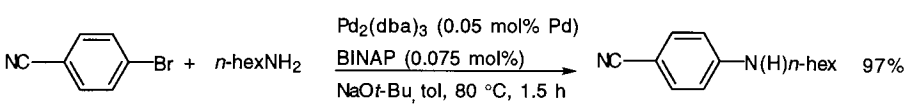


4. *N*-Arylation of primary amines

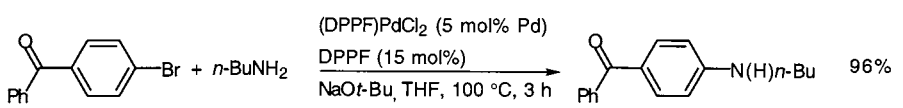
4.1. Cross-couplings of aliphatic amines with aryl bromides and iodides

The chemistry observed in the coupling of primary aliphatic amines resembled that of acyclic secondary amines: relative to other amine types, these reactions tended to produce more of the reduced arene by-product. For instance, using $(o\text{-tolyl}_3P)_2PdCl_2$ as the catalyst system, reaction of *n*-hexylamine with the electron-poor 4-bromobenzophenone (conditions which should disfavor reduced arene formation) afforded a 72% yield of product, but with ca. 27% formation of the reduced arene byproduct [18]. As in the case of secondary amines, we noted that the use of BINAP resulted in significant improvements. Whereas the catalyst system $Pd_2(dba)_3/P(o\text{-tolyl})_3$ (2 mol% Pd) afforded only a 35% yield in attempts to cross-couple *n*-hexylamine with 5-bromo-*m*-xylene, the yield was 88% when $Pd_2(dba)_3$/BINAP (0.5 mol% Pd) was used [20]. Other examples shown below demonstrate that the effectiveness of BINAP is general, affording higher yields for both electron-poor and electron-rich aryl bromides.



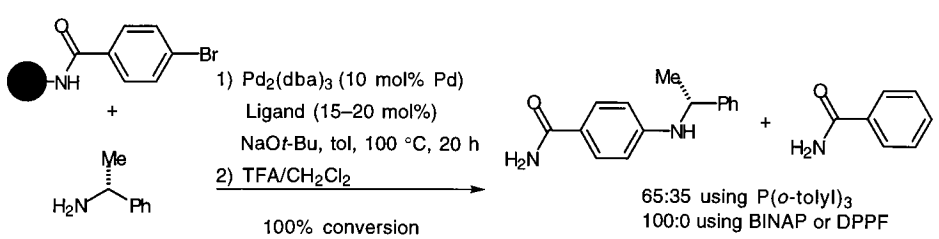


At the same time, Hartwig and his group demonstrated that $(DPPF)PdCl_2$ also constitutes an effective catalyst system for the *N*-arylation of a variety of primary aliphatic amines with electron-poor aryl bromides [36].



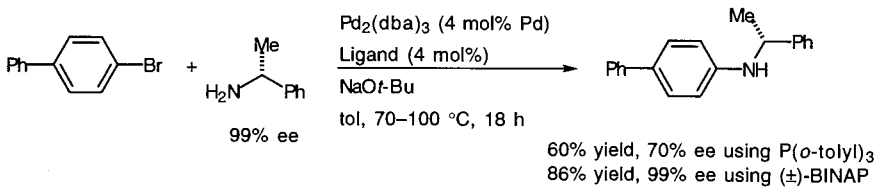
With respect to a more electron-donating aryl bromides, we did note in our report that with DPPF as ligand, the reaction of *n*-hexylamine with 5-bromo-*m*-xylene gives a 2.2:1 ratio of mono:doubly arylated amine. In contrast, a 39:1 ratio was seen when BINAP was used [20].

The use of chelating ligands such as BINAP and DPPF and the resulting decrease in reduced arene side-products has been observed in solid-phase applications as well.

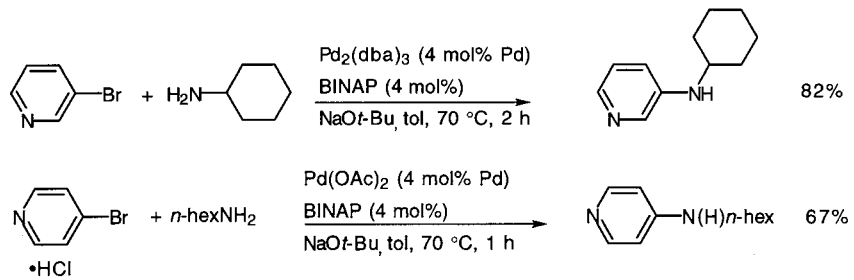


Using a 4-bromobenzamide-linked resin, Ward and Farina found that the coupling reaction with α-methylbenzylamine afforded a 65:35 ratio of product to reduced arene using $P(o\text{-tolyl})_3$ as ligand, whereas an approximately 100:0 ratio was achieved using either BINAP or DPPF as ligand [73].

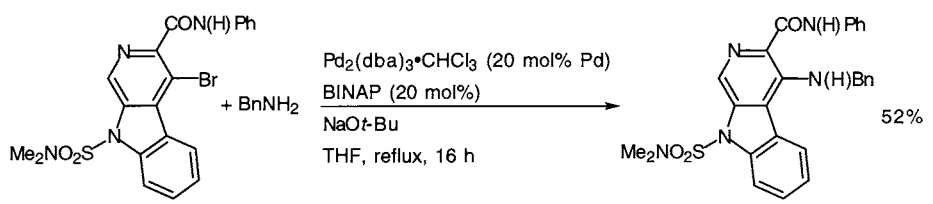
The substitution of BINAP for $P(o\text{-tolyl})_3$ also resulted in dramatic improvements in two other areas—the cross-coupling of optically active α-chiral amines, and the coupling of primary amines with bromopyridines. For instance, the *N*-arylation of 4-bromobiphenyl with α-methylbenzylamine (98% ee) using $P(o\text{-tolyl})_3$ as ligand afforded the corresponding secondary amine in modest yield (60%) and of decreased ee (70%), but in higher yield (86%) with no loss of optical purity when (±)-BINAP was used as the ligand [25].



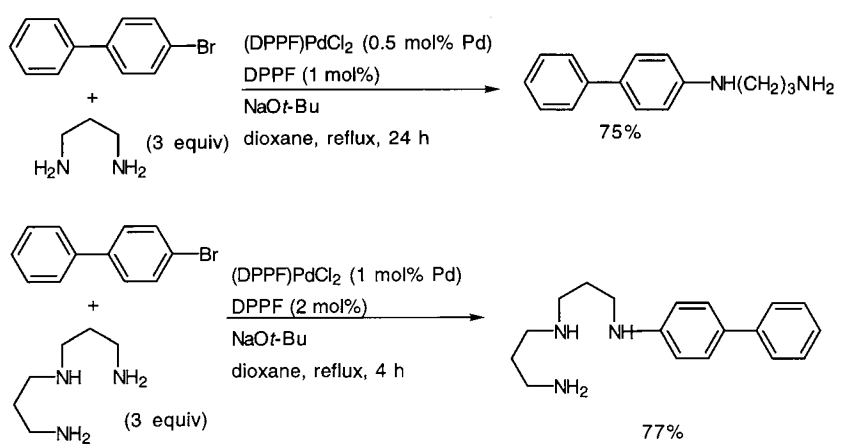
BINAP was also useful in the coupling of 3-bromopyridines with cyclohexylamine (82% yield), and in the coupling of 4-bromopyridine hydrochloride with *n*-hexylamine (67% yield) [22].



Dodd and Batch have recently demonstrated how this methodology can be used to introduce amino substituents onto the skeleton of 3-carboxy-β-carbolines [74].

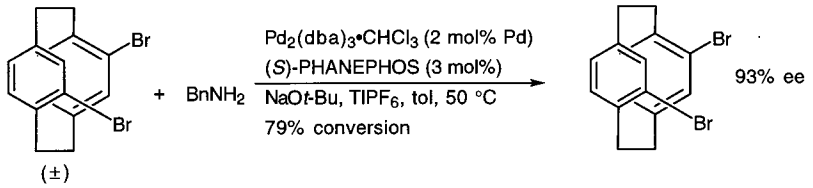


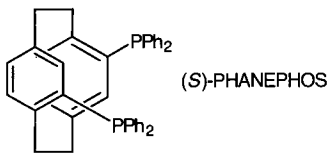
In addition to allowing for the selective monoarylation of primary amines, the Pd-catalyzed methodology also displays high selectivity in the monoarylation of polyamines. Beletskaya, Guilard, and Bessmertnykh have shown that a catalyst system prepared from $PdCl_2$ and DPPF catalyzes the monoarylation of 1,3-diaminopropane (three equivalent) with 4-bromobiphenyl in good yield [75]. Similarly, triamines and tetraamines are also monoarylated, preferentially at the primary amino terminus, in high yield.



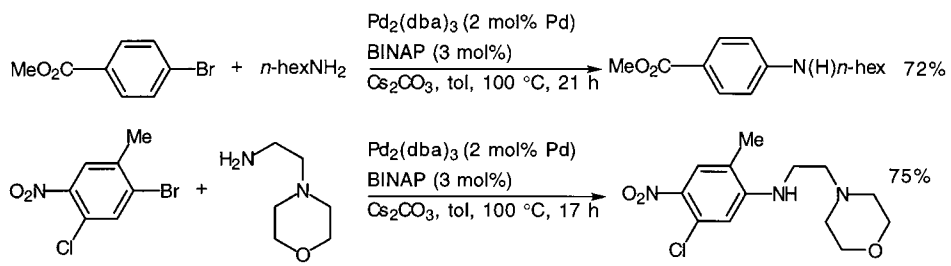
In a novel application of the use of chiral bisphosphine ligands, Rossen, Pye, and co-workers have found that the Pd-catalyzed amination of (±)-4,12-dibromo[2.2]paracyclophane with benzylamine, using (*S*)-(4,12-bis-(diphenylphosphino)[2.2]-paracyclophane [(*S*)-PHANEPHOS] as ligand effects a net kinetic resolution, where depending on the reaction conditions, the enantiomeric discrimination factor[12] varies from 3 to 13. In contrast, only a two-fold rate difference between the enantiomers was observed for the analogous Pd/BINAP catalyst system [76].

[12] The enantiomeric discrimination factor (*s*) is the ratio defined by the rate at which the faster reacting enantiomer reacts relative to the slower reacting enantiomer, and is calculated from the conversion (*C*) and the ee according to $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

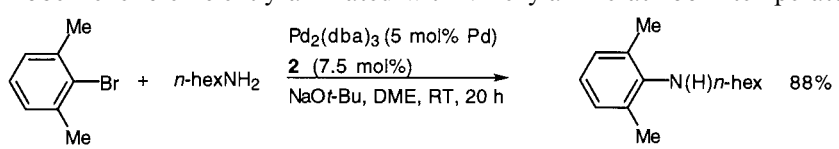




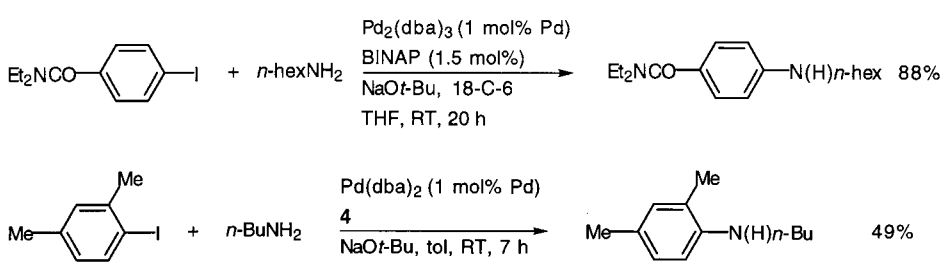
Where functional group compatibility is an issue, as was the case with secondary amines, we found that by utilizing Cs_2CO_3 as base, primary amines can be coupled with aryl bromides containing either methyl esters or nitro groups [28].



By virtue of the greater activity of the aminophosphine ligand **2**, even the sterically encumbered 2,6-dimethylbromobenzene is efficiently aminated with *n*-hexylamine at room temperature [59].



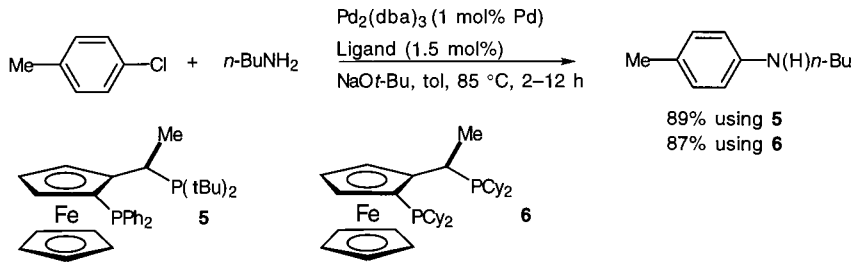
As with secondary amines, when aryl iodides are employed in Pd-catalyzed amination reactions in conjunction with a crown ether, the reactions can be conducted at or slightly above ambient temperature. Thus the diethyl amide of 4-iodobenzoic acid was successfully coupled with *n*-hexylamine in 88% at room temperature using BINAP as ligand, and in 78% yield using Tol-BINAP as ligand [27]. Using ferrocenyl ligand **4**, Hartwig demonstrated that an electronically neutral, *o*-substituted iodide could be aminated in moderate yield with a primary amine at room temperature, but without the need to employ 18-crown-6 [72].



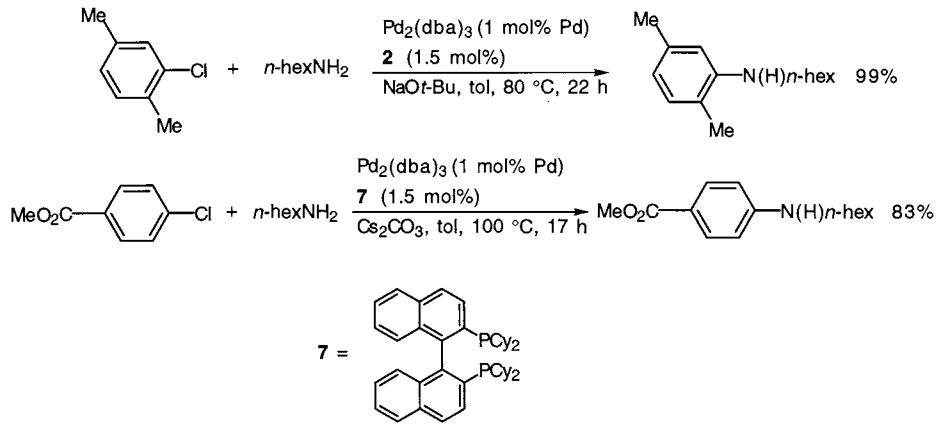
4.2. Cross-coupling of aliphatic amines with aryl chlorides

Chelating phosphine ligands have proven effective in the coupling of aliphatic amines with aryl chlorides. *n*-Butylamine is coupled very efficiently with 4-chlorotoluene using either of the known ferrocenyl-derived ligands **5** and **6** [72][13].

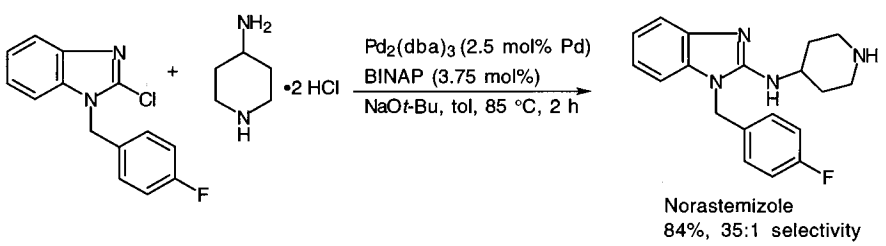
[13] For the use of **5**, see reference [77]. For the use of **6**, see references [78,79].



The cyclohexyl-phosphine ligands **2** and **7** were also found to be highly effective in Pd-catalyzed aminations of aryl chlorides, providing high yields even when employing electron-rich aryl chlorides, and an 83% yield for a methyl ester [59].

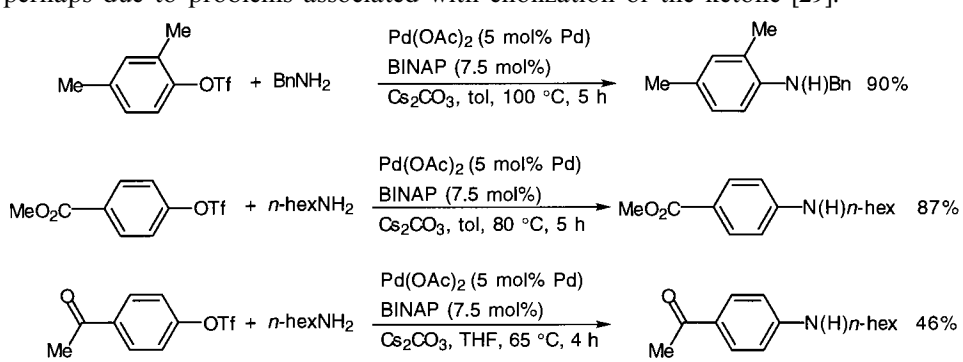


In a related process, Senanayake and co-workers have coupled the primary amino terminus of 4-aminopiperidine with a chlorobenzimidazole to afford the *N*-arylated product (the antihistamine norastemizaole) in 84% yield with 35:1 regioselectivity [80].

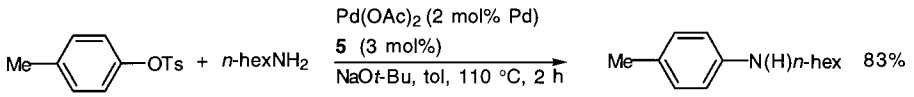


4.3. Cross-coupling of aliphatic amines with aryl sulfonates

Under standard conditions for the amination of aryl triflates (Pd/BINAP, Cs_2CO_3), benzylamine was coupled with the triflate of 2,4-dimethylphenol in 90% yield. While aryl triflate substrates containing methyl esters can also be aminated, attempted coupling of *n*-hexylamine with the triflate of 4-hydroxyacetophenone resulted in only fair yields, perhaps due to problems associated with enolization of the ketone [29].

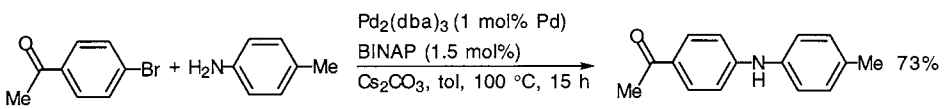


Although the leaving group ability of tosylates is orders of magnitude lower than that of triflates [81], Hartwig and Hamann have shown that **5** is an efficient ligand for the amination of aryl tosylates with primary amines [72].

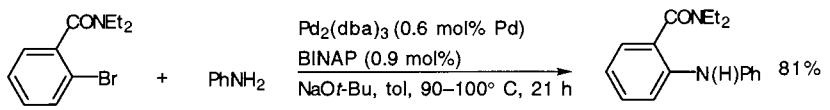


4.4. Cross-coupling of primary anilines with aryl bromides and iodides

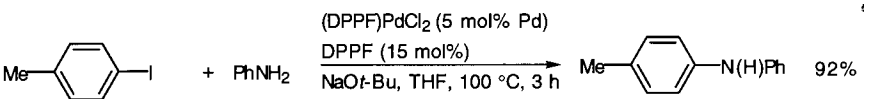
An interest in the synthesis of oligoanilines were an inspiration for our group to develop Pd-catalyzed couplings of primary anilines with aryl bromides. Using standard conditions [$Pd(OAc)_2$ and BINAP], we found that anilines were effectively coupled with a variety of aryl bromides [20].



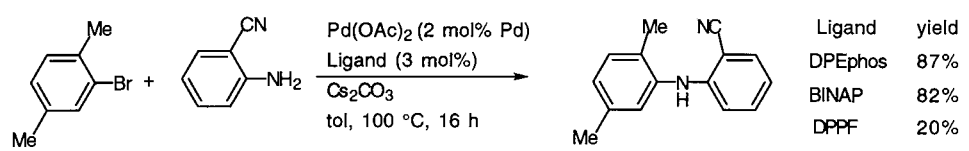
This methodology has subsequently been applied by Snieckus and co-workers to prepare intermediates in the preparation of acridones [82].

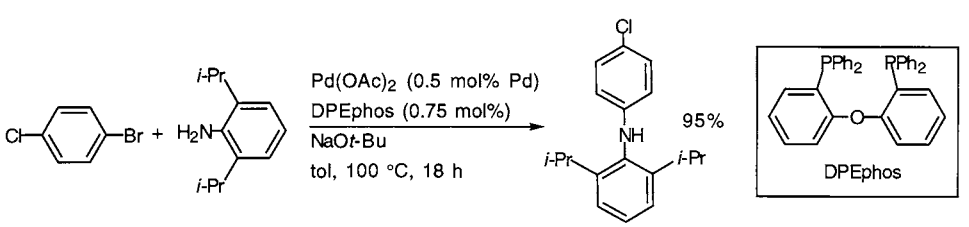


Similarly, Hartwig and co-workers have demonstrated the utility of $(DPPF)PdCl_2$-catalyzed reactions of aryl bromides and iodides with anilines [36].

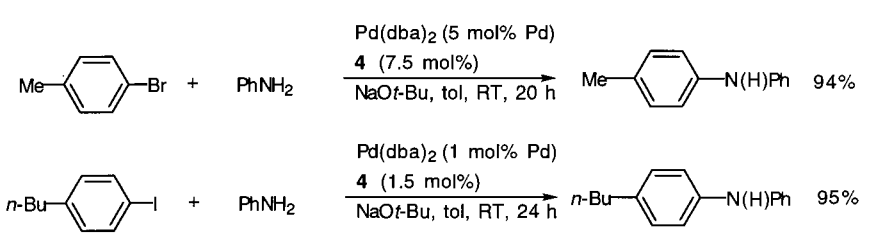


During a search for inexpensive ligands we investigated the use of bis[2-(diphenylphosphino)phenyl] ether (DPEphos). This ligand, reported by van Leeuwen et al. [83], is easily prepared from diphenyl ether by double lithiation, followed by trapping with chlorodiphenylphosphine. In a comparative study, DPEphos, BINAP, and DPPF were combined with $Pd(OAc)_2$, and the resulting systems were assayed for their effectiveness in catalyzing the *N*-arylation of primary anilines. DPEphos was found to be as good BINAP in the cases studied, and as good as or superior to DPPF [33].



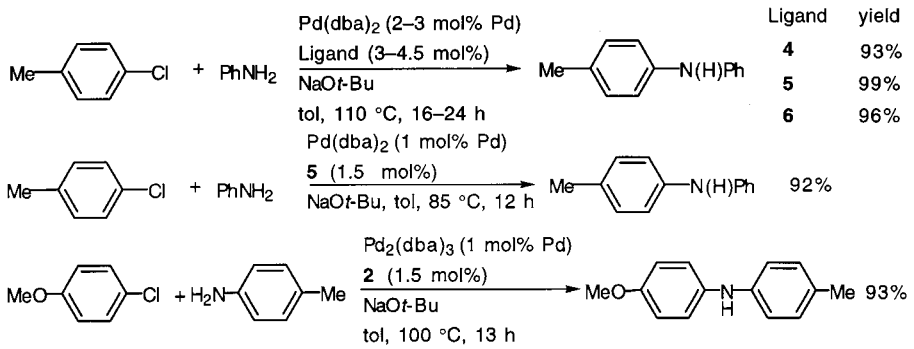


Hindered, chelating alkylphosphines have also been employed by Hartwig and Hamann, who showed that aniline reacts with 4-bromotoluene and *p*-(*n*-butyl)iodobenzene in high yields at room temperature. These results underscore the high activity of the **4**/Pd(0) catalyst system [72].



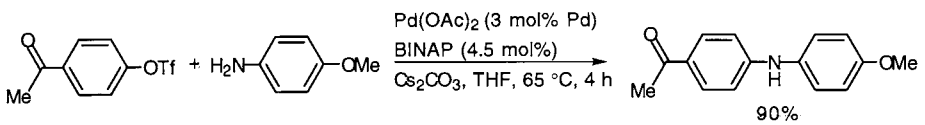
4.5. Cross-coupling of anilines with aryl chlorides

Despite the lower reactivity often displayed by aryl chlorides in Pd-catalyzed aminations, Hartwig and Hamann have shown that ferrocenyl-derived ligands **4**–**6** provide nearly quantitative-yielding aminations of unactivated aryl chlorides with aniline [72]. Similarly, we have demonstrated the versatility of aminophosphine ligand **2** in the Pd-catalyzed coupling of *p*-chloroanisole with *p*-methylaniline [59].

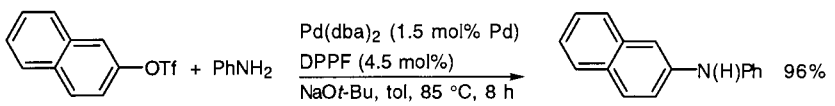


4.6. Cross-coupling of anilines with aryl sulfonates

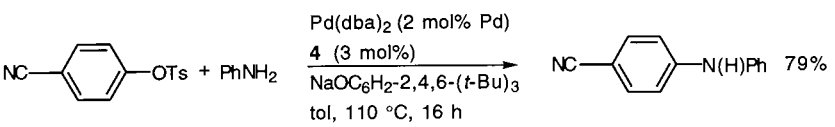
We have shown that using standard conditions, [$Pd(OAc)_2$, BINAP, Cs_2CO_3 as base] primary anilines can be coupled with electron-poor triflates in high yields, even with substrates containing an enolizable ketone [29].



With NaO*t*-Bu as base, Hartwig and co-workers have demonstrated the utility of DPPF as ligand in cross-couplings of anilines with unactivated aryl triflates [37].

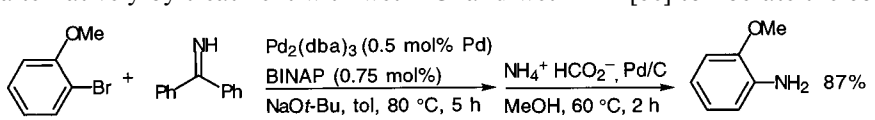


Hartwig and Hamann have since shown that even the less reactive tosylate functionality can participate in aniline coupling reactions. Using the ferrocenyl-derived ligand **4**, they succeeded in the cross-coupling of aniline with the tosylate of 4-cyanophenol in 79% yield [72].

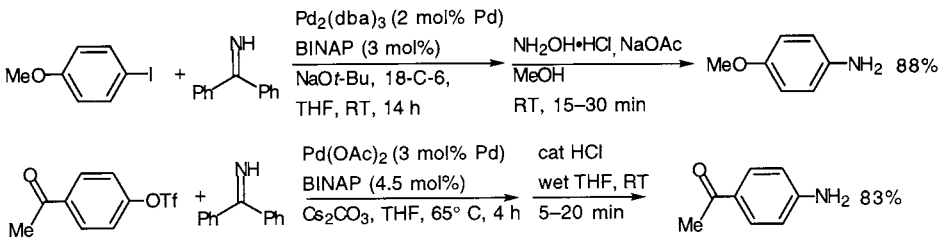


5. *N*-Arylation of ammonia surrogates

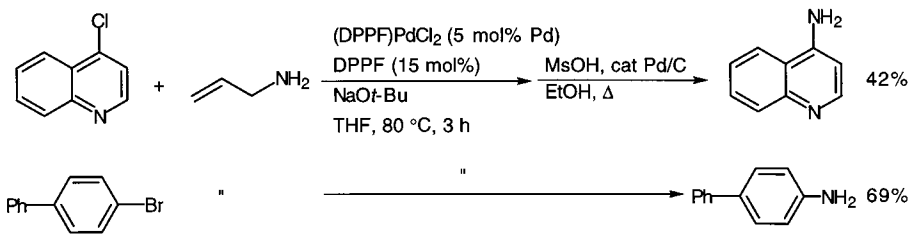
Benzophenone imine has been used extensively in our group as a surrogate for ammonia in Pd-catalyzed aminations of aryl halides and aryl triflates. In addition to the practical feature that it is commercially available, it has also been found to impart high crystallinity to its derivatives, is stable to base and mild acid, yet can be cleaved under a variety of controlled conditions. We have found benzophenone imine to undergo the widest range of *N*-arylation reactions, wherein the use of Pd/BINAP conditions are suitable in reactions with aryl bromides, iodides, and triflates, as is shown below [30]. Upon completion of reaction, the benzophenone moiety of the coupled products can be cleaved by catalytic hydrogenation with ammonium formate using Pd/C [84], or by transamination with hydroxylamine [85], or alternatively by treatment with wet HCl and wet THF [86] to liberate the corresponding primary aniline derivative[14].



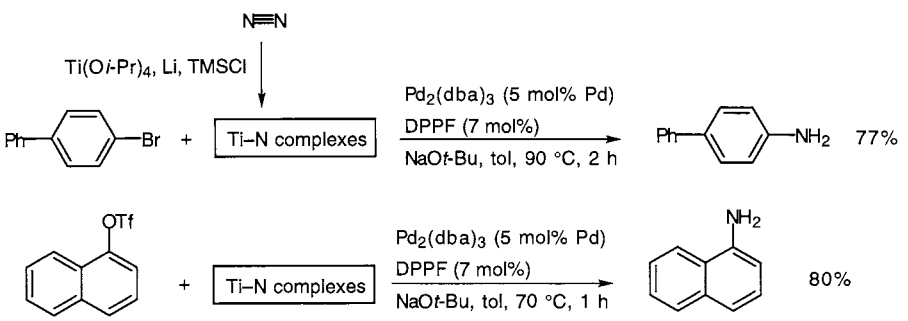
[14] Hartwig has also described the Pd-catalyzed coupling reaction of benzophenone imine. See reference [40].



Putman and co-workers have developed an alternative protocol, based on the use of allylamine or diallylamine. In most cases, Pd-catalyzed *N*-arylation of allylamine proceeded in good yield, as did subsequent cleavage with methanesulfonic acid using catalytic Pd/C to afford the primary aniline products [87].

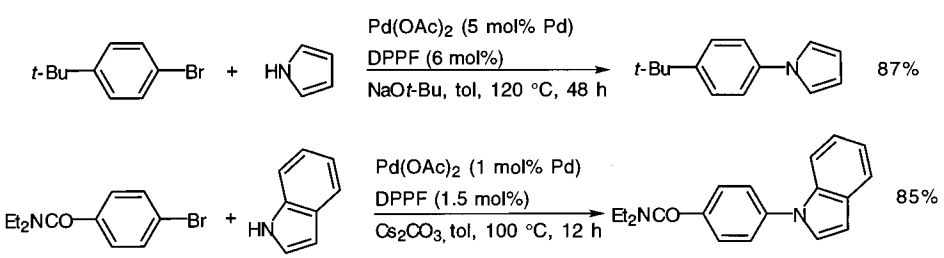


In a recent development, Mori and Hori have shown that molecular nitrogen can serve as the nitrogen source in the conversion of aryl bromides and aryl triflates to unsubstituted aniline derivatives [88]. In their protocol, titanium-based nitrogen fixation complexes were prepared in situ from dinitrogen, Ti(O*i*-Pr)$_4$, Li, and TMSCl. In the presence of Pd(0), ligand, aryl bromide, and NaO*t*-Bu, the nitrogen moiety likely undergoes transmetalation to form a palladium amide, which upon reductive elimination and workup affords the primary aniline derivative.



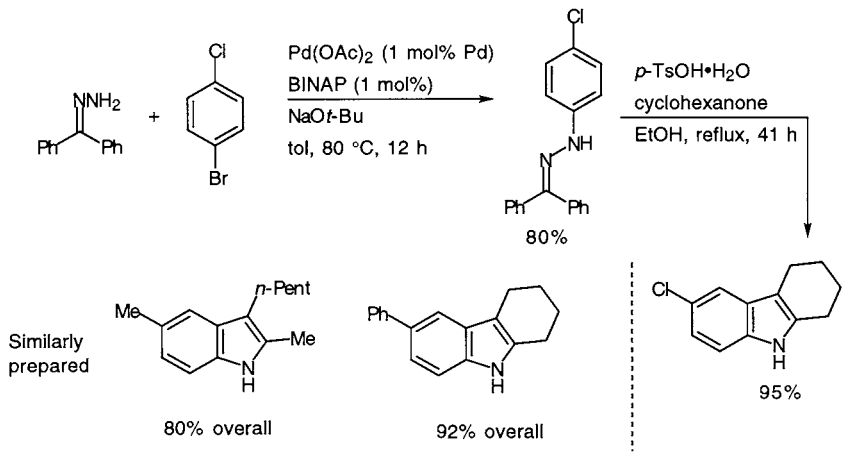
6. *N*-Arylation of other nitrogen-containing substrates

Pyrroles, indoles, and carbazoles constitute a special class of nitrogenous bases. Under standard Pd-catalyzed *N*-arylation conditions, these compounds can be prepared in high yield using both electron-rich and electron-poor aryl bromides. However, the former requires long reaction times at high temperatures, and no examples of *o*-substituted aryl bromide substrates were reported [40].



Using standard conditions, benzophenone hydrazone undergoes clean Pd-catalyzed cross-coupling reactions with a variety of aryl bromides. Although these *N*-arylated benzophenone hydrazones are not in and of themselves generally useful, we have found that they are convenient one-step precursors to a variety of indole products [89]. Treatment of the *N*-aryl hydrazone with an enolizable ketone in the presence of *p*-toluenesulfonic acid monohydrate

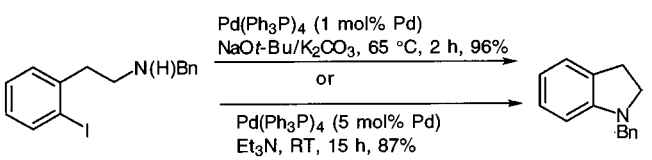
directly affords the corresponding indole, presumably via hydrolysis of the *N*-aryl benzophenone hydrazone, condensation of the resulting *N*-aryl hydrazine with the enolizable ketone, followed by a Fischer indolization reaction[15,16].



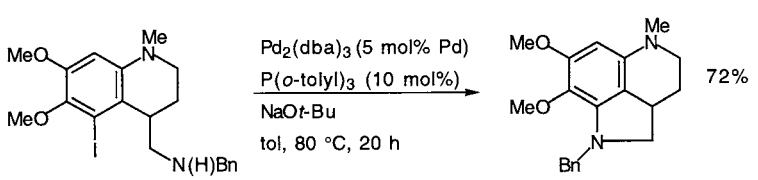
7. Intramolecular *N*-arylation reactions

Boger and co-workers were the first to disclose a palladium-mediated intramolecular closure of an amine onto an aryl bromide, although this reaction required stoichiometric quantities of palladium [92–94]. Following our leads into the use of in situ-generated aminostannanes for intermolecular Pd-catalyzed cross-coupling reactions, we were able to adapt that methodology to intramolecular ring closures [23].

As in the case of intermolecular cyclizations, the Pd-catalyzed *N*-arylation reaction could be conducted in the absence of a main group metal. In this study, aryl iodides were found to be better substrates than aryl bromides. It was also noted that the ring closure could also be carried out at room temperature, using Et_3N as solvent (and also functioning as base) [23].



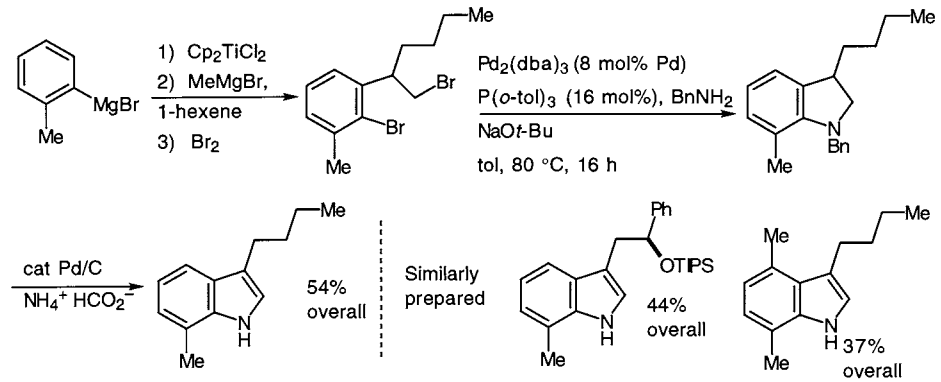
In an application of this methodology to the formal total synthesis of a number of quinoline-containing alkaloids, we effected a Pd-catalyzed 5-membered ring closure of a secondary amine onto an aryl iodide using the catalyst precursors $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ [19].



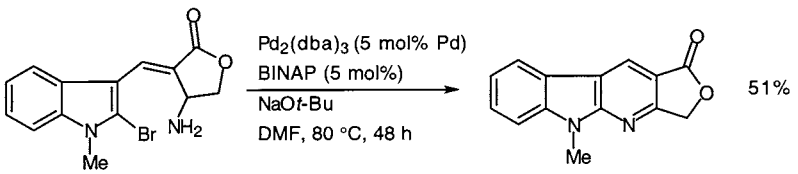
In conjunction with our studies on the use of titanocene-stabilized benzyne complexes, we have developed a route wherein cyclization of a secondary benzylic amine onto an aryl bromide is the key step. Starting from an aryl bromide, a terminal olefin, and benzylamine, a number of structurally diverse indoles can be prepared in reasonable overall yields [32].

[15] Hartwig has also described the Pd-catalyzed coupling reaction of benzophenone hydrazone. See reference [90].

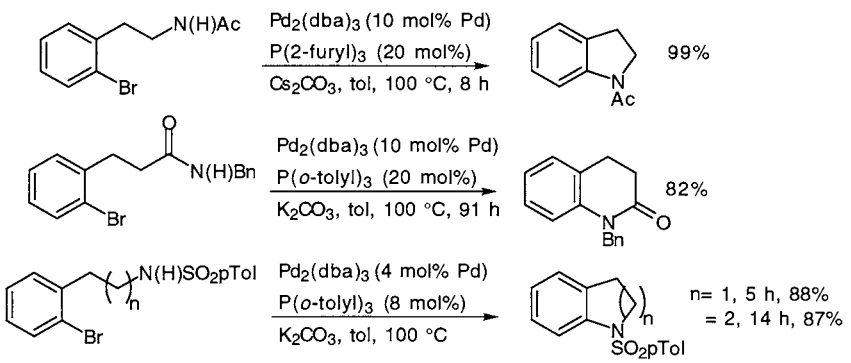
[16] For a review on the Fischer indolization reaction. See reference [91].



In other synthetic applications, Dodd and Abouabdellah have also utilized an intramolecular Pd-catalyzed amination reaction in the preparation of pyrido[2,3-b]indoles, where ring closure, presumably followed by air oxidation affords the tricyclic pyridoindole [95].

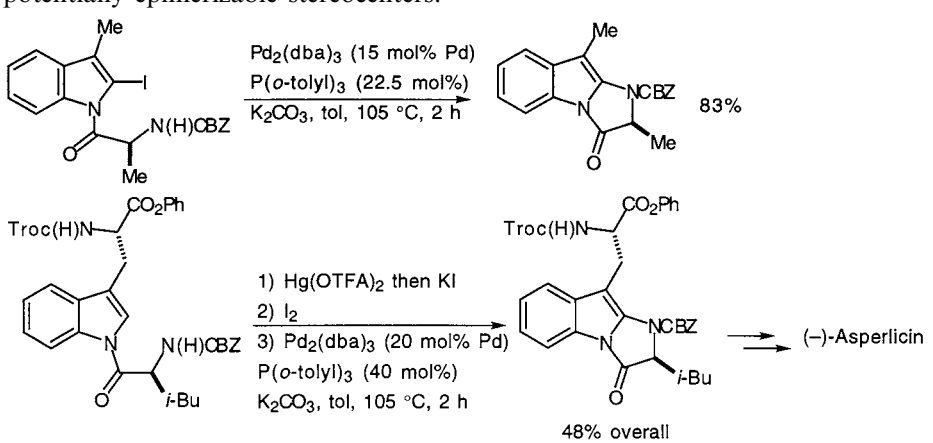


Though our attempts at conducting the intermolecular version were not successful, we have developed conditions for intramolecular amide cyclizations, as well as cyclizations of benzamides (to generate lactams) [19].



The former case proceeds optimally for five-membered rings (99 vs. 44% yield for 6-membered rings, while the latter case affords higher yields of 6-membered rings (82 vs. 59% yield for 5-membered ring formation). In both cases, the use of aryl bromides was preferred over the use of aryl iodides. Similarly, sulfonamides could also be cyclized to form both five- and six-membered rings [19].

Snider and co-workers have shown that carbamates readily undergo intramolecular Pd-catalyzed ring closing reactions in high yields. They were able to apply this reaction to the total synthesis of (−)-asperlicin [96]. Of interest in the Pd-catalyzed cyclization is not only the selectivity of the ring-closure, but also the preservation of two potentially epimerizable stereocenters.



8. Conclusions

In summary, the Pd-catalyzed *N*-arylation reaction is a broadly useful method for the construction of a wide variety of substrates. Central to the development was the ongoing development of new ligand systems and the careful optimization of reaction conditions and reagents, supplemented by a sound mechanistic understanding of both organic and organometallic chemistry. It is anticipated that future studies will not only improve the scope and understanding of this process, but like the predecessors before [41–43], will lead to new applications of Pd-catalyzed cross-coupling reactions.

Acknowledgements

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