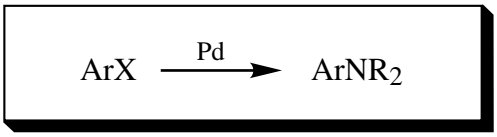


III.3.2 Palladium-Catalyzed Amination of Aryl Halides and Related Reactions

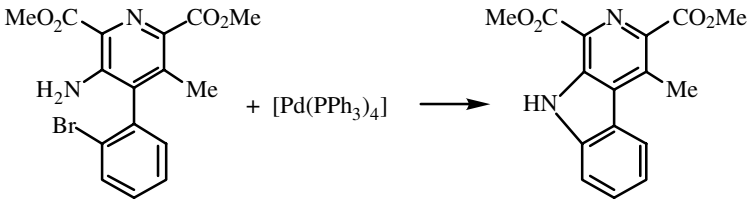
JOHN F. HARTWIG

A. INTRODUCTION TO AMINATION

A.i. Cross-Coupling and Early Amination Studies

From reading the other sections of this book, one readily sees that palladium complexes serve as catalysts for a variety of C—C bond-forming cross-coupling processes. This cross-coupling chemistry involves the metal-catalyzed reactions between nucleophiles and electrophiles that display a wide variety of steric and electronic properties. It is, therefore, surprising that carbon–heteroatom bond formation by cross-coupling processes lay close to dormant until roughly five years ago.

There were a few isolated examples of coupling reactions that form C—P and C—S bonds.[1] Tunney and Stille had reported the Pd-catalyzed formation of the C—P bonds in aromatic phosphines,[2] and several groups had reported the formation of C—S bonds in sulfides using catalysts based on both palladium and nickel.[3]–[6] In addition there were suggestions that simple procedures for C—N bond formation could be developed and that palladium complexes could act as catalysts for C—N bond-forming cross-coupling processes. For example, Boger and co-workers used stoichiometric amounts of palladium to form aromatic C—N bonds in a β-carbolide natural product by an intramolecular process (Eq. 1).[7]–[9] Perhaps more closely related to the work discussed in detail here,



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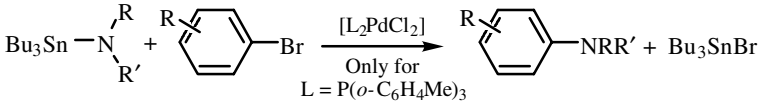


(2)

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0 © 2002 John Wiley & Sons, Inc.

Kosugi and co-workers reported that palladium complexes with P(*o*-tolyl)$_3$ as ligand would catalyze the formation of arylamines from aryl halides and aminostannanes (Eq. 2).[10],[11] A subsequent full paper demonstrated the scope and limitations of this chemistry. Although a small range of aromatic halides and aminostannanes were shown to undergo this process, the work of Kosugi and co-workers revealed one class of catalyst that could be used to form tertiary amines. It also demonstrated the potential for palladium chemistry to provide a general route to arylamines and other related compounds by aromatic C—N bond formation.

A.ii. Basic Principles

Some fundamental inorganic chemistry that is important for understanding which complexes will undergo the aromatic C—N and C—O bond-forming processes will be presented before the catalytic transformations. First, the three reaction types involved in the catalytic cycle to form arylamines are similar to those found in the catalytic cycle for C—C bond formation: oxidative addition of aryl halide to Pd(0) complexes, "transmetallation" that converts an arylpalladium halide complex to an arylpalladium amido complex, and reductive elimination to form a C—N or C—O bond. The oxidative addition step is identical to the addition that initiates C—C bond-forming cross-couplings,[12]–[15] but the steps that form the arylpalladium amido complexes and that produce the arylamine product are different. The mechanism for these steps is discussed after presentation of the scope of the amination process.

Several properties of amido and alkoxo complexes are different from those of alkyl complexes, and initially one might expect these properties to generate large differences in reactivity. First, amido groups are harder ligands than alkyls, and alkoxo groups are even harder than amides.[16],[17] Low-valent metal centers such as those in Pd(II) phosphine complexes are soft. This mismatch of the hard ligand with the soft Pd(II) center[18]–[20] had been predicted to produce highly reactive species, and low-valent amido and alkoxo complexes often resisted isolation and characterization.[16],[17] Most significant for the cross-coupling, it was believed that this class of amido or alkoxo complex would undergo rapid β-hydrogen elimination to form metal hydrides. Indeed, reaction with basic alcohol solutions is a standard method for metal reduction.[16] Moreover, reductive eliminations of amines and ethers had not been observed prior to the work discussed in this section.

Second, amido and alkoxo ligands can act as π-donors. This property, in combination with the presence of filled metal d orbitals, was another means to rationalize the typically high reactivity of late metal amido and alkoxo complexes.[17] Furthermore, the nitrogen and oxygen electron pairs allow these groups to act as efficient bridging ligands to generate multinuclear complexes. There are many bridging arylamido, hydroxo, and phenoxo complexes of late metal systems.[17],[21]–[24] Presumably, it is important to prevent formation of these dimeric complexes to observe efficient catalysis.[23]–[25]

Before considering the different types of amination reactions, one must also understand the structural aspects of phosphine ligands. Standard cone angles can predict steric properties,[26] but one must keep in mind that many conformations are possible for symmetrical phosphines and even more conformations are available for unsymmetrical phosphines, making it difficult to calculate a cone angle in many cases. The relative geometries of the two phosphines in chelating ligands is also important. "Natural bite angle" is a property that has been used to describe the P—Pd—P angle (more generally P—M—P).[27]–[29] In general, Pd(0) complexes adopt sterically preferred geometries such as tetrahedral, trigonal planar, or linear, because they are d^{10}, and Pd(II) complexes prefer square planar or

T-shaped geometries because they are d^8. Thus, one Pd(0) or Pd(II) complex may be more or less stable than another because of the natural bite angle of the bisphosphine ligand. Of course, more complex phosphine ligands are available, including those with accompanying nitrogen or oxygen donors.

Phosphine electronic properties also vary widely. Alkylphosphines are stronger σ-donors than are arylphosphines, and arylphosphines of different donating ability have been created by changing substituents on the phosphine aromatic groups. The electronic properties of different phosphine ligands have been assessed by measuring the C—O stretching frequencies of $Ni(CO)_3L$ complexes.[26] However, it is difficult to assess how a particular change in stretching frequency will translate to differences in reactivity, and it is even more difficult to predict how these electronic perturbations will balance the relative rates of different steps in the catalytic cycle.[30] Nevertheless, this measurement provides a relative donating ability of different phosphine ligands.

A.iii. Classes of Amination Reactions

When choosing the appropriate catalyst for the amination processes, it is suitable to divide the types of substrates into categories. The amines can be divided into four categories: secondary alkylamines, secondary arylamines, primary alkylamines, and primary arylamines. Alkylamines can, of course, undergo β-hydrogen elimination as intermediate palladium amides, while the arylamines cannot. Similarly, indoles, imines, hydrazones, primary amides, and carbamates cannot. These nitrogen nucleophiles can be divided into two classes: weakly nucleophilic reagents such as indoles, pyrroles, carbazoles, amides, and carbamates, and more strongly nucleophilic reagents such as hydrazones and imines. The aryl electrophiles can also be divided into categories with different reactivity patterns. Aryl iodides, bromides, and chlorides have dramatically different reactivity. Aryl triflates and tosylates should also be considered separately from halides because not all catalysts that react with aryl halides react with aryl triflates, and most do not react with aryl tosylates. Highly reactive aryl electrophiles bearing *p*-CN, *p*-C(O)R, or *p*-NO_2 groups should also be considered separately from unactivated or deactivated aryl groups such as those bearing alkyl, alkoxy, and amino substituents.

The number of different ligands that can be used in amination chemistry is becoming bewildering. The intention of this review is to assist researchers wishing to conduct Pd-catalyzed aminations of aryl halides in their selection of a catalyst for a particular transformation. Although a synopsis of mechanistic data is provided in the final section, reviews with more detailed accounts of the mechanistic aspects of these reactions can be found elsewhere.[31]–[33] Several reviews of catalyst development for Pd-catalyzed amination have been published, and a review of Pd-catalyzed carbon–heteroatom bond formation has been published.[31],[34]–[37] However, catalyst development for these processes has been rapid, and this review contains several new systems and synthetic applications. This development is likely to continue in the near future. Thus, some comments and predictions are made by the author about certain transformations that are likely to be developed based on known synthetic and mechanistic information.

A.iv. Overview of Catalyst Selection

Table 1 provides a classification of the types of amination reactions and the classes of catalysts that are most appropriate for the different reactions. Of course, catalyst development is an ongoing and evolving area of research, and this table includes results with systems in

TABLE 1 Summary of Appropriate Catalyst Choice for Aromatic C-N Bond Formation

N-substrate / Ar-X	1° Alkyl	1° Aryl	2° Alkyl	2° Aryl	Hydrazone	Imine	Indole	Carbamate/ Amide
ArBr	BINAP[a]	P(*t*-Bu)$_3$ DPPF DPEphos BINAP	P(*t*-Bu)$_3$ PPF-OMe (**1**) BINAP P(*o*-tol)$_3$	P(*t*-Bu)$_3$ DPPF P(*o*-tol)$_3$	DPPF BINAP	DPPF BINAP	P(*t*-Bu)$_3$ DPPF	P(*t*-Bu)$_3$ PPh_3 for intramol.
ArCl	PPF-P(*t*-Bu)$_2$ P(*t*-Bu)$_3$	P(*t*-Bu)$_3$	P(*t*-Bu)$_3$ Guram's ligand (**4**) $ArPR_2$ (**2**)	P(*t*-Bu)$_3$			P(*t*-Bu)$_3$	P(*t*-Bu)$_3$
ArI	BINAP	DPPF BINAP	DPPF BINAP					
ArOTf	BINAP	DPPF BINAP	BINAP DPPF	DPPF	BINAP			
ArOTs	PPF-P(*t*-Bu)$_2$		D′BPF					
Heteroaryl-X	BINAP	BINAP	P(*t*-Bu)$_3$ BINAP		BINAP			

[a]BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DPPF = 1,1′-bis(diphenylphosphino)ferrocene; PPF-OMe (**1**) = 1-[(2-diphenylphosphino)ferrocenyl]ethyl methyl ether; PPF-P(*t*-Bu)$_2$ = 1-[(2-diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphopshine; D*t*-BPF = 1,1′-bis(di-*t*-butylphosphino)ferrocene; Guram's ligand (**4b**) = dicyclohexy1 [2-(2-methyl-1,3-dioxolan-2-yl)phenyl]phosphine; $ArPR_2$ (**2**) = 2-dimethylamino-2′-dicyclohexylphoshino-1,1′-biphenyl.

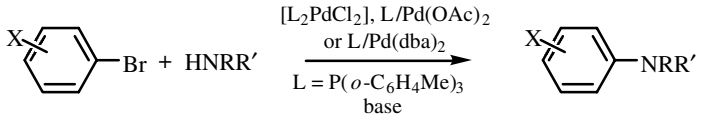
the open literature by May 15, 1999, and some results in papers submitted by the author prior to this date. The ordering of ligands within each category is certainly subjective, and one ligand may be more or less effective within the categories for a particular substrate combination.

In general, arylphosphine ligands are suitable for reactions with aryl bromides, iodides, and activated aryl chlorides, but not for those with unactivated aryl chlorides. Furthermore, monophosphines tend to be less suitable ligands for amination of aryl triflates or tosylates than are chelating phosphines, although exceptions exist. Finally, it was originally believed that chelating ligands were necessary for reactions of halopyridines,[38] but amination chemistry with bromopyridines has now been accomplished with the simple monophosphine P(*t*-Bu)$_3$.[39] In general, monophosphines can be used for reactions of aryl halides with secondary amines, and many reactions of acyclic or cyclic secondary amines with aryl halides occur in high yield when using catalysts bearing *t*-butylphosphines, such as those generated by a 1:1 ratio of P(*t*-Bu)$_3$ and Pd(dba)$_2$.[40] Although more expensive ligands that are commercially available in optically pure form give good yields for reactions of secondary amines,[41] their reaction rates are lower and they do not provide higher yields; similarly, the standard chelating ligands for aromatic C—N bond formation, BINAP and DPPF, provide no advantage over P(*t*-Bu)$_3$ in most cases. In general, chelating ligands provide high yields for reactions with primary alkylamines or with arylamines.[42],[43] The chelating ligands tend to prevent rapid β-hydrogen elimination by the primary amido intermediate,[23],[42] although reactions of primary amines with aryl halides can be conducted with *t*-butylphosphine ligands. The chelating ligands also tend to reduce diarylation of the primary amine.[43] Until recently, reactions of primary arylamines with aryl halides also required chelating phosphines. The reason for the success of these systems is unclear, but it has recently been shown that a 1:1 ratio of P(*t*-Bu)$_3$/Pd(dba)$_2$ will catalyze the amination of aryl bromides using primary arylamines at room temperature.[40]

B. SPECIFIC EXAMPLES OF AMINATION

B.i. Secondary Alkylamines

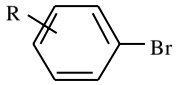
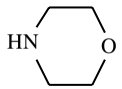
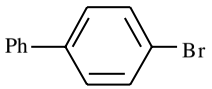
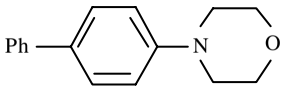
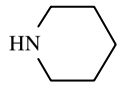
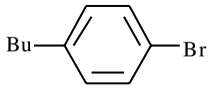
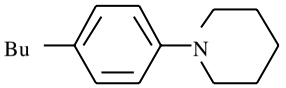
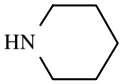
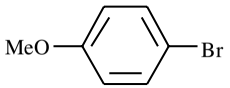
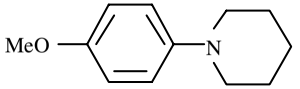
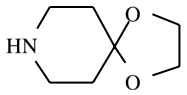
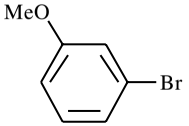
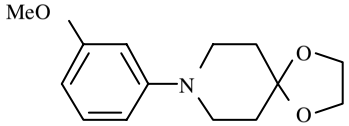
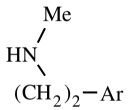
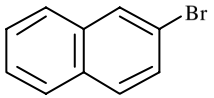
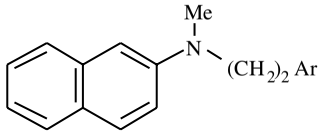
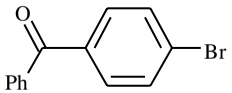
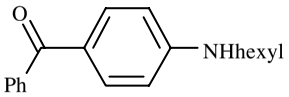
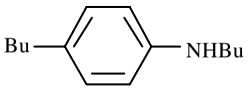
This section will cover the amination of secondary alkylamines, defined here as amines containing two alkyl groups or one alkyl and one aryl group bound to nitrogen. The reactions of secondary amines with aryl bromides, along with the reaction of primary amines with activated aryl bromides in the presence of stoichiometric amounts of base and a palladium catalyst containing P(*o*-tolyl)$_3$ as ligand, were the first aminations of aryl halides that did not involve main-group amido reagents (**Table 2**).[44],[45] Under these conditions, one could prepare dialkylanilines from either cyclic or acyclic secondary amines at 80 °C in aromatic or ether solvents (Eq. 3). Reactions of cyclic secondary amines occurred in significantly higher yields with some aryl halides. Reactions using *t*-butoxide as base



(3)

X = *o*, *m*, or *p*- alkyl, phenacyl, amino, alkoxy
base = NaO-*t*-Bu, or LiN(SiMe$_3$)$_2$

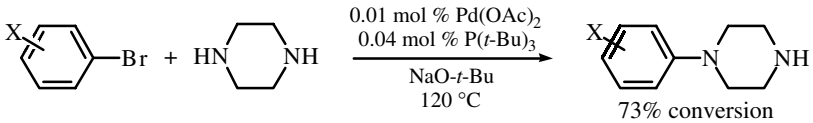
TABLE 2. Initial Tin-Free Aminations of Aryl Halides Catalyzed by L_2PdCl_2, L = P (o-$C_6H_4Me)_3$

Amine		Base	Product	Yield (%)
		NaO -t-Bu		86
		$LiN(TMS)_2$		89
		$LiN(TMS)_2$		89
		NaO-t-Bu		81
		NaO-t-Bu		78
H_2Nhexyl		NaO-t-Bu		72
H_2NBu	R = Bu	$LiN(TMS)_2$		<2

occurred in higher yields than those with silylamide bases. Sodium counterion was important; lithium *t*-butoxide gave no reaction and potassium *t*-butoxide gave low yields and dark-colored reaction solutions.[44]

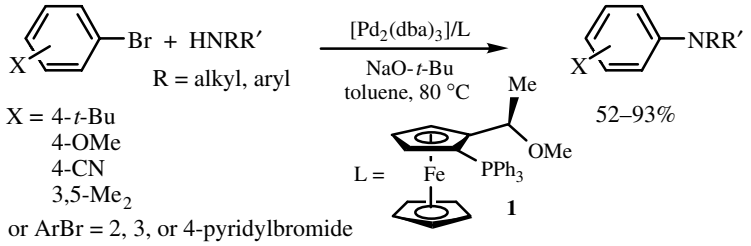
A second development in the formation of dialkylanilines was the use of chelating phosphines. For example, Hartwig and Buchwald concurrently reported the use of BINAP and DPPF for amination chemistry.[42],[43] These ligands are suitable for some amination chemistry with secondary alkyl amines. In some cases, turnover numbers were improved over the original system for the reactions of secondary amines with aryl bromides,[43] but the improvement in yield for reactions of secondary amines over that observed with the original catalyst system was modest. Moreover, the reactions of secondary amines using catalysts derived from BINAP and DPPF typically require higher catalyst loads and are less efficient than those developed subsequently containing *t*-butylmonophosphines. However, these catalysts did allow for reactions of secondary alkylamines with aryl iodides. Even after screening various reaction conditions, the original system was not particularly valuable for aminations of aryl iodides.[46] Most important for this section of the review, the catalysts with chelating ligands still gave variable yields for amination with acyclic secondary amines.

A remarkable advance was reported by Nishiyama, Yamamoto, and Koie, which involved the use of P(*t*-Bu)$_3$ for the amination of cyclic secondary amines with high turnovers (Eq. 4).[39],[47] With this simple, commercially available ligand, they were able to obtain roughly 7000 turnover numbers for the amination of aryl bromides with piperazine, although at high temperatures. Little cross-coupling with this ligand had been reported previously, and this paper precedes the use of P(*t*-Bu)$_3$ in other types of C—C bond-forming cross-coupling chemistry.[48]–[50]



73% conversion
88% selectivity
100% conversion with 0.02 mol % (4)

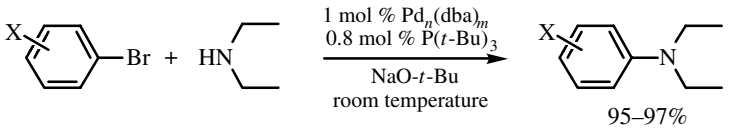
The solution to the problem of catalysts for a general reaction of acyclic secondary amines with aryl halides began with the use of Kumada's phosphinoether ligand **1** (Eq. 5).[41] With palladium catalysts bearing Kumada's ligand, high yields were observed for this type of amination reaction. However, the ligand is extremely expensive in its commercially available optically pure form, and the synthesis is multistep. Nevertheless,



52–93% (5)

this ligand led Buchwald's group and Guram at Symyx to prepare more straightforward ligands with N and O donor atoms accompanying the phosphine. Biaryl-based P,N ligands containing alkyl substituents at phosphorus (**2** in **Figure 1**) provided an efficient catalyst for this class of reaction.[51] Although perhaps simpler to prepare than Kumada's systems, the preparation of these ligands was multistep and the ligand is susceptible to air oxidation. Guram prepared diphenylphosphino and dicyclohexylphosphinoether ligands **4a,b** with phenyl backbones. These ligands are readily prepared in two steps from inexpensive 2-bromoacetophenone and provide high yields for reactions of cyclic and acyclic secondary amines.[52],[53]

Two other groups investigated P,N ligands for amination chemistry with secondary amines. Uemura and co-workers have prepared ligands similar to those of Kumada, but based on arene chromium complexes rather than ferrocenes.[54] Catalysts containing ligand **3** in **Figure 1** provide good yields for some aminations with dialkylamines. For example, reactions of unactivated aryl halides with diethylamine, *N*-ethylaniline, or cyclohexyl ethylamine occurred in yields ranging from 73% to 90%. A P,N ligand with an imine nitrogen donor was prepared and used for amination by Arques and co-workers.[55] However, a single amination reaction was reported and it was run at 160 °C.



(6)

Thus, the least expensive catalyst system for low-temperature, high-yield amination of secondary amines, including acyclic secondary alkylamines, is one recently reported and based on Koie's finding at high temperature. This system is conveniently generated by mixing a 1:0.8 ratio of Pd$_n$(dba)$_m$ and P(*t*-Bu$_3$)$_3$ (Eq. 6).[40] Hartwig's group reasoned that the use of this palladium precursor would avoid any loss of catalyst or ligand during reduction to Pd(0) and that a 1:1 ratio of ligand/palladium would ensure that the reaction solution was void of free ligand that inhibits the rate of the reaction. With this catalyst system containing commercially available components, room-temperature (r.t.) amination of aryl bromides was conducted with cyclic and acyclic secondary alkylamines in yields that are essentially quantitative. The full scope of this chemistry has not been explored—reactions of highly hindered aryl halides, heterocyclic halides, and branched secondary amines have not been conducted—but this simple catalyst system appears to provide a general catalyst for the reaction of aryl bromides with secondary alkylamines. One should be aware that the P(*t*-Bu)$_3$ ligand is susceptible to air oxidation, although much more

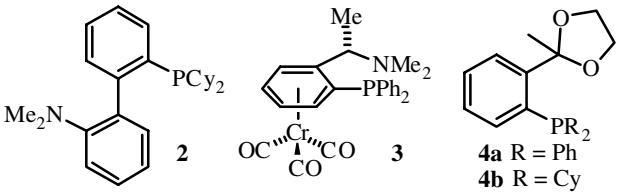
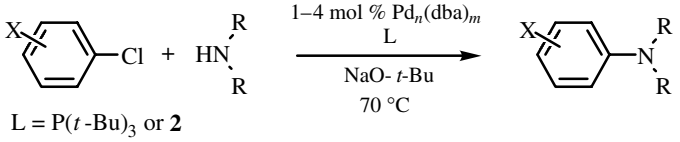


Figure 1

slowly than typical trialkylphosphines. Solutions (10%) of the ligand in hexanes are now avaiable from Strem in conventional or Sure/Seal packaging.

The amination of aryl chlorides is significantly more difficult than the amination of aryl bromides because of the decreased reactivity of chloroarenes.[56] Their low cost, however, makes them important substrates for mild coupling chemistry. In general, highly activated aryl chlorides such as 4-chlorobenzonitrile or 4-chlorobenzophenone react similarly to bromobenzene in the oxidative addition step, and the standard arylphosphine ligands are, therefore, suitable for Pd-catalyzed chemistry with these substrates. Indeed, the first amination of aryl chlorides was conducted with these activated substrates and the standard ligand systems.[57]

However, alkylphosphines are typically required for Pd-catalyzed reactions with unactivated aryl chlorides, and the first Pd-catalyzed amination of unactivated aryl chlorides employed PCy_3 as ligand (Cy = cyclohexyl).[58] Although good yields were observed in selected cases, the catalyst containing this ligand was not suitable for most amines. Thus, new ligand systems were sought for a more general catalyst to conduct aminations of aryl chlorides. Hartwig's group prepared a *t*-butyl analog of DPPF, D′BPF (1,1-bis-di-*t*-butylphosphinoferrocene), which demonstrated that sterically hindered alkylphosphines were particularly well suited for the amination of aryl bromides at low temperatures and for the aminations of aryl chlorides at temperatures more reasonable for chemistry of functionalized molecules than the typical 140 °C required for other types of Pd-catalyzed chemistry with aryl chlorides.[59] Using ligand **2** described above, Buchwald and coworkers reported the amination of unactivated aryl chlorides with secondary amines at temperatures as low as 70–80 °C, and the amination of highly activated aryl chlorides at room temperature (Eq. 7).[51]

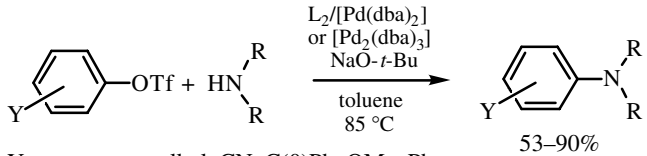


L = P(*t*-Bu)$_3$ or **2** (7)

Again, the simple catalyst system of Pd(dba)$_2$ and P(*t*-Bu)$_3$ in a 1:1 ratio allowed for the amination of unactivated aryl chlorides with cyclic or acyclic secondary amines at 70 °C using 1–5 mol % of catalyst (Eq. 7).[40] Catalyst loads that are lower by an order of magnitude can be used at 100–110 °C.[60] The reactions of activated aryl chlorides occurred at room temperature.

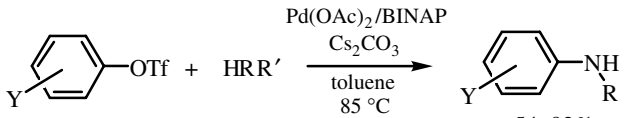
The amination of aryl sulfonates did not occur with the aryl monophosphines that were used originally for aryl halide amination. Instead, it was the use of chelating phosphines that first allowed for the amination of aryl triflates.[61]–[63] The procedures used originally, *t*-butoxide base and either BINAP or DPPF as ligand, allowed for the amination of aryl triflates in good yields in many cases, as summarized in Eq. 8. However, cleavage of the triflate to phenol competed with amination, particularly in the case of electron-poor aryl triflates. The yields of these reactions were improved in two ways. First, slow addition of triflate to ensure low concentration of this reagent improved yields in some cases.[61] More generally, the use of Cs_2CO_3 as base allowed for the reaction to occur smoothly without triflate cleavage (Eq. 9).[63] The arylpalladium triflate intermediate probably coordinates amine more readily than the arylpalladium halide complexes

because of the lability of the triflate ligand. If this occurs, amine coordination to a cationic metal center will significantly increase the acidity of the N—H bond, and a weaker base can be used.



Y = *o*, *m*, or *p* -alkyl, CN, C(0)Ph, OMe, Ph
L_2 = DPPF or BINAP

(8)

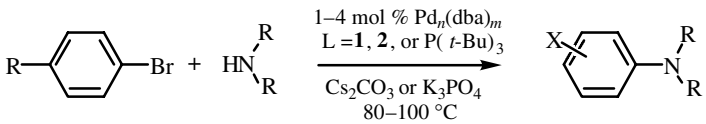


Y = *o* -alkyl, *p*-CN, *p*-C(0)Ph,
p, o -C(0)Me, *p*-OMe

(9)

B.ii. Choice of Base

The strong NaO-*t*-Bu base used in the standard amination conditions can limit the types of substrates that are suitable for this chemistry. For example, reagents containing nitroarenes, enolizable hydrogens, and labile esters are unsuitable. For this reason, Buchwald's group sought amination procedures that used weaker bases (Eq. 10).[64] As discussed in the preceding paragraph, the reactions of amines with aryl triflates instead of aryl halides allows for the use of Cs_2CO_3 as base. Furthermore, reactions of activated aryl halides can be conducted using Cs_2CO_3 as base instead of *t*-butoxide, without requiring a change of catalyst. However, reactions of unactivated aryl halides with this weaker base requires a different catalyst. Catalysts containing Kumada's P,O ligand first allowed for aminations of unactivated aryl halides using Cs_2CO_3 as base.[64] More recently, Buchwald has used biaryl P,N ligands for the amination of aryl halides using Cs_2CO_3 and the less expensive and less toxic K_3PO_4.[51] Finally, Hartwig showed that the catalyst containing commercially available P(*t*-Bu)$_3$ allows for the reaction of unactivated aryl bromides with secondary amines using Cs_2CO_3 or K_3PO_4 as base.[40] Thus, monophosphines appear to generate the most active catalysts for reactions using the weaker bases.



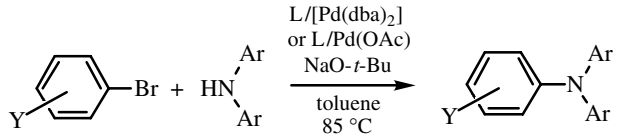
R = *p*-Bu^t, *p*-OMe, C(O)Me, C(O)OMe , base = Cs_2CO_3 for L = **1**
R = C(O)OMe, C(O)Me, base = K_3PO_4 for L = **2**
R = Me, base = K_3PO_4 or Cs_2CO_3 for P(*t*-Bu)$_3$

(10)

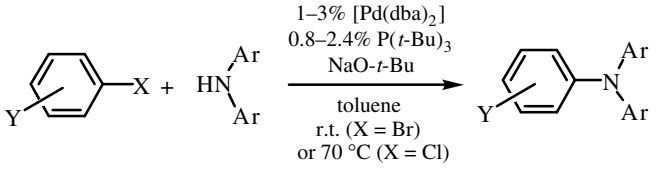
B.iii. Diarylamines

The reactions of diarylamines with aryl halides is more straightforward than the reaction of secondary alkylamines because these substrates possess no hydrogens on the α carbon and cannot, therefore, undergo β-hydrogen elimination as palladium amides. However, competitive formation of arene by an unknown mechanism remains one side product. For the most part, the synthesis of triarylamines has focused on the preparation of discrete molecules and polymers that are important for electronic materials applications.[65]–[67]

In general, three commercial ligand systems are highly effective for the formation of triarylamines, as summarized in Eq. 11. The original P(*o*-tolyl)$_3$ ligand gives good yields in most cases, but catalyst loads of 5–10% can be required.[65] In some cases, palladium complexes bearing DPPF as ligand are more effective catalysts for the formation of triarylamines and can even produce unsymmetrical triarylamines in one step by addition of two aryl halides sequentially to an aniline.[66] However, catalysts bearing P(*t*-Bu)$_3$ as ligand are now the most active catalysts for formation of triarylamines from diarylamines and aryl halides. Workers at Tosoh described the use of this ligand at high temperatures for formation of triarylamines,[47] and Hartwig's group has shown that these ligands will form triarylamines at room temperature (r.t.) when a 1:1 ligand/palladium ratio is used (Eq. 12).[40]



Y = *o*, *m*, or *p*-alkyl, CN, C(0)Ph, OMe, Ph
L = P(*o*-tol)$_3$, DPPF or P(*t*-Bu)$_3$ (11)

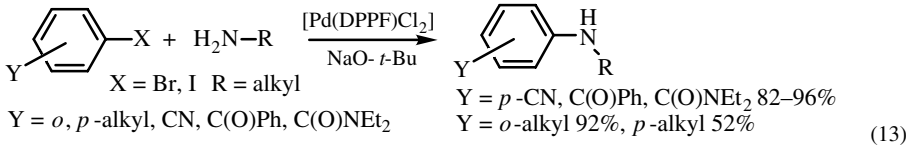


X = Cl, Br
Y = *o*, *m*, or *p*-alkyl, CN, COPh, OMe, Ph (12)

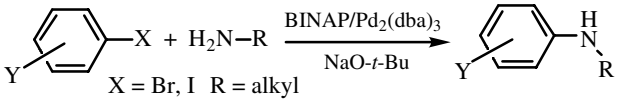
Complexes containing P(*t*-Bu)$_3$ as ligand will also catalyze the reaction of unactivated aryl chlorides with diarylamines.[40] Thus far, the reaction of aryl triflates with diarylamines has only been reported with catalysts bearing chelating phosphines. A few representative examples of the reactions of diarylamines with aryl triflates do occur in nearly quantitative yield when using DPPF-ligated palladium as catalyst.[61] Reactions of diarylamines with aryl nonaflates as part of the synthesis of discrete oligomeric triarylamines has also been reported.[68]

B.iv. Primary Alkylamines

As mentioned in the introduction, the catalysts that give the highest yields for the reactions of primary alkylamines with aryl halides in a general fashion are different from the catalysts that give the highest yields for reactions of secondary alkylamines. Like the reactions of acyclic secondary alkylamines, the reactions of primary alkylamines have been among the most difficult transformations. The current solutions to these two problems are different. Catalysts containing BINAP as ligand are the most selective for reactions of primary alkylamines with aryl bromides (**Table 3**),[43] and catalysts containing PPF-(P-*t*-Bu_2) are the most selective for reactions of primary alkylamines with aryl chlorides.[59] Faster rates have been observed with P(*t*-Bu)$_3$, but some diarylation occurs when reactions of unhindered aryl halides are run in the absence of an excess amount of the primary amine.[60]



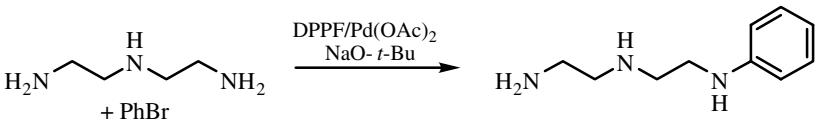
(13)



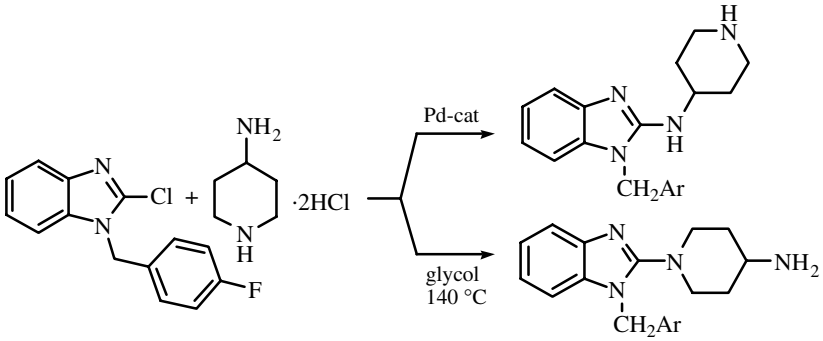
(14)

Hartwig's and Buchwald's groups simultaneously described catalyst systems that allow one to conduct high-yield aminations of aryl halides using primary alkylamines (Eqs. 13 and 14).[42],[43] In general, reactions of hindered aryl halides give high yields with a broader scope of catalyst because diarylation of the primary amine does not occur[30] and because either reductive elimination occurs more rapidly or β-hydrogen elimination occurs more slowly from these hindered arylpalladium amido complexes. Thus, either ligand is suitable for reactions of primary alkylamines with these substrates. Reactions employing BINAP often give higher turnover numbers, however. With unhindered aryl halides, palladium complexes containing *rac*-BINAP are more effective than those containing DPPF (**Table 3**). With a mixture of $Pd(OAc)_2$ or $Pd_2(dba)_3$ and BINAP, high yields and turnover numbers in the range of 100–200 are observed. Rossen and co-workers used PHANEPHOS (**Figure 2**) as a ligand for palladium in the reaction of benzylamine with a dibromocyclophane.[69] Palladium complexes of this ligand reacted similarly to those with BINAP, but only a few reactions were investigated.

The selectivity for arylation of primary versus secondary amines using palladium catalysts with chelating ligands has been investigated. Beletskaya, Bessermertnykh, and Guilard conducted reactions of polyamines, such as that in Eq. 15, with phenyl bromide using (DPPF)$PdCl_2$ as catalyst.[70] Good yields of the products resulting from reaction of the primary amine portion of the polyamine were obtained. Senanayake and co-workers reported the high selectivity for arylation of primary over secondary amines using palladium complexes of BINAP for the synthesis of biologically active arylamines, as shown in Eq. 16.[71]

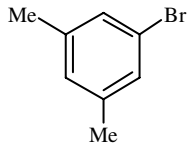
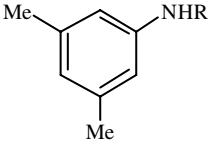
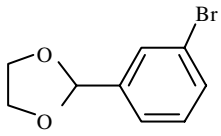
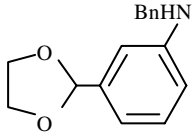
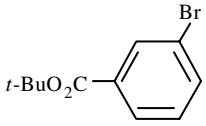
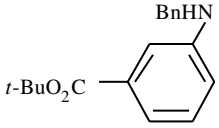
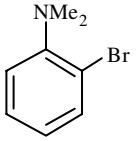
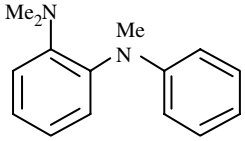
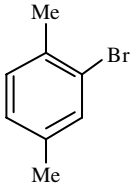
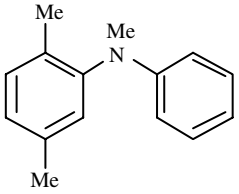


(15)



(16)

TABLE 3. Selected Aryl Bromide Aminations Catalyzed by BINAP/$Pd_2(dba)_3$

Entry	Halide	Amine	Product	Catalyst (%)	Time (h)	Isolated Yield (%)
1		RNH_2		0.5	2	88
				0.5	4	79
				0.05	7	79
2		H_2NBn		0.5	2	81
3		H_2NBn		0.5	3.5	71
4				1.0	39	66
5				0.5	3	94

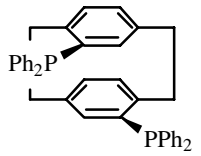
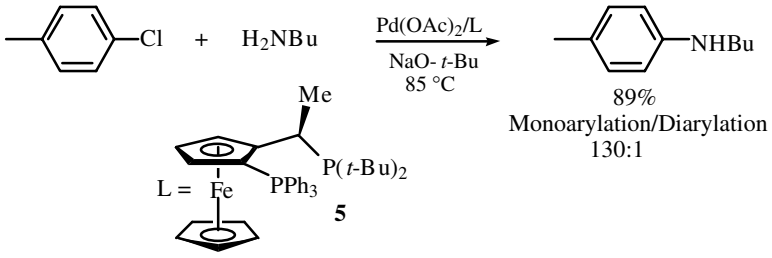


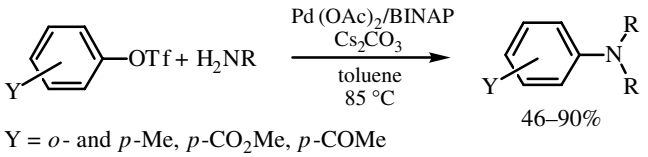
Figure 2. PHANEPHOS

For reactions of unactivated aryl chlorides with primary amines, arylphosphines are again ineffective. Sterically hindered alkylphosphine ligands are required for reactions of aryl chlorides, but the highest selectivity in reactions of primary alkylamines also requires that the phosphine be tightly chelated to the metal center. The chelation helps prevent competing β-hydrogen elimination of the arylpalladium amido intermediate (*vide infra*), and the greater steric hindrance of bisphosphine palladium complexes apparently prevents diarylation. Some ligands originally introduced by Togni and co-workers and Bläser and Spindler[72],[73] for asymmetric hydrogenation chemistry fit this description. The ligand PPF-P(*t*-Bu)$_2$ (**5**, Eq. 17) is an electron-rich bisphosphine that is commercially available from Strem and has a strong conformational preference for chelation because of the benzylic methyl group. Complexes of this ligand are, to date, the most selective catalysts for formation of monoaryl alkylamines from aryl chlorides that are unactivated and that are sterically unhindered.[59] Because reactions of primary alkylamines with sterically hindered aryl halides are less susceptible to formation of diarylalkylamine products and are less susceptible to competing reduction, sterically hindered alkylmonophosphine ligands, such as **2**, do successfully catalyze the reactions of primary amines with sterically hindered aryl chlorides.[51]

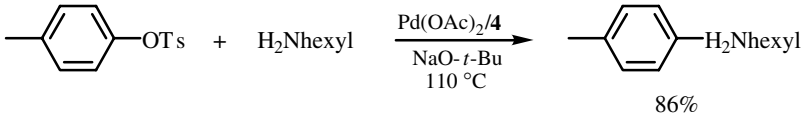


(17)

The reactions of primary alkylamines with aryl triflates occurs in a fashion similar to the reaction of secondary amines with aryl halides. Specifically, complexes containing BINAP provide the highest yields for unhindered substrates.[62] The use of Cs_2CO_3 as base presumably leads to a general high-yield amination of aryl triflates using primary alkylamines (Eq. 18), although reactions of primary amines with aryl triflates that do not bear ortho substituents have not been reported.[63] Reactions of aryl tosylates are desirable because of the low cost and greater ease of handling of the reagents used to form tosylates. Palladium chemistry involving unactivated aryl tosylates is rare.[74] The reaction of *p*-tolyltosylate with hexylamine using NaO-*t*-Bu base and a palladium catalyst containing PPF-P(*t*-Bu)$_2$ as ligand may be the first Pd-catalyzed reaction of an unactivated tosylate (Eq. 19).[59]



Y = *o*- and *p*-Me, *p*-CO_2Me, *p*-COMe (18)

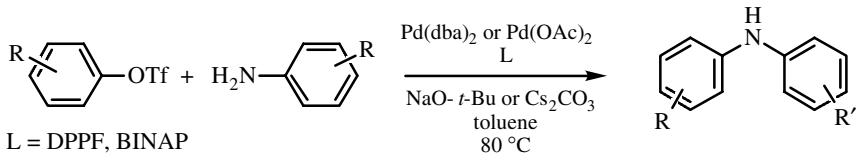


(19)

B.v. Primary Arylamines

The reactions of primary arylamines with aryl halides are simpler to catalyze than those of primary alkylamines because β-hydrogen elimination will not compete with reductive elimination. However, diarylation of the aniline can be a competing process, and for some reason the original catalyst system containing P(*o*-tolyl)$_3$ showed low activity for the reactions of aniline with aryl halides.

Many palladium complexes will catalyze the reaction of an aryl bromide with aniline, and the precise ligand that is optimal for a particular reaction is difficult to predict. In the experience of the author's group during the synthesis of di- and triarylamine precursors to materials, reactions catalyzed by palladium complexes of DPPF and P(*t*-Bu)$_3$ give high yields,[68],[75] and the ligands are commercially available and inexpensive. However, small amounts of triarylamine do form from reactions with these catalysts. Thus, the groups of Meyer, Kanbara, and Buchwald have used BINAP for the synthesis of polymeric or discrete oligomeric anilines[76]–[79] and Meyer and Kanbara present arguments that the polymeric materials they produce have little if any cross-linking. Buchwald has also introduced van Leeuwen's DPEphos (**Figure 3**) as a superior ligand for forming diarylamines in certain cases.[80] Kocovsky and co-workers have reported that complexes of MAP (**Figure 3**), a binaphthyl P,N ligand with a dimethylamino and diphenylamino group on the 2 and 2′ positions of the 1,1′-binaphthyl backbone, provide rates for arylation of a binaphthylamine that are faster than those observed when using BINAP as ligand.[81]



L = DPPF, BINAP (20)

The reactions of aryl triflates with primary arylamines have been reported with only chelating ligands (Eq. 20), but the hindered alkylphosphines may be effective, considering their utility in coupling aryl halides with primary arylamines. Presumably because β-hydrogen elimination does not compete with coupling and the amine is more hindered than a linear alkylamine, DPPF gives essentially quantitative yields in these reactions.[61] The turnover numbers were not assessed for these reactions; catalysts with BINAP and DPEphos as ligand have shown good turnover numbers.[62],[63],[80] The reactions of

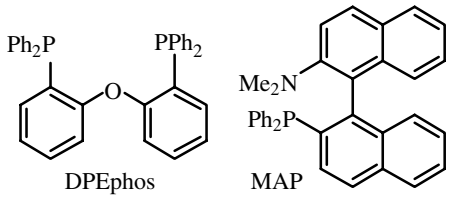
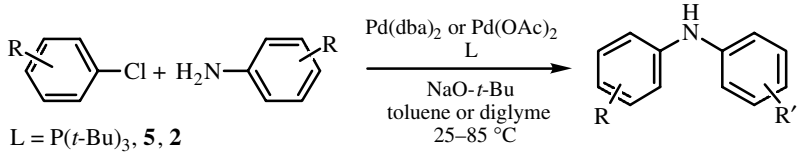


Figure 3

unactivated aryl tosylates with anilines have not been investigated, but the reaction of aniline with an activated aryl tosylate was catalyzed by complexes of D′BPF in high yield under relatively mild conditions.[59]

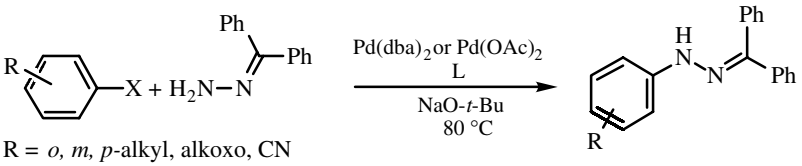
The reaction of aryl chlorides with primary arylamines again requires the use of alkylphosphine ligands (Eq. 21). PPF-P(*t*-Bu)$_2$ and the cyclohexyl analogs of these ligands give excellent yields of diarylamines from unactivated aryl chlorides and anilines.[59] Palladium complexes of the *t*-butyl analog of DPPF, D′BPF, will also catalyze these reactions in high yields.[59] In addition to complexes of bisphosphines, alkylmonophosphines can catalyze this class of amination.[51] For example, biaryldialkylphosphines will catalyze the amination of unactivated aryl chlorides in good yields. Although the scope of the catalytic chemistry of P(*t*-Bu)$_3$ complexes has not been completely covered, these simple complexes will catalyze the formation of diarylamines from unactivated aryl chlorides in high yields. The reaction of aniline with phenyl chloride occurs even at room temperature.[40]



L = P(*t*-Bu)$_3$, **5**, **2** (21)

B.vi. Hydrazones

N-Arylhydrazones are useful agricultural materials. Moreover, they can be cleaved to form *N*-arylhydrazines for pyrazole synthesis, and the hydrazine portion can be transferred to ketones to serve as substrates for the Fischer indole synthesis.[82] The reactions of benzophenone hydrazone with aryl halides have been reported,[82],[83] and to date these reactions are best conducted with chelating phosphine ligands such as DPPF and BINAP, as shown in Eq. 22. These catalyst systems have been the only ones reported for hydrazone arylation. The chemistry of hydrazonato complexes is similar to that of anilides and diarylamides.[83] Thus, the reactions of aryl chlorides with hydrazones should be accessible in the future using alkylphosphine ligands.

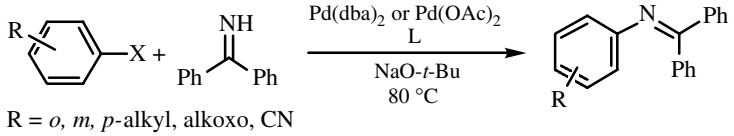


R = *o, m, p*-alkyl, alkoxo, CN
L = DPPF, BINAP (22)

The reactions of benzophenone hydrazone with aryl bromides are remarkably general using either DPPF or BINAP as the ligand for palladium. The lower cost of DPPF may make this catalyst more favorable. Sterically hindered, unhindered, electron-rich or electron-poor aryl bromides all give high yields of *N*-arylhydrazones using benzophenone hydrazone as substrate. Reactions of hydrazones other than diphenylhydrazone were less successful. Thus, a scheme was developed to use the *N*-aryl diphenylhydrazone products as precursors to other hydrazones by transfer of the *N*-arylhydrazine to a ketone bearing enolizable hydrogens using acid catalysis.[82] Of course, the products from these exchange reactions are suitable for the Fisher indole synthesis, and a number of different indoles were prepared by this reaction sequence. Because of the selectivity for monoarylation of diphenylhydrazone, one can prepare *N,N*-diphenylhydrazones with two different aromatic groups bound to the terminal nitrogen, and these diarylhydrazones were again suitable for Fisher indole syntheses after exchange of the *N,N*-diphenylhydrazine moiety.

B.vii. Imines

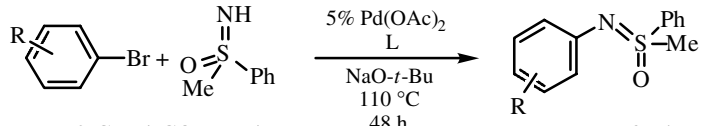
One strategy to prepare protected anilines is the reaction of diallylamine with aryl halides using the catalysts best suited for reactions of secondary amines.[84] The formation of *N*-aryl benzophenone imines by Pd-catalyzed C—N bond formation is a second strategy that allows for straightforward deprotection to the parent aniline.[85],[86] Benzophenone imine is commercially available.



R = *o, m, p*-alkyl, alkoxo, CN
L = DPPF, BINAP

(23)

Palladium complexes containing DPPF and BINAP have been reported as catalysts for this transformation (Eq. 23). In both cases the reactions occur in nearly quantitative yields with essentially any class of aryl bromide or iodide that has been tested. The increased acidity and/or the increased binding constant of imines for transition metals allows this chemistry to be conducted with Cs_2CO_3 as well as NaO-*t*-Bu as base. Because both ligands used in these publications are arylphosphines, they will not catalyze the reactions of benzophenone imine with chloroarenes. However, the similarity of the complexes of deprotonated benzophenone imine to complexes of anilides[85] again suggests that reactions with aryl chlorides can be conducted with sterically hindered alkylphosphine ligands. Although not reported, it is also likely that K_3PO_4 could be used instead of Cs_2CO_3 for these reactions. Sulfoximines are less nucleophilic than ketimines, but in some cases, sulfoximines react with aryl halides under Pd-catalyzed conditions.[87] DPPF- and BINAP-ligated palladium act as catalysts to couple *S*-methyl, *S*-phenyl sulfoximines with electron-poor or electron-neutral aryl halides at 110 °C for long reaction times, as summarized in Eq. 24.[87] These products can be used as ligands for asymmetric catalysis.



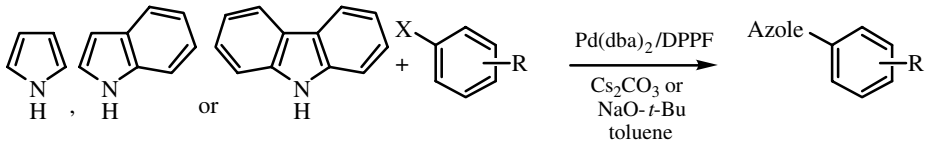
R = H, 2-CN, 4-CO_2Me, 4-*t*-Bu
L = DPPF, BINAP

L = DPPF 87%
L = BINAP 67–94%

(24)

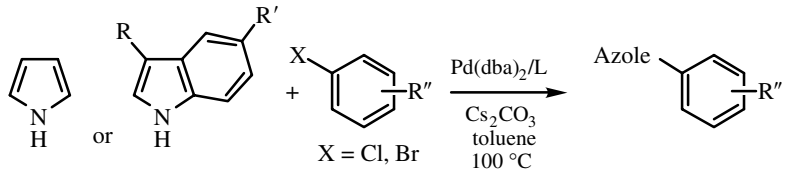
B.viii. Indoles, Pyroles, and Carbazoles

The *N*-arylation of certain azoles can be conducted using palladium catalysts. The reactions of pyrazoles and imidazoles have not been reported, and palladium chemistry may never compete with more classic Ullmann chemistry using copper catalysts. However, azoles containing a single nitrogen are suitable substrates for Pd-catalyzed *N*-arylation processes. The first reports of Pd-catalyzed azole arylation (Eq. 25) involved catalysts bearing DPPF as ligand.[85] These reactions of pyrrole, indole, and carbazole with activated aryl halides occurred at 80–100 °C. The reaction of pyrrole and indole with unactivated aryl halides such as bromobenzene, 4-bromo-*t*-butylbenzene, and 3-methoxy bromobenzene also occurred in high yields. However, the conditions of these reactions were more severe than is typical for the Pd-catalyzed aromatic C—N bond formation.



(25)

Improved catalysts were necessary for this synthetic chemistry to occur with broader scope under milder conditions. Faster rates were observed for the reaction of indole and pyrrole with aryl halides when catalyzed by palladium complexes formed by combining a 1:1 ratio of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ (Eq. 26).[40] For example, reactions of bromoanisole occurred with 1 mol % catalyst at 100 °C over 12 h. In this case, it was mandatory to use a weaker base than NaO-*t*-Bu, and the reported chemistry employed Cs_2CO_3. It was previously demonstrated that high concentrations of azolyl anion are detrimental to the arylation process because stable, anionic bis-azolyl palladium complexes, such as **6a** in **Scheme 1**, are formed even when chelating ligands are present,[85] while neutral complexes such as **6b** are required for reductive elimination to occur in high yields. Despite these improvements, the *N*-arylation of pyrrole, indole, and carbazole is not completely general. Competing formation of *N*- and *C*(3)-arylation products were observed when reacting indole and pyrrole with aryl bromides containing ortho substituents. However, these hindered aryl halides do undergo clean C—N bond formation with indoles that are substituted in the 3-position. Thus, reaction of 2-bromotoluene with 3-methylindole occurred in high yield. Reactions of aryl halides with carbazole were slow and gave low yields, indicating that this catalyst system is, indeed, more sensitive to steric effects in this type of C—N bond formation than it is in the chemistry involving amine substrates.



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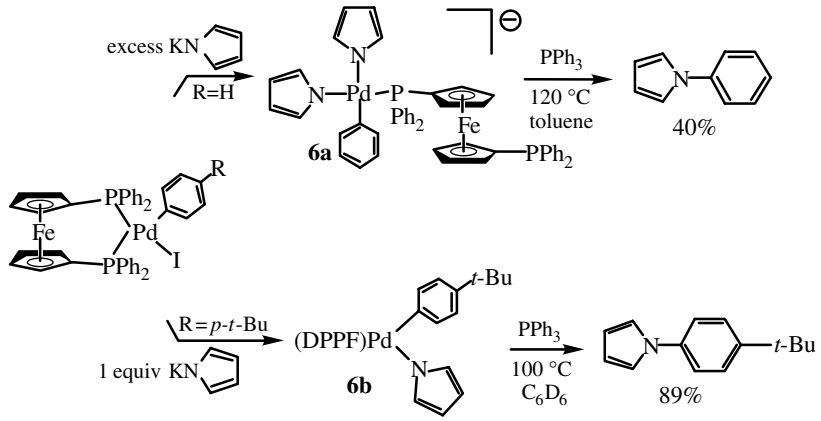


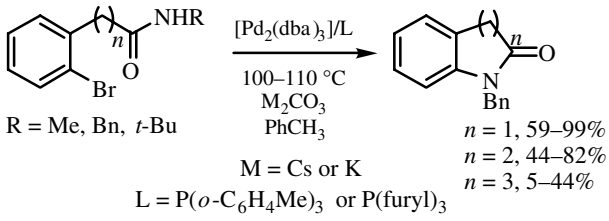
Scheme 1

Reaction of indole and pyrrole with chloroarenes also occurred in good yields in many cases using this catalyst system. For example, chlorotoluene reacted to give the products of C—N bond formation in yields that were similar to the reactions of bromoarenes. However, the reactions with aryl chlorides were slower than those of aryl bromides. Thus, reaction of the deactivated chloroanisole with indole occurred too slowly to provide useful yields under mild conditions.

B.ix. Amides, Sulfonamides, and Carbamates

As demonstrated by the greater difficulty in forming *N*-aryl azoles than *N*-arylamines, the palladium chemistry occurs more readily with substrates containing a more nucleophilic nitrogen. Thus, reagents containing a nitrogen located α to a carbonyl or sulfonyl group undergo arylation processes less readily than do simple amines. However, intramolecular reaction of aryl halides with pendant amide or sulfonamide functionality was reported early in the development of Pd-catalyzed aromatic C—N bond formation (Eqs. 27 and 28).[88] A number of reaction conditions and catalysts were tested. In short, monophosphines including PPh_3 were effective for these cyclizations, and carbonate bases proved to be optimal in most cases. The formation of five- and six-membered rings occurred in good yields, but the formation of seven-membered rings occurred in low yields.

No intermolecular reactions of acyclic sulfonamides or amides with aryl halides have been reported, but the arylation of lactams has been published. Shakespeare showed that a combination of $Pd(OAc)_2$ and DPPF formed *N*-aryllactams in good yields when using five-membered lactams (Eq. 29).[89] Reaction times were long for couplings involving



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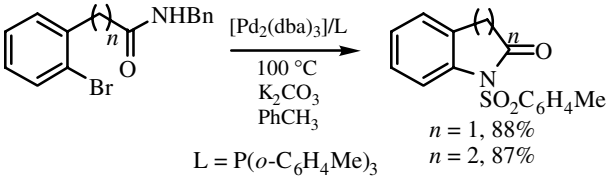

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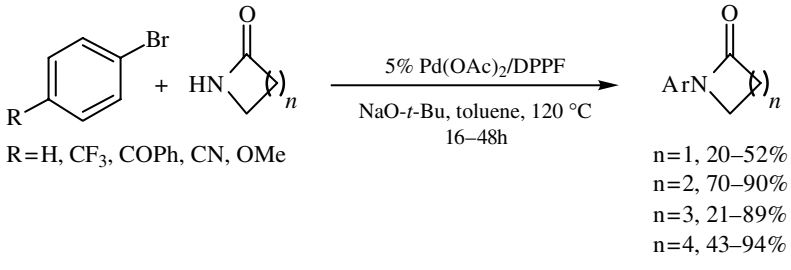
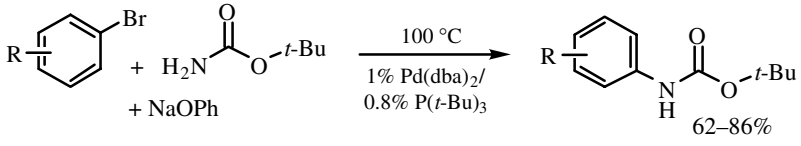


(29)

electron-neutral aryl halides, but good yields were observed. Four-, six- and seven-membered lactams reacted with unactivated aryl halides in poor yield, but they reacted with activated aryl halides to give good yields. No reaction was, of course, observed in the absence of catalyst.

Carbamates possess a more electron-rich nitrogen than amides or sulfonamides, and the intermolecular reaction of *t*-butylcarbamate with aryl halides to form *t*-Boc-protected anilines has been realized (Eq. 30).[40] As one might expect from the increased rates for amine and indole arylation using the $Pd(dba)_2/P(t\text{-}Bu)_3$ catalyst, it is this system that allows for the arylation of *t*-butylcarbamate. Reaction of other carbamates, such as methyl or benzyl carbamate and oxazolinone, occurred in lower yield. However, reaction of *t*-butyl carbamate with bromoarenes occurred at 100 °C in yields ranging from 62% to 86% with electron-rich, electron-neutral, and sterically hindered or unhindered bromoarenes. Reactions of chloroarenes were again slower, but did occur at 130 °C to give Boc-protected aniline in 59% yield for reaction of chlorotoluene.



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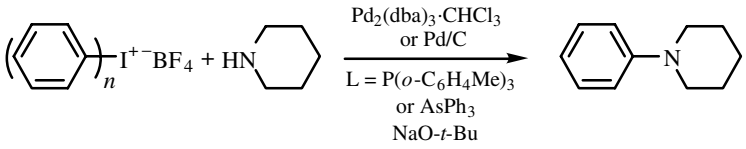
B.x. Additional Aryl Electrophiles

In addition to the aryl halides and sulfonates that have been used most commonly in Pd-catalyzed cross-coupling and that have been discussed above for amination, diphenyliodonium salts have been reported as aryl electrophiles for amination chemistry (Eq. 31).[90] Perhaps most significant, the use of diphenyliodonium salts as electrophile led to room-temperature amination chemistry using the original P(*o*-tolyl)$_3$ ligand system, as well as with Ph_3As. Only chemistry with secondary amines was reported.



(31)

B.xi. Use of Cocatalysts

Some of the optimized procedures for Stille and Sonogashira reactions involve the addition of copper cocatalysts to accelerate the cross-coupling procedures. A word of caution should be provided on the role of these additives in Pd-catalyzed amination procedures. Beletskaya and Davydov have reported the arylation of benzotriazole and of diarylamines in polar organic or aqueous organic solvents using a combination of palladium and copper as catalyst.[91]–[93] The arylation of amino acids has been reported under similar conditions.[94] However, these reaction conditions are similar to classic Ullmann procedures for the synthesis of arylamines, except for the addition of palladium to the reaction mixture. In one case, subsequent work showed that the palladium species was not an essential component and that copper alone was the true catalyst in their reactions. An unusual accelerating effect of amino acid coordination to copper was used to explain the low-temperature Ullmann conditions.[95] Beletskaya, however, showed that lower yields and a mixture of *N*1 and *N*2 arylation products were observed from the reactions of benzotriazole in the absence of copper and no reaction was observed in the absence of palladium. The conditions for this chemistry are, however, distinct enough from those of the majority of the aryl halide aminations to support the idea that a different mechanism may operate.

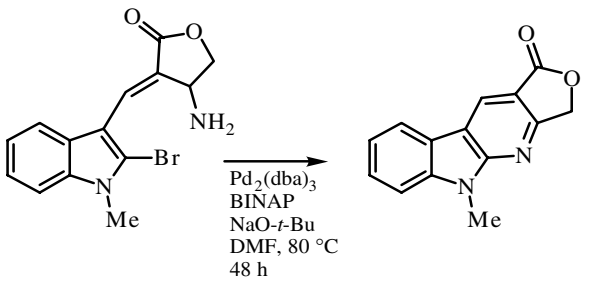
C. APPLICATIONS AND SPECIAL EXAMPLES OF AMINATION

C.i. Biologically Relevant Materials

A number of groups have investigated the Pd-catalyzed amination of aromatic electrophiles for a particular application or synthetic problem. These synthetic applications can be divided loosely into four categories: synthesis of biologically active molecules, synthesis of materials for electronics or ion binding, amination in solid-phase organic synthesis, and synthesis of new ligands for transition metals.

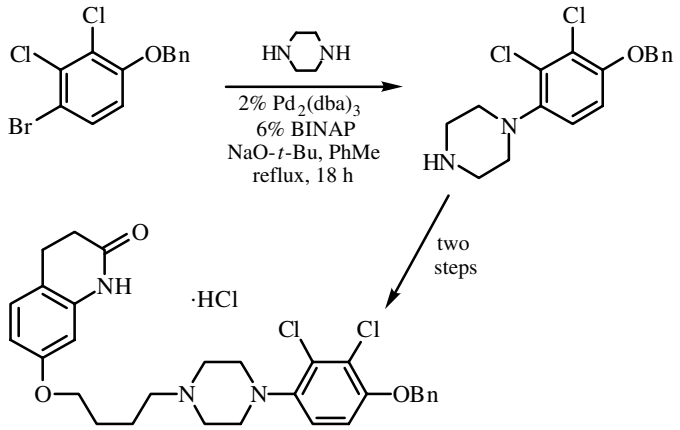
As stated in the introduction, stoichiometric amounts of palladium complexes were used in the synthesis of a β-carbolide natural product.[7]–[9] With catalytic procedures now

available and the importance of amine and aromatic molecules in the pharmaceutical industry, synthetic applications of the amination chemistry are beginning to emerge. For example, an intramolecular Pd-catalyzed amination of a heteroaromatic halide has been used as a step in the synthesis of an α-carboline natural product analog (Eq. 32).[96] As discussed above, the diphenylhydrazone arylation can also be used for nitrogen heterocycle synthesis.[82]



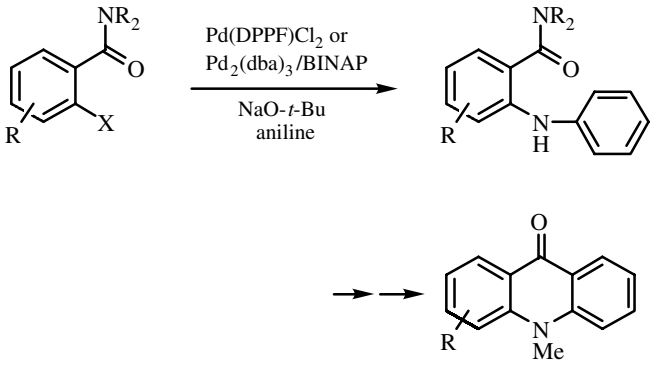
(32)

N-Arylpiperazines are common substructures of biologically active molecules, and, therefore, the reaction of monoprotected and unprotected piperazines with aryl halides has been studied. In particular, the monoarylation of piperazines was the reaction for which Nishiyama, Yamamoto, and Koie initially applied catalysts bearing P(*t*-Bu)$_3$ as ligand to obtain high turnover numbers at high tempera-tures.[39] Two other reports of piperazine arylation, one using a Boc-protected piperazine[97] and one an unprotected piperazine, used the original P(*o*-tolyl)$_3$/Pd(0) catalyst system.[98] Morita and co-workers have used the arylation of piperazines as a crucial step in the synthesis of a metabolite of Aripiprazole, as shown in Eq. 33.[99] This reaction involved the use of a tetrasubstituted dichloro bromoarene as substrate to give a product that is readily converted to the final target.



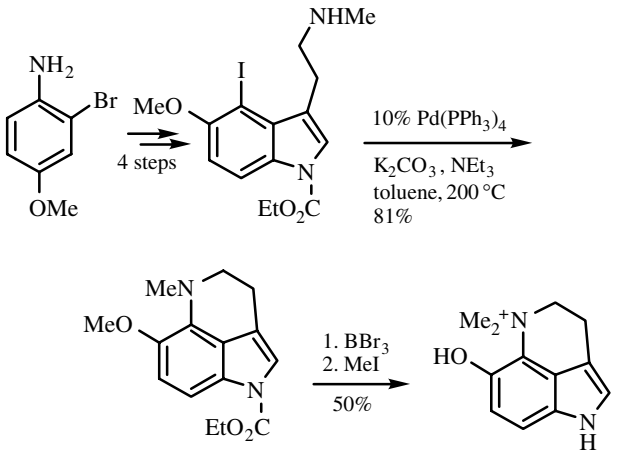
(33)

The ability to prepare haloarenes selectively by an ortho-metallation halogenation sequence allows for the selective delivery of an amino group to a substituted aromatic structure. Snieckus and co-workers have used directed metallation to form aryl halides that were subsequently reacted with anilines to prepare diarylamines (Eq. 34).[100]



(34)

A few reports on the synthesis of more complex molecules have appeared. In addition to the α-carboline synthesis in Eq. 32, Pd-catalyzed amination and a combination of zironocene benzyne and Pd-catalyzed amination chemistry was used by Peat and Buchwald to conduct the formal total synthesis of tetrahydropyrroloquinolines (Eqs. 35 and 36).[101] Senanayake and co-workers have published several demonstrations of the use of Pd-catalyzed amination for the preparation of pharmaceutically relevant materials. For example, the reaction of primary amines with chloro-1,3-azoles has been used to produce the H-1-antihistaminic Norastemizole.[102] As shown in Eq. 37, the palladium chemistry is dictated by the steric properties of the amines. This property creates selectivity that complements the thermal chemistry, which is dictated by amine nucleophilicity. As discussed above, they showed that the high selectivity for arylation of primary over secondary amines with catalysts containing BINAP as ligand allows for the rapid assembly of multiamino-based structures.[71] They have also conducted the amination of aryl triazolones to generate the two enantiomeric versions of Hydroxyitraconazole (**Figure 4**).[103] The coupling of primary amines with aryl halides has also been used to modify glycosylamines. Glycosylamines were coupled with 6-chloropurines, as shown in Eq. 38, to prepare models of spicamycin and septacidin, two *Streptomyces* metabolites that have antitumor activity.[104] Although temperatures were high



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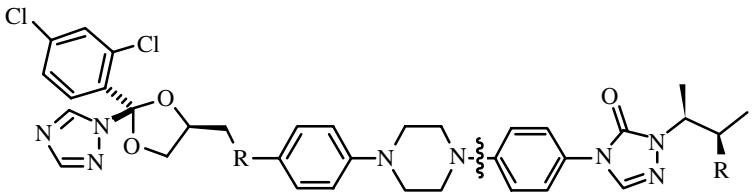
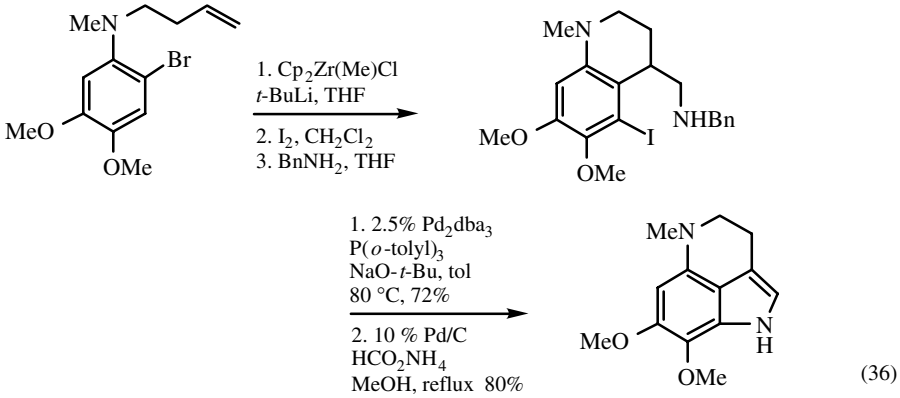


Figure 4

(140 °C), good yields of the desired *N*-aryl glycosylamine were obtained when using BINAP as ligand, NaO-*t*-Bu as base, and either MPM or SEM as the N9 protective group. The gluco isomer was also amenable to Pd-catalyzed arylation, although two anomers were obtained as products.



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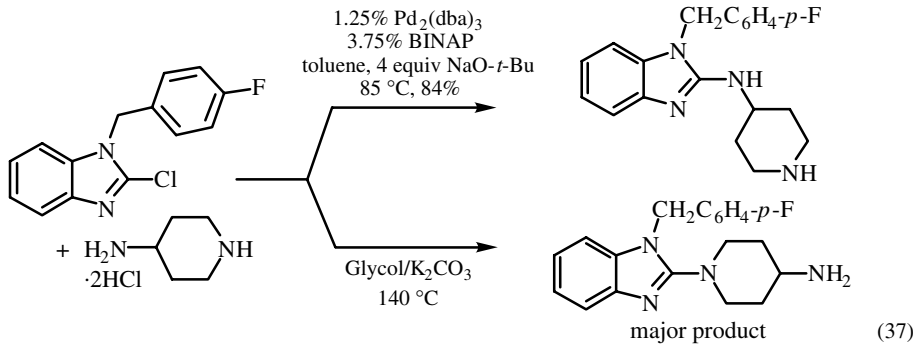

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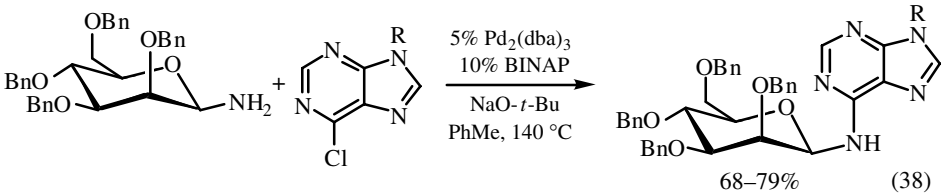

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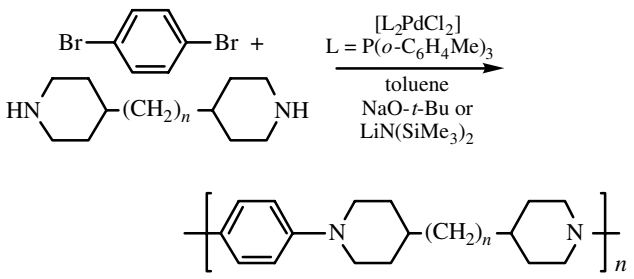
C.ii. Solid-Phase Amination Reactions

Two papers have been published on the use of Pd-catalyzed amination using solid-supported aryl halides. Willoughby and Chapman at Merck and Ward and Farina at Boehringer Ingelheim have used P(*o*-tolyl)$_3$ and BINAP complexes as catalysts for these reactions.[105],[106] In general, these reactions appear to occur in a similar fashion to those in solution phase. Reactions of primary alkylamines were improved by the use of chelating phosphine ligands. These reactions have also been used for a variety of unpublished high-throughput syntheses of arylamines.

C.iii. Applications of Palladium-Catalyzed Amination in Materials Science

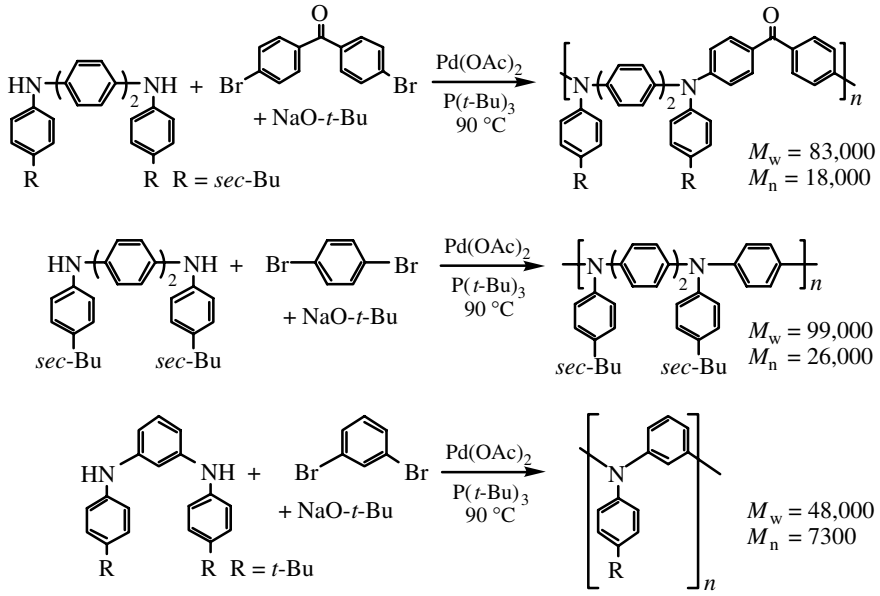
An additional synthetic arena that has been and will continue to be affected by the advent of Pd-catalyzed aromatic C—N bond formation is materials science. Arylamine materials are important because they generate delocalized radicals upon oxidation. Their electron-rich character makes them easily oxidized. Poly(*p*-aniline) is a conductive polymer in its partially oxidized and protonated form,[107]–[109] and poly(*m*-aniline) has been a synthetic target for generating high-spin materials.[76],[110]–[113] *N*,*N*′,*N*″,*N*-tetraarylphenylenediamines are useful as hole-transport materials,[114],[115] and oligomeric versions of arylamines have been prepared over the years for fundamental studies on high-spin structures.[116]–[121] Most of the previous syntheses of these materials relied on coupling of aniline or diarylamines with aryl halides by chemical or electrochemical oxidation, or by copper-mediated aromatic substitution that occurs at high temperatures and in variable yields.

C.iii.a. ***Polymer Synthesis.*** The first application of Pd-catalyzed amination chemistry for materials applications was reported in brief form by Kanbara and co-workers on the synthesis of polymers from dihalobenzenes and dialkyldiamines using the original P(*o*-tolyl)$_3$ catalyst system (Eq. 39).[122] Molecular weights were modest, with M_w values below 6000. Yields were low, and polydispersities were lower than the theoretical limit for a step-growth polymerization. Thus, large amounts of oligomers were most likely formed, and the higher molecular weight material probably precipitated selectively. A subsequent full paper reported the use of some of the more recently developed catalysts for formation of dialkyldiamine-linked arylamine polymers as well as one example of a triarylamine polymer.[123] Again molecular weights were modest. The highest M_w was 14,000, and probably the most important example, the formation of a triarylamine polymer, was surprisingly formed with the highest molecular weight using P(*o*-tolyl)$_3$ as ligand. Nevertheless, this work did demonstrate the ability to use this palladium chemistry for polymer synthesis.



(39)

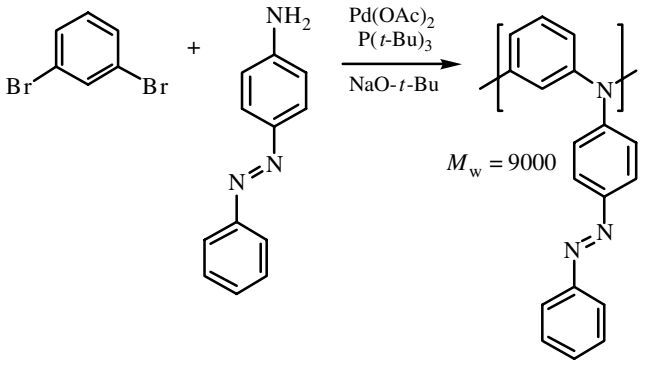
Concurrently, Goodson and Hartwig used the original catalyst system to prepare a series of soluble triarylamine polymers.[124] Most recently, Goodson, Hauck, and Hartwig reported a detailed study on the use of improved catalysts and synthetic strategies to prepare pure, soluble, linear triarylamine polymers with high molecular weights (**Scheme 2**).[125] A large number of ligands were prepared and tested for their ability to catalyze the formation of triarylamines in quantitative yields. A phosphinoether ligand and P(*t*-Bu)$_3$ were chosen as the most effective. True polymeric *N*-aryl versions of poly(*p*-anilines), poly(*m*-anilines), alternating poly(*m*-aniline)poly(*p*-aniline)s, and alternating donor–acceptor copolymers were all prepared. In the cases of polymerizations using substrates with *m*-linkages, cyclization to form tetraazacyclophanes occurred in competition with polymerization. The polymerization of oligomeric fragments and/or the separation of the macrocycles from polymer by size-exclusion chromatography provided purely linear polymer. Incorporation of phosphine into the polymer after ligand P—C bond cleavage or ligand metallation is common in the formation of polymers by Pd-catalyzed cross-coupling.[126],[127] The materials formed with P(*t*-Bu)$_3$ as catalyst contained no phosphorus, as determined by long ^{31}P NMR spectroscopic acquisitions and by ^{1}H NMR spectrometry. Thus, the use of P(*t*-Bu)$_3$ as ligand is important to observe coupling in yields that are high enough to generate polymer, to employ low catalyst loads, and to prevent metallation or P—C cleavage reactions of the phosphine ligand.



Scheme 2

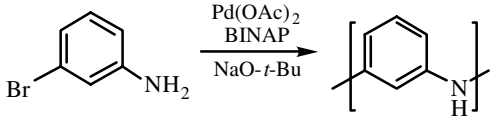
An alternative approach to the synthesis of triarylamine polymers is the reaction of a dihalobenzene with a primary arylamine. In this case, the catalyst must be able to form both diarylamines from anilines and triarylamines from the diarylamine product in nearly quantitative yields. The discussion of catalysts above shows that complexes of P(*t*-Bu)$_3$ effectively catalyze both these transformations. Kanbara and co-workers have used this

catalyst system in addition to others as comparison for this type of polycondensation (Eq. 40).[128] Polymers with M_w values in the range of 9000 were obtained when using 4-aminoazobenzene and 1,3-dibromobenzene as monomers and in the range of 19,000 when using 4-aminoazobenzene and bis(4-bromophenyl)ether as monomers.



(40)

Kanbara, Meyer, and co-workers investigated the synthesis of parent poly(*m*-aniline) from 3-bromoaniline using BINAP-ligated palladium as catalyst (Eq. 41).[76],[77] The product polymer was soluble in the organic solvents DMF, DMSO, NMP, and formic acid. The solubility of these materials is in contrast with the insolubility of the poly(*m*-aniline) prepared by the same synthetic route but using copper catalysts.[111] It is well known that copper halides mediate the formation of triarylamines from diarylamines and aryl halides,[116] and the selectivity for the formation of diarylamines and triarylamines is apparently not high enough to prevent formation of crosslinked polymers. In contrast, the Pd-catalyzed chemistry that involves BINAP as ligand is highly selective for formation of diarylamines from aryl halides and aniline.[43] The solubility of the material produced by this catalyst system suggests that crosslinking is either absent or less prevalent in these polymers than it is in the polymer produced by the copper chemistry. Meyer, and co-workers carefully analyzed molecular weights of the polymer, yields of small molecule model coupling reactions, and NMR spectra of the polymer.[76] Molecular weight data varied dramatically as a function of solvent, and the yields of the small molecule coupling reactions suggest that the data in THF are a more accurate description of the polymer molecular weight. Moreover, their NMR studies suggested that ligand was contained in the polymer. Thus, formation of pure poly(*m*-aniline) will require further catalyst development.[80]



GPC in NMP	GPC in THF
M_w = 39,000	M_w = 8800
PDI = 3.6	M_n =1.6

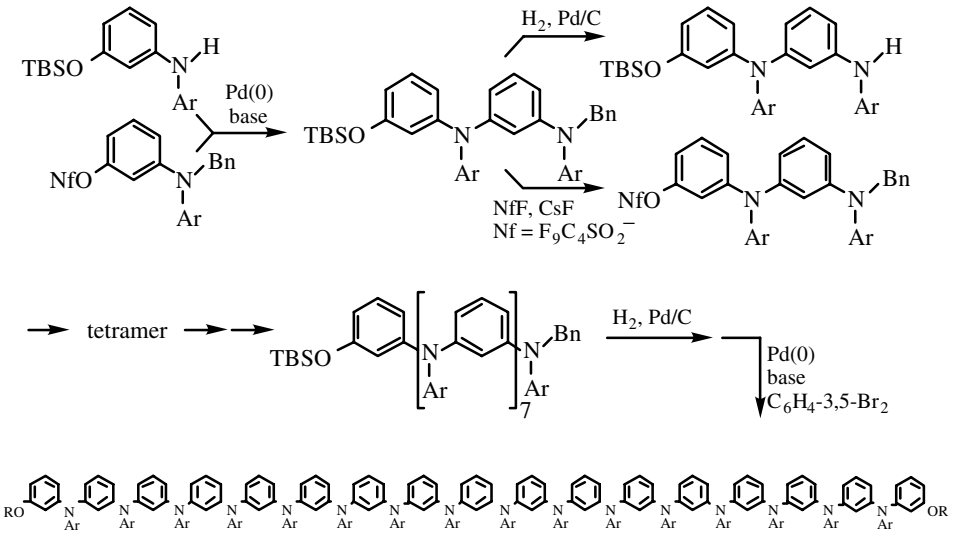
(41)

The synthesis of polymers with pendant arylamines has also been accomplished using palladium chemistry. For example, reaction of poly(4-bromostyrene) with a diarylamine containing a pendant azobenzene occurred to give the modified polymer in good yield.[129] An alternative route for the preparation of polymers containing arylamine side-chains is the construction of polymers from monomers that have triarylamine moieties pendant to

the functionality that forms polymer. Using Pd-catalyzed amination chemistry, Grubbs, Marder, Kippelen, Peyghambarian, and co-workers have constructed monomers containing pendant triarylamines for use in ring-opening metathesis polymerizations that generate materials with hole-transport properties.[67]

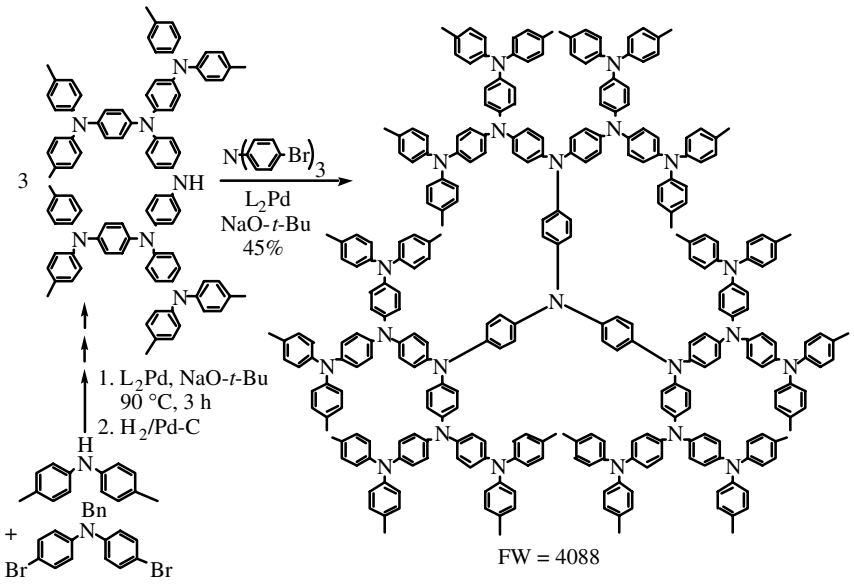
C.iii.b. ***Synthesis of Discrete Oligomers.*** Buchwald's group and Hartwig's group have both used exponential growth strategies to prepare discrete arylamine materials. Buchwald, Sadighi, and Singer prepared oligomers based on diarylamine structures,[78],[79] and Louie and Hartwig prepared discrete triarylamine oligomers.[68] The exponential growth strategy relies on orthogonal protection of two functional groups at the termini of the oligomers. Buchwald's group used *N*-aryl benzophenone imines as protected anilines and trimethylsilylarenes as masked aryl halides. In addition, Boc groups were used to protect internal diarylamine nitrogens in the monomer units. This protection served to make the materials soluble and to make them less susceptible to air or chemical oxidation. BINAP-ligated palladium complexes were used to conduct the couplings to form the diarylamine linkages. Deprotection of the Boc group and the end-functionalized termini produced materials suitable for studies on the electronic properties of polyanilines with variable chain lengths.

The synthesis of triarylamine materials of variable chain length[68] was conducted by using palladium chemistry to couple diarylamines with aryl nonaflates, as shown in **Scheme 3**. The diarylamines were protected with an *N*-benzyl group, and the aryl nonaflate was masked as a TBS-protected phenol. The TBS-protected phenol was directly converted to the nonaflate using CsF and $F_9C_4SO_2F$, and the benzyl group was, of course, removed by hydrogenolysis. The C—N bonds of the chain were constructed using a complex containing DPPF as ligand; bromide additive appeared to increase reaction yields, but it is unclear how large an effect this additive had on this amination process. The product materials were soluble in organic solvents by virtue of methoxy substitution on the pendant *N*-aryl groups.



Scheme 3

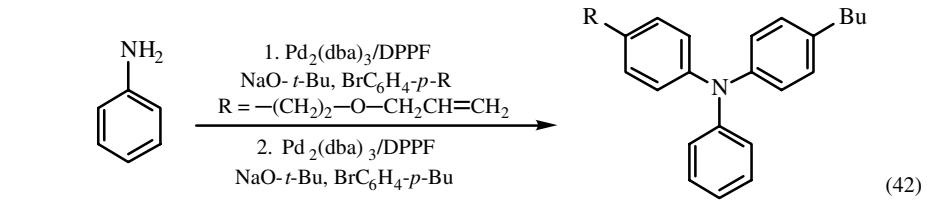
Hyperbranched triarylamine materials were also prepared using the amination chemistry. Louie and Hartwig reported the synthesis of a third-generation triarylamine dendrimer with nitrogen branch points using the original catalyst system (**Scheme 4**).[65] Excellent yields were obtained, allowing the dendrimers to be prepared on large scale. Presumably, analogous syntheses that are even more efficient can now be conducted with the more recently developed catalyst systems. These dendrimers generate highly delocalized radical cations. Multiple arylations of polybromobenzenes were also conducted to generate electron-rich arylamines. Tribromotriphenylamine and 1,3,5-tribromobenzene all react cleanly with *N*-aryl piperazines using either P(*o*-tolyl)$_3$ or BINAP-ligated catalysts to form hexamine products.[130] Reactions of other polyhalogenated arenes have also been reported.[131]



Scheme 4

C.iii.c. ***Preparation of Small Molecules for Materials Science.*** Pd-catalyzed amination has also been used to prepare small molecules that are useful as hole-transport materials, selective metal-cation detection systems, and dyestuffs. As mentioned briefly in the section on reacting diarylamines with aryl halides, Marder and co-workers used palladium chemistry to form triarylamines, which are useful as hole-transport layers. Reactions of primary arylamines with aryl halides using DPPF-ligated palladium as catalyst allows for the selective addition of one aryl halide, followed by the addition of a second aryl halide to form mixed triarylamines, as shown in Eq. 42. This procedure has been used to generate unsymmetrical triarylamines that are analogs of TPD, as shown in Eq. 43.[66] In addition, they have used aminoferrocene as a substrate to conduct diarylations to form *N*, *N*-diarylaminoferrocenes.[132]

To produce arylamine-based ion sensors, aza-18-crown-6 was reacted with 9-bromoanthracene using palladium catalysts to form the *N*-aryl azacrown in modest yield (Eq. 44).[133] Of the reactions using the four ligands P(*o*-tolyl)$_3$, BINAP, DPPP, and DPPF (DPPP = 1,3-diphenylphosphinopropane), the one containing DPPF as ligand occurred in



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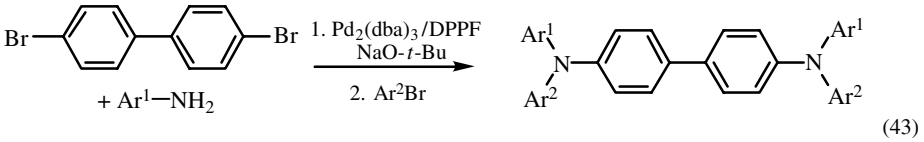

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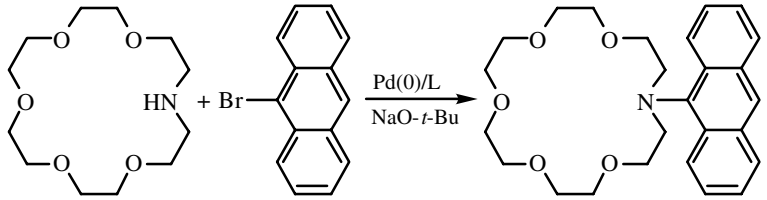
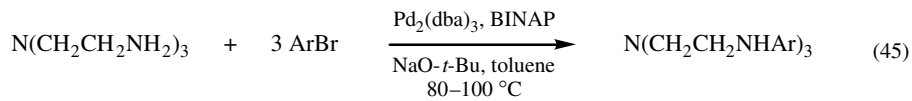


(44)

the highest yield (29%). Ipaktschi and Sharifi reported the Pd-catalyzed synthesis of 2,7-diamino fluorenones by two indirect routes due to the base sensitivity of fluorenones. [134] First, 2,7-dibromofluorene was coupled to secondary amines, and subsequent oxidation of the product formed the diaminofluorenone. Alternatively, reaction of aminostannanes derived from secondary amines with 2,7-dibromofluorenone gave yields of the fluorenone ranging from 42% to 58%.

C.iv. Applications in Ligand Synthesis

Amido compounds are finding increasing importance in early transition metal chemistry as supporting ligands, while materials with both phosphorus and nitrogen donor atoms are finding increased use as non-C_2-symmetric ligands for asymmetric catalysis. Thus, the amination chemistry can provide a useful method for ligand synthesis, and several reports of such methods for ligand preparation have appeared. Schrock and co-workers reported a Pd-catalyzed synthesis of triamido ligands that are useful for conducting α-olefin polymerization using group IV metals (Eq. 45).[135] Similar chemistry has been used by Cabanal-Duvillard and Mangeney to prepare *N*,*N*′-diaryldiamines.[136] Their precursor was the C_2-symmetric 1,2-diphenyl-1,2-diaminoethane that has been used as a building block for ligands used in asymmetric catalysis. Kocovsky and co-workers has reacted his NOBIN aminoalcohol with phenyl bromide to modify this basic ligand structure.[81],[137],[138] Singer and Buchwald have also conducted Pd-catalyzed amination on binaphthyl ligand substructures. They reacted benzophenone imine with the triflate formed from homochiral binaphthol to prepare similar N,O ligands.[139]



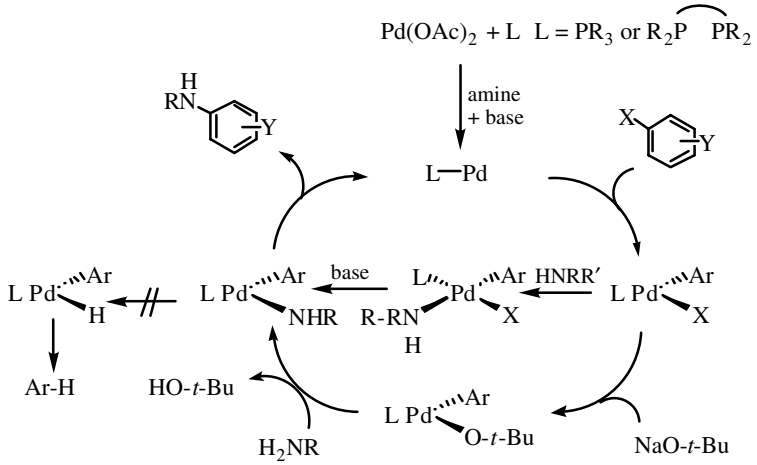
(45)

D. MECHANISM OF PALLADIUM-CATALYZED AMINATION OF ARYL HALIDES

D.i. Background

The mechanistic aspects of Pd-catalyzed amination of aryl halides have been studied extensively. This section provides a summary of the conceptual information that has emerged from these studies and that is useful for understanding why a particular catalyst is effective for a certain class of amination reaction and for the design of even more effective catalysts. The three steps of the catalytic cycle have been studied with some of the ligands, typically the ligands used early in the development of this chemistry. Clearly, there will be differences between the mechanism for reactions catalyzed by the recently developed, highly active systems and those catalyzed by the earlier systems that have been the subject of mechanistic analysis. Nevertheless, basic principles about the catalytic process will apply to all systems. Considering the increased ionic character of the Pd—N or Pd—O bonds versus Pd—C bonds, and the potential for π-repulsion between the filled metal d- and heteroatom p-orbitals, it is remarkable that these complexes behave as similarly as they do to more classic transition metal alkyls. Most striking is the ability to conduct C—N bond formation with metal amido complexes bearing β-hydrogens; β-hydrogen elimination from late metal amido complexes was typically believed to be faster than that from transition metal alkyl complexes. Instead, β-hydrogen elimination from amides may be slower.[140]

The overall mechanism for Pd-catalyzed amination of aryl halides is shown in **Scheme 5**. Initially, a Pd (0) complex is rapidly formed from $Pd(OAc)_2$ and phosphine ligand in the presence of amine and base.[59] If $Pd(dba)_2$ is used, then either bisphosphine Pd(0) complexes are formed, as with $P(t\text{-Bu})_3$,[141] or mixed phosphine/dba Pd(0) complexes are formed as with arylphosphines.[14] In some cases, dba appears to be consumed under the reaction conditions, and simple bis-ligand Pd(0) complexes are formed.[59] The mechanism for reduction of Pd(II) to Pd(0) has been studied,[142] but the process occurs more rapidly in the presence of amine and base than in the absence of these reagents, even when the amine cannot undergo β-hydrogen elimination.

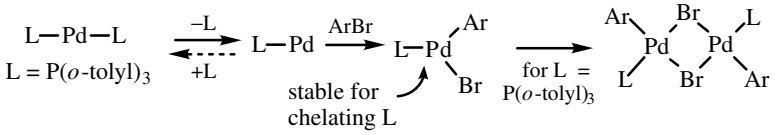


Scheme 5

The Pd(0) complex undergoes oxidative addition of aryl halide, and the resulting arylpalladium halide is converted to an arylpalladium amide in the presence of amine and base. The arylpalladium amide can then undergo either β-hydrogen elimination to produce arene product and regenerate Pd(0), or it can undergo reductive elimination to form the desired arylamine product and Pd(0). This selectivity is important for determining reaction yields. It is most common that a different step of the cycle dictates the reaction rate. For reactions of amines with aryl halides in the presence of alkoxide base catalyzed by BINAP or DPPF complexes, the resting state of the catalyst is the Pd(0) species.[51],[59] Thus, oxidative addition is the turnover limiting step. In reactions that employ weak bases, it is likely, although not experimentally verified, that the resting state is the arylpalladium halide. Slower generation of an arylpalladium amide complex from an arylpalladium halide is likely to occur with weaker bases. Only in special cases is the reductive elimination turnover limiting. For example, the formation of *N*-aryl azoles and *N*-aryl carbamates may involve reductive elimination processes that are slow enough to act as the turnover limiting step. The mechanistic discussion below will summarize the experimental data pertaining to the three steps of the cycle involving the palladium complexes that are useful for carbon–heteroatom bond formation.

D.ii. Oxidative Addition

Extensive studies have been conducted on the oxidative addition of aryl halides to Pd(0) complexes ligated by PPh_3 in different media and with different additives.[13],[143] However, palladium complexes containing these ligands are not active catalysts for the amination. Instead, one must consider the mechanism for oxidative addition of aryl halides to palladium bound by P(*o*-tolyl)$_3$, DPPF, BINAP, and P(*t*-Bu)$_3$. Fewer data have been reported on these systems. Amatore and co-workers have studied the addition of aryl halides to Pd(0) complexes formed by the addition of chelating ligands to $Pd_2(dba)_3$.[14] Addition of these ligands to $Pd_2(dba)_3$ generates mixed phosphine/dba complexes. The kinetic behavior of the complex containing BINAP as phosphine ligand indicated that two competing pathways for addition occur, one by direct reaction of aryl halide with (BINAP)Pd(dba) and one from the (BINAP)Pd intermediate formed by dba dissociation.



(46)

Hartwig and co-workers studied the addition of aryl halides to isolated homoleptic Pd(0) complexes containing P(*o*-tolyl)$_3$, DPPF, or BINAP (Eq. 46).[144],[145] Kinetic studies of the reactions between aryl halides and the L_2Pd complex containing P(*o*-tolyl)$_3$ as ligand in aromatic or THF solvent showed that carbon–halogen bond cleavage occurs by a monophosphine Pd(0) species that does not contain solvent directly coordinated to the metal center. An associative mechanism involving reversible displacement of phosphine by aryl halide to make a dative ArX complex prior to carbon–halogen bond cleavage has been ruled out,[146] leaving reaction by the monophosphine Pd(0) species the remaining mechanism. The palladium complexes $(DPPF)_2Pd$ and $(BINAP)_2Pd$ also undergo dissociation of ligand, this time to form a (chelate)Pd(0) intermediate that undergoes oxidative

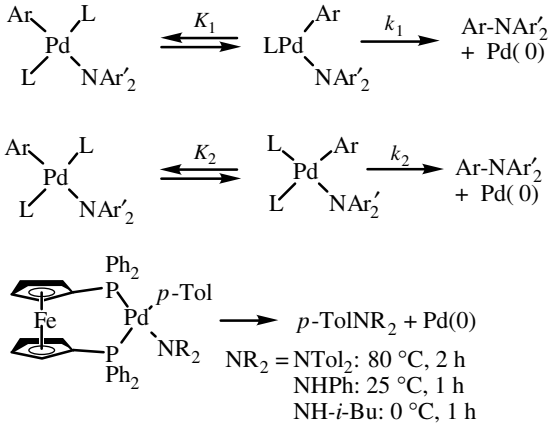
addition. In the case of addition to $(BINAP)_2Pd(0)$, reactions conducted with high ratios of aryl bromide to free phosphine were zero order in aryl bromide. Under these conditions, dissociation of phosphine is rate determining. These conditions of high aryl bromide to free ligand are, of course, the conditions that mimic those of the catalytic reaction. Thus, one can predict that the catalytic process will depend only on the rate of ligand dissociation and will be zero order in amine, aryl halide, and base. These predictions have been confirmed experimentally.[145]

D.iii. Reductive Elimination and β-Hydrogen Elimination

The most detailed studies have been conducted on the reductive elimination step of the catalytic cycle; fewer studies have been conducted on β-hydrogen elimination from late metal amido complexes. Several principles have emerged from this study. First, C—N bond-forming reductive elimination can occur from either three-coordinate monophosphine or four-coordinate bis-phosphine complexes.[23] Elimination from the three-coordinate species appears to be faster. Second, β-hydrogen elimination from initially square planar amido complexes appears to occur predominantly or exclusively from a three-coordinate intermediate formed by phosphine dissociation.[140] Thus, chelating ligands tend to block β-hydrogen elimination, while allowing formation of arylamine products by reductive elimination from a cis, four-coordinate species. Third, the rate of reductive elimination is strongly dependent on the nucleophilicity of the heteroatom and electrophilicity of the palladium-bound aryl group.[23],[147] Complexes containing covalent ligands with more nucleophilic heteroatoms bound to palladium undergo reductive elimination more rapidly than those with less nucleophilic heteroatoms bound to palladium. A complementary effect of the aryl group's electronic properties on the rate of reductive elimination is observed. Electron-withdrawing substituents on the aryl group bound to palladium accelerate the rate of reductive elimination.[23],[147]–[149] Fourth, steric properties of the phosphine ligand appear to dominate electronic properties. Sterically hindered alkylphosphine ligands, which are strong electron donors, appear to provide faster rates for reductive elimination than smaller alkylphosphine ligands or even smaller arylphosphines.[150]

Direct observations of arylamine reductive elimination encompass complexes containing P(*o*-tolyl)$_3$,[151] DPPF, and PPh_3 as ligand. Complexes of the latter two ligands were stable enough to isolate and fully characterize. Kinetic studies on the elimination from PPh_3 complexes revealed the competing elimination from both three- and four-coordinate intermediates (**Scheme 6**).[23] Because some complexes were dimeric and others monomeric, a direct comparison of reaction rates for different types of amido complexes could not be made. However, the isolation and subsequent reaction chemistry of DPPF-ligated arylpalladium amides did provide complexes that underwent reductive elimination without prior rearrangements. Thus, one could readily determine that complexes with more electron-rich amide ligands reacted faster **Scheme 6**, and those with electron-poor aryl groups reacted faster. Furthermore, the generation and characterization of DPPF-ligated palladium alkylamido complexes in solution allowed a direct observation of the improved selectivity for reductive elimination over β-hydrogen elimination in the case of complexes containing primary alkylamido ligands.[23],[42]

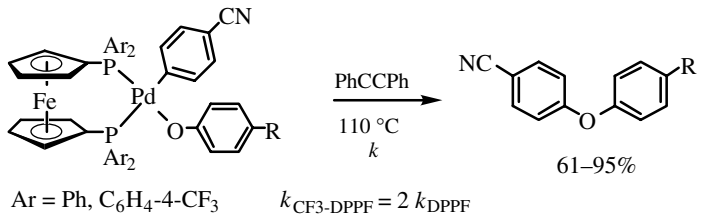
The effects of chelating ligand structure on reductive elimination and β-hydrogen elimination have not been studied extensively. However, one study did evaluate the ratios of products formed from the catalytic process as the ligand bite angle, the aryl group's electronic, and the aryl group's steric properties were systematically perturbed.[30]



Scheme 6

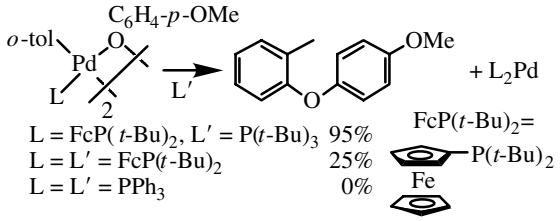
A second study provided an analysis of the effect of ligand structure on the reductive elimination of diaryl ethers.[150]

In general, electronic effects produced minor changes in product distribution of the catalytic process and rate of reductive elimination.[30] Moreover, the electronic effect on product distribution in the catalytic amination was surprising: the more electron-rich phosphine gave better ratios of arylamine to arene. This trend is the opposite of what one would expect from conventional acceleration of reductive elimination and deceleration of β-hydrogen elimination by reduction of electron density at the metal center.[152] As part of the studies of ligand effects on the reductive elimination of diaryl ethers, an arylpalladium phenoxide complex containing a DPPF analog that had p-CF_3 substituents on each of the ligand aryl groups was prepared. This complex underwent reductive elimination of diaryl ether only twice as fast as the simple DPPF complex (Eq. 47).[153]



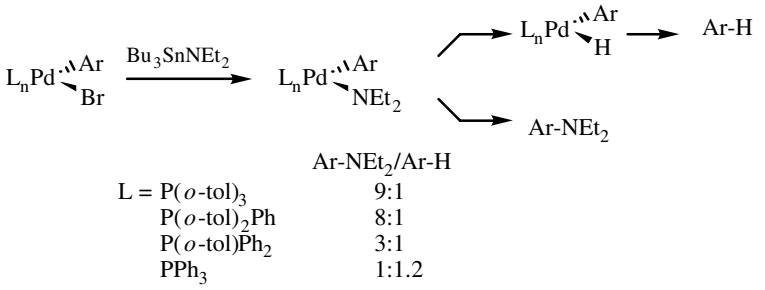
(47)

Steric properties of the ligand have a more pronounced effect on the rate of reductive elimination. Arylpalladium phenoxide complexes containing a sterically hindered monophosphine P(Fc)(t-Bu)$_2$ (Fc = ferrocenyl) underwent reductive elimination of diaryl ethers, even when the palladium-bound aryl group was unactivated, as shown in Eq. 48.[150] Arylpalladium phenoxide intermediates containing P(t-Bu)$_3$ as ligand underwent this reductive elimination in essentially quantitative yield. Reductive elimination of diaryl ether from DPPF-ligated palladium complexes with unactivated aryl groups on the metal did not occur. Thus, the steric hindrance of the ligand, as well as the presence of a single phosphine donor atom provide large rate accelerations.



(48)

Two mechanistic studies on β-hydrogen elimination from monomeric square planar amido complexes have been conducted. A third study on reversible β-hydrogen elimination from dimeric rhodium complexes has been reported.[154] The first mechanistic study evaluated the steric effects of the phosphine ligand on the selectivity for reductive elimination versus β-hydrogen elimination from monophosphine arylpalladium dialkylamido intermediates.[155] This study showed that an increased size of the phosphine ligand accelerates the rate of reductive elimination relative to that of β-hydrogen elimination (Eq. 49). These results are rationalized by the decrease in coordination number resulting from reductive elimination and increasing coordination number resulting from β-hydrogen elimination, which generates a hydride and imine ligand from an amide. A second mechanistic study involved primary alkylamido and *N*-alkyl arylamido complexes of Ir(I) that were isoelectronic with the arylpalladium(II) amido complexes of the catalytic cycle (Eq. 50).[140] This study showed that β-hydrogen elimination from amides can be dramatically slower than β-hydrogen elimination from the analogous alkyl complexes (70–110 °C versus 0 °C). It also showed that β-hydrogen elimination occurred from a three-coordinate intermediate as is typical for β-hydrogen elimination from square planar alkyl complexes.



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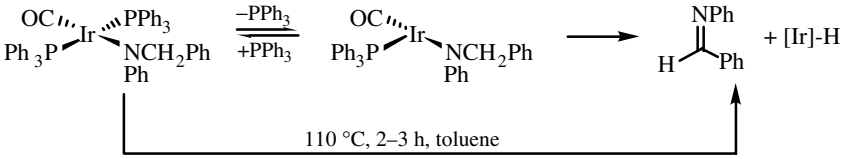


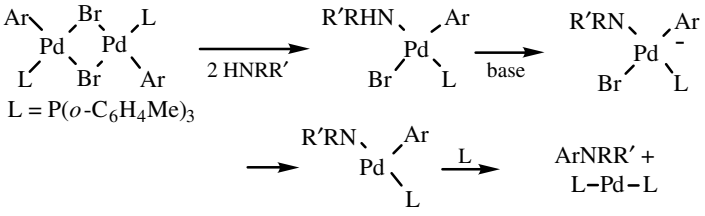
(50)

D.iv. Formation of Amido Complexes in the Catalytic Process

Three general mechanisms can be envisioned for the formation of amido complexes from arylpalladium halides: direct substitution of halide by alkali amide generated by simple deprotonation of free amine by free base, coordination of amine to the metal center followed by deprotonation of the more acidic coordinated amine, or formation of a palladium alkoxide

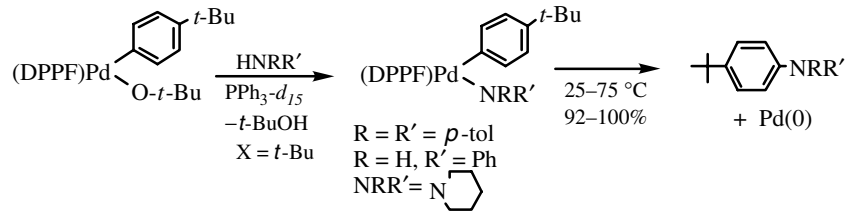
complex that reacts with amine to form a palladium amide and alcohol. The mechanism followed for this step of the cycle depends on the identity of the catalyst, base, and nitrogen substrate. In general, the first mechanism should be avoided because alkali amides react with aryl halides to generate benzyne intermediates and to undergo electron transfer processes.[156],[157] In addition, stabilized nitrogen anions such as pyrrolyl or anilide ions can generate stable ate complexes with palladium.[23],[85] Therefore, a low concentration of most nitrogen anions is desired. In special cases such as the reactions of diarylamines, Pd-catalyzed amination using anionic amide reagents can provide good yields,[65] but there is generally no advantage to this procedure over the use of a weaker base in the presence of amine.

The second mechanism involving deprotonation of coordinated amine is the most likely pathway for reactions catalyzed by palladium monophosphine complexes (Eq. 51). The catalytically active arylpalladium halide intermediate with bulky monophosphine ligands are three-coordinate complexes that can bind amine.[158]–[161] These mixed amine phosphine complexes can then undergo deprotonation by bases whose conjugate acids are weaker than the amine substrate. For example, alkylamine complexes of arylpalladium halides containing P(*o*-tolyl)$_3$ as ligand have been deprotonated at low temperature by silylamide base to give the coupled product after generation of the palladium amide.[151] Presumably, this general mechanism operates when carbonate or phosphate bases are employed, although the deprotonation process is probably at the surface of the solid base for reactions in aromatic solvents. The mechanism is less clear for the generation of palladium amides when weak bases and palladium complexes bearing chelating phosphines are used. Most likely, deprotonation of a five-coordinate amine complex occurs, but replacement of halide by amine and deprotonation of the resulting cationic amine complex is an alternative pathway. This latter mechanism most likely occurs during catalytic amination of aryl triflates using carbonate or phosphate base because of the lability of the triflate ligand. No mechanistic data have been obtained to support these pathways involving complexes with chelating ligands, although they have been frequently proposed.



(51)

The final pathway, which involves alkoxide intermediates, has been shown to occur when reactions employ NaO-*t*-Bu as base and DPPF as ligand (Eq. 52).[162] DPPF-ligated arylpalladium *t*-butoxide complexes have been isolated. Reactions of these complexes with arylamines led to rapid formation of the amido complex and subsequent reductive elimination of diarylamine. Reactions with secondary alkylamines led to formation of dialkylanilines, presumably through the intermediacy of an arylpalladium dialkylamido intermediate. Reaction of the DPPF-ligated, arylpalladium halide complexes with alkoxide and dialkylamine together first formed the alkoxide complex. This complex subsequently reacted with amine and reductively eliminated the dialkylaniline. The observation of the alkoxide complex in this reaction strongly suggests the intermediacy of the alkoxide complex in the catalytic reactions.[153]



(52)

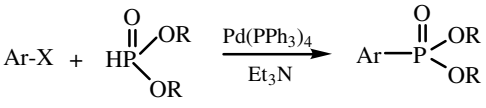
E. PALLADIUM-CATALYZED FORMATION OF PHOSPHINES AND ARSINES FROM ARYL HALIDES

E.i. Introduction to P—C and As—C Bond Formation

The number of phosphine ligands, particularly nonracemic chiral phosphine ligands, that are being prepared each year has been expanding tremendously. One method that has assisted in the synthesis of these ligands is the Pd-catalyzed formation of aromatic P—C bonds. Similar methods can be used to prepare aromatic arsines. One of the original procedures for Pd-catalyzed P—C bond formation was published by Hirao using dialkyl phosphonates, and Stille subsequently used silylphosphides as reagents. Procedures involving secondary phosphines in the presence of base are now used commonly, as are reactions of secondary phosphine oxides in the presence of base. The coupling of phosphine boranes has also been used. The latter two procedures provide the benefit of air-stable phosphorus reagents and products, and they involve reagents and products that are weak ligands for the metal center. Coordination of a phosphine product to the palladium can alter the catalyst struture. Thus, chelating ligands are sometimes used in the synthesis of phosphines by the Pd-catalyzed method.

E.ii. Specific Examples of Palladium-Catalyzed P—C and P—As Bond Formation

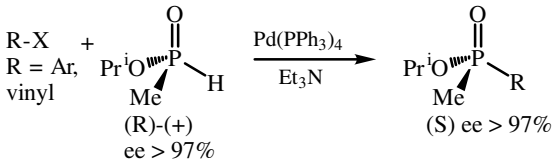
E.ii.a. ***Synthesis of P(V) Coupling Products.*** In 1980 and 1982, Hirao and co-workers reported the coupling of vinyl and aryl halides with *O,O*-dialkylphosphonates to prepare vinyl and aryl dialkylphosphonates.[163],[164] This reaction is shown for aryl halides in Eq. 53 and was one of the first catalytic P—C bond-forming processes. During this time, they also reported the coupling of aryl bromides with dialkylphosphonates.[165] In both these studies, the reactions were run in the presence of triethylamine as base at 90 °C with $Pd(PPh_3)_4$ as catalyst. The formation of aryl phosphonates was successful with many aryl iodides and bromides, including those with the substituents *p*-CH_3, *p*-Cl, *p*-H_3CO, *p*-NO_2, and *p*-CN. Typical yields ranged from 64% to 96%, but low yields were observed when protic functional groups were present.



(53)

Xu, Li, Xia, Huang, and co-workers have reported a range of P—C bond-forming processes involving the coupling of aryl and vinyl halides with phosphorus(V) reagents. For example, they have reported the cross-coupling reaction of aryl and vinyl bromides

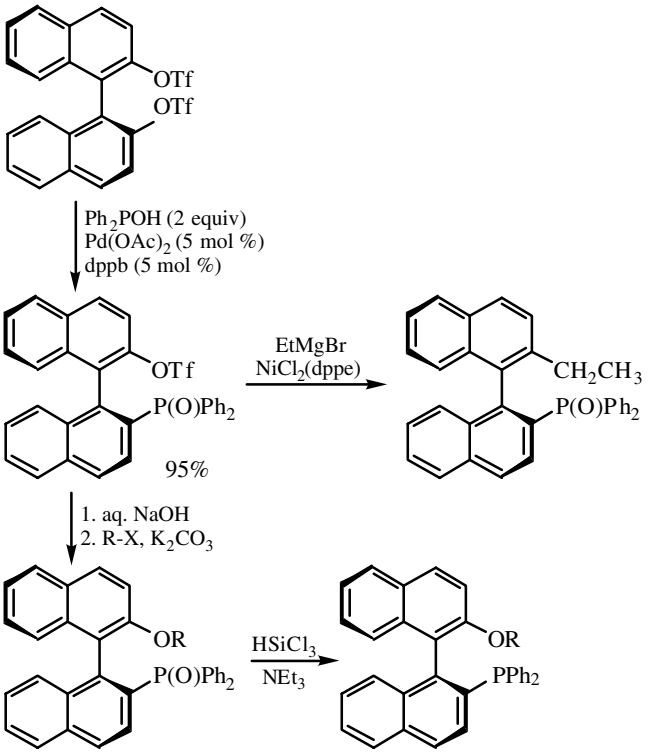
with monoalkyl benzenephosphonites (RO)(Ph)P(= O)H), isopropyl methylphosphinates (RO)(Me)P(= O)H), and secondary phosphine oxides using the same catalyst and base as Hirao used to give unsymmetrical alkyl diarylphosphinates,[166] isopropyl alkenylmethylphosphinates,[167] isopropyl arylmethylphosphinates,[168] and tertiary phosphine oxides. In general, the yields were high for the coupling of aryl and vinyl bromides with phosphonites and for the coupling of electron-poor aryl halides with secondary phosphine oxides. Lower yields were observed for the coupling of secondary phosphine oxides with aryl halides bearing electron-donating substituents. Xu and co-workers also used similar chemistry to prepare alkenylbenzylphenylphosphine oxides[169] and alkylarylphenylphosphine oxides.[170] In the work on the preparation of phosphinates, the authors initiated the reactions with nonracemic chiral phosphorus(V) reagents. They found that the phosphorus stereochemistry was retained, providing a route to optically active phosphinates.[167],[168] In addition, these phosphorus reagents allowed for an analysis of the stereochemistry of the reaction involved in the catalytic cycle.[171] The stereochemistry was retained in the overall process, and it was established previously in studies on C—C bond-forming reductive elimination that concerted reductive eliminations proceed with retention of configuration.[172] Assuming the P—C bond-forming reductive elimination also occurs by retention of configuration, the formation of the Pd—P bond in the palladaphosphinate intermediate also occurs with retention of configuration by what is proposed to be a front-side attack of the phenylpalladium bromide on the phosphorus nucleophile.



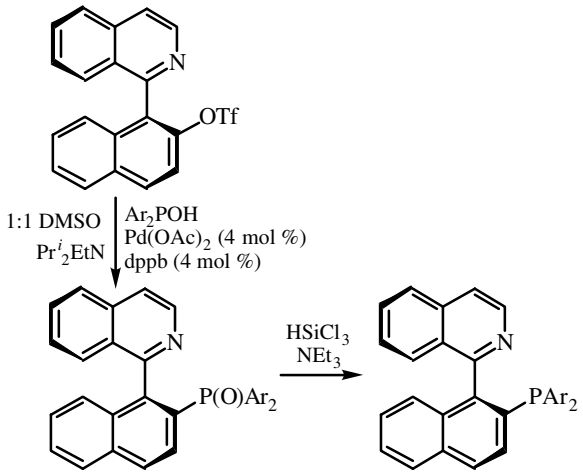
(54)

The similar reaction of diarylphosphine oxides with aryl halides and triflates has been used more recently to prepare a variety of ligands for asymmetric catalysis. Many of these reactions involve additions of secondary phosphine oxides to di- or monotriflates derived from binaphthol because the triflates are more accessible than 2,2′-1,1′-dibromobinaphthol. Workers at Syntex described a procedure to use the ditriflate of binaphthol to prepare mixed phosphine oxide, hydroxo ligands, and the monophosphine oxide, binaphthyldiphenylphosphine oxide.[173] Hayashi then developed a route to a number of chiral monodentate phosphine ligands with a 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyl structure (Eq. 55).[174] Reaction of the ditriflate with diphenylphosphine oxide in the presence of a catalyst generated from $Pd(OAc)_2$ and bis-1,4-(diphenylphosphino)butane gave the substitution product in 95% yield. This product was hydrolyzed, alkylated, and reduced in good yield in all cases except when a methoxymethyl group was installed. In this case reduction followed by alkylation gave the best results. The monosubstitution product was also converted to a 2-alkyl-2′-phosphino-1,1′-binaphthyl ligand by a Ni-catalyzed Grignard reaction at the remaining triflate. Most recently, Kocovsky has used a similar synthetic approach to convert his 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) to amino phosphino binaphthyl (MAP) ligands. Conversion of NOBIN to the triflate and phosphination followed by reduction generates the MAP ligands.[175],[176] Finally, Cho and

Shibasaki have prepared mixed diphenylphosphino diphenylarsino ligands by reacting diphenylarsine in the presence of 10% DPPE-ligated Ni(0) with the monophosphine monotriflate that is generated by P—C coupling of a secondary phosphine oxide and reduction with silane.[177] Doucet and Brown used this general method to prepare QUINAP, as shown in Eq. 56.[178]

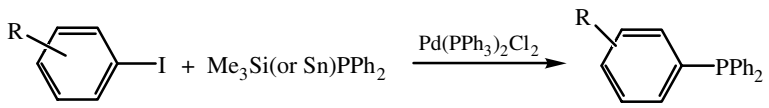


(55)



(56)

E.ii.b. ***Synthesis of Phosphorus(III) Coupling Products.*** In many cases, secondary phosphines, rather than secondary phosphine oxides, can be used as substrates. In one case, phosphine oxides were generated even when starting with secondary phosphines,[179] but this result is atypical. In 1980, Sokolov and co-workers published a stoichiometric P—C bond-forming process to generate one of Kumada's phosphino amine ligands,[180] and in 1987, Tunney and Stille reported catalytic P—C bond-forming cross-coupling reactions to generate phosphine products. As shown in Eq. 57, Stille used stannyl and silylphosphides, with the less toxic silylphosphides reacting at a satisfactory rate.[2] The catalyst used was either $(PPh_3)_2PdCl_2$ or $(CH_3CN)_2PdCl_2$. Yields ranged from 55% to 94%, and the reaction tolerated a variety of functional groups on the arene, including esters, ketones, trifluoromethyl groups, and amides. Aldehyde, hydroxyl, amino, and nitro groups were not tolerated. Related chemistry using silylphosphides has been used by Mathey to prepare phosphino-substituted phosphinines from bromophosphinines[181] and by Beletskaya to prepare both 2-alkenylphosphines from vinyl halides and unsymmetrical secondary phosphines from silylphosphines.[182],[183]



(57)

It is now common that secondary phosphine and base are used instead of isolated silylphosphine reagents. A paper by Cai and co-workers from Merck Process Research showed that the single substitution products of phosphine oxides with the ditriflate of binaphthol could be converted under catalytic conditions to the disubstitution products with either secondary phosphine or phosphine oxide.[184] Thus, $(DPPE)NiCl_2$ catalyzes the double addition of diphenylphosphine to the ditriflate to generate BINAP. A number of researchers have either used this system or palladium catalysts to generate phosphines. McCarthy and Guiry and Shibasaki and co-workers each used Ni- catalyzed processes to prepare phosphines from aryl halides and secondary phosphines. Guiry prepared QUINAP analogs and Shibasaki prepared BINAs.[185],[186] Others have used palladium catalysts with similar reagents. Beletskaya and co-workers showed that not only silylphosphines but secondary aryl phosphines and base would react with vinyl halides in the presence of palladium catalysts to form α- or β-alkoxy- and α- or β-aminovinyl phosphines.[187] Stelzer and co-workers used water-soluble secondary phosphines, aryl halides, and base in the presence of palladium acetate or $(PPh_3)_4Pd(0)$ catalyst to generate water-soluble tertiary phosphines,[188] and Casalnuovo and Calabrese reported the use of water-soluble catalysts to conduct the coupling of dialkylphosphonates with aryl halides in aqueous acetonitrile mixtures.[189]

Several methods have been adopted to manage the air sensitivity of either the secondary phosphine reagents or tertiary phosphine products. For example, Gilbertson used Pd-catalyzed chemistry to install a phosphino group into a peptide.[190] Conversion of a tyrosine or related unnatural aromatic residue to a triflate and subsequent coupling gave the peptide phosphine. This product was protected as the phosphine sulfide *in situ* for chromatography. The sulfide can be converted to the phosphine using Rainey nickel.[191] In an alternative procedure, Oshiki and Imamoto have shown that the secondary phosphine boranes can be used under Pd-catalyzed procedures (5% PPh_3-ligated Pd(0),

K_2CO_3) to prepare tertiary phosphine borane products.[192] Straightforward deprotection of the phosphine borane by addition of amines such as DABCO are known.[193] In this case, resolved secondary phosphine boranes were used and the products showed stereochemistry that depended on the sovent and base used.[192] Lipshutz and co-workers subsequently developed a procedure for using phosphine boranes with aryl triflates and nonaflates to generate phosphine borane products.[194] A final procedure that involves the convenient use of diorganophosphine chlorides and aryl halides is based on nickel catalysts, but will be mentioned briefly. Laneman and co-workers reported a procedure by which aryl or vinyl bromides or triflates react with diaryl chlorophosphines using $NiCl_2$(DPPE) and stoichiometric zinc as reductant to generate triarylphosphines in yields ranging from 45% to 95%. The aryl triflates gave the highest yields.[195]

E.ii.c. ***Mechanism of Palladium-Catalyzed P—C Bond Formation.*** Little mechanistic information has been generated about the P—C bond-forming catalytic process, but the mechanism certainly involves oxidative addition of aryl halide, and most likely involves formation of a palladium phosphide and reductive elimination of phosphine. Transition metal phosphide chemistry is a large body of literature, but few reductive eliminations of phosphines have been reported. Fryzuk and co-workers reported an alkyliridium phosphido complex that reductively eliminates phosphine,[196] while Glueck and co-workers reported more closely related methylplatinum phosphides that resist such reductive elimination.[197] Brown and co-workers did recently generate arylpalladium phosphidoborane complexes at low temperature by addition of $KPh_2P(BH_3)$ to DPPP-ligated arylpalladium halide complexes.[198] In the case of the C_6F_5 complex, the arylpalladium phosphidoborane complex was stable enough to isolate and obtain X-ray structural data. Most of the arylpalladium phosphidoborane complexes were unstable at room temperature, and their reductive elimination behavior was not investigated in detail.

F. FUTURE PROSPECTS

A glance at the chart of catalysts and transformations shows the types of aromatic C—N bond formation that are unknown or need improvement. The development of catalysts for formation of aryl phosphines by Pd-catalyzed methods has seen less attention, and the improved catalysts for the amination chemistry may also improve the C—P bond-forming processes in certain cases. Furthermore, general procedures for obtaining fast rates with weakly basic conditions for C—N bond formation are desired in most cases. Improvements in rate and turnover number for most aromatic carbon–heteroatom bond formation using aryl chlorides is needed. The development of new catalysts that accomplish these goals and the recent development of highly active catalysts will continue to create new mechanistic questions about the origin of their activity. They also will provide the potential to apply Pd-catalyzed aromatic carbon–heteroatom bond formation to additional synthetic problems. The analysis of these reactions and their use in complex syntheses are likely to accompany the development of improved catalysts in the future.

REFERENCES

[1] D. Barañano, G. Mann, and J. F. Hartwig, *Curr. Org. Chem.*, 1997, 1, 287.

[2] S. E. Tunney and J. K. Stille, *J. Org. Chem.*, **1987**, *52*, 748.

[3] T. Migita, T. Shimiza, Y. Asami, J. Shiobara, Y. Kato, and M. Kosugi, *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1385.
[4] M. Kosugi, T. Ogata, M. Terada, H. Sano, and T. Migita, *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 3657.
[5] K. Takagi, *Chem. Lett.*, **1987**, 2221.
[6] T. Yamamoto and Y. Sekine, *Inorg. Chim. Acta*, **1984**, *83*, 47.
[7] D. L. Boger and J. S. Panek, *Tetrahedron Lett.*, **1984**, *25*, 3175.
[8] D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **1985**, *50*, 5782.
[9] D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **1985**, *50*, 5790.
[10] M. Kosugi, M. Kameyama, and T. Migita, *Chem. Lett.*, **1983**, 927.
[11] M. Kosugi, M. Kameyama, H. Sano, and T. Migita, *Nippon Kagaku Kaishi*, **1985**, *3*, 547.
[12] J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.*, **1977**, *10*, 434–442.
[13] C. Amatore, A. Jutand, and A. Suarez, *J. Am. Chem. Soc.*, **1993**, *115*, 9531.
[14] C. Amatore, G. Broeker, A. Jutand, and F. Khalil, *J. Am. Chem. Soc.*, **1997**, *119*, 5176.
[15] A. L. Casado and P. Espinet, *Organometallics*, **1998**, *17*, 954.
[16] H. Bryndza and W. Tam, *Chem. Rev.*, **1988**, *88*, 1163–1188.
[17] M. D. Fryzuk and C. D. Montgomery, *Coord. Chem. Rev.*, **1989**, *95*, 1–40.
[18] R. G. Pearson, *J. Am. Chem. Soc.*, **1963**, *85*, 3533.
[19] R. G. Pearson, *J. Chem. Ed.*, **1968**, *45*, 643.
[20] R. G. Pearson, *J. Chem. Ed.*, **1968**, *45*, 581.
[21] S. Park, A. L. Rheingold, and D. M. Roundhill, *Organometallics*, **1991**, *10*, 615.
[22] L. A. Villanueva, K. A. Abboud, and J. M. Boncella, *Organometallics*, **1994**, *13*, 3921.
[23] M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **1997**, *119*, 8232.
[24] M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **1995**, *117*, 4708.
[25] J. Louie and J. F. Hartwig, *J. Am. Chem. Soc.*, **1995**, *117*, 11598.
[26] C. A. Tolman, *Chem. Rev.*, **1977**, *77*, 313.
[27] C. P. Casey, G. T. Whiteker, M. G. Melville, L. M. Petrovich, J. A. Gavney Jr., and D. R. Powell, *J. Am. Chem. Soc.*, **1992**, *114*, 5535.
[28] C. P. Casey and G. T. Whiteker, *Isr. J. Chem.*, **1990**, *30*, 299.
[29] P. Dierkes and P. W. N. M. van Leeuwen, *J. Chem. Soc. Dalton Trans.*, **1999**, 1519.
[30] B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, **1998**, *120*, 3694.
[31] For a review see: J. F. Hartwig, *Synlett*, **1997**, 329.
[32] J. F. Hartwig, *Acc. Chem. Res.*, **1998**, *31*, 852–860.
[33] J. F. Hartwig, in *Modern Amination Methods*, A. Ricci, Ed., Wiley-VCH, Weinheim, 2000, 195–257.
[34] J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 2046.
[35] J. P. Wolfe, S. Wagaw, J.-F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.*, **1998**, *31*, 805–818.
[36] C. G. Frost and P. Mendonca, *J. Chem. Soc. Perkin Trans. and 1*, **1998**, 2615.
[37] B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **1999**, *576*, 125.
[38] S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, **1996**, *61*, 7240.
[39] M. Nishiyama, T. Yamamoto, and Y. Koie, *Tetrahedron Lett.*, **1998**, *39*, 617.
[40] J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, and L. M. Alcazar-Roman, *J. Org. Chem.*, **1999**, *64*, 5575.
[41] J.-F. Marcoux, S. Wagaw, and S. L. Buchwald, *J. Org. Chem.*, **1997**, *62*, 1568.
[42] M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **1996**, *118*, 7217.
[43] J. P. Wolfe, S. Wagaw, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1996**, *118*, 7215.

[44] J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, **1995**, *36*, 3609.
[45] A. S. Guram, R. A. Rennels, and S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1348.
[46] J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **1996**, *61*, 1133.
[47] T. Yamamoto, M. Nishiyama, and Y. Koie, *Tetrahedron Lett.*, **1998**, *39*, 2367.
[48] M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, **1999**, *121*, 1473.
[49] A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 3387.
[50] A. F. Littke and G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10.
[51] D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 9722.
[52] X. Bei, T. Uno, J. Norris, H. W. Turner, W. H. Weinberg, and A. S. Guram, *Organometallics*, **1999**, *18*, 1840.
[53] X. Bei, A. S. Guram, H. W. Turner, and W. H. Weinberg, *Tetrahedron Lett.*, **1999**, *40*, 1237.
[54] K. Kamikawa, S. Sugimoto, and M. Uemura, *J. Org. Chem.*, **1998**, *63*, 8407.
[55] P. Molina, A. Arques, and A. Garcia, *Tetrahedron Lett.*, **1997**, *38*, 7613.
[56] V. V. Grushin and H. Alper, *Chem. Rev.*, **1994**, *94*, 1047–1062.
[57] M. Beller, T. H. Reirmeier, C. Reisinger, and W. A. Herrman, *Tetrahedron Lett.*, **1997**, *38*, 2073.
[58] N. P. Reddy and M. Tanaka, *Tetrahedron Lett.*, **1997**, *38*, 4807.
[59] B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, **1998**, *120*, 7369.
[60] J. F. Hartwig, unpublished results.
[61] J. Louie, M. S. Driver, B. C. Hamann, and J. F. Hartwig, *J. Org. Chem.*, **1997**, *62*, 1268.
[62] J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **1997**, *62*, 1264.
[63] J. Åhman and S. L. Buchwald, *Tetrahedron Lett.*, **1997**, *38*, 6363.
[64] J. P. Wolfe and S. L. Buchwald, *Tetrahedron Lett.*, **1997**, *38*, 6359.
[65] J. Louie and J. F. Hartwig, *J. Am. Chem. Soc.*, **1997**, *119*, 11695.
[66] S. Thayumanavan, S. Barlow, and S. R. Marder, *Chem. Mater.*, **1997**, *9*, 3231.
[67] E. Bellmann, S. Shaheen, S. Thayumanavan, S. Barlow, R. Grubbs, S. Marder, B. Kippelen, and N. Peyghambarian, *Chem. Mater.*, **1998**, *10*, 1668.
[68] J. Louie and J. F. Hartwig, *Macromolecules*, **1998**, *31*, 6737.
[69] K. Rossen, P. J. Pye, A. Maliakal, and R. P. Volante, *J. Org. Chem.*, **1997**, *62*, 6462.
[70] I. P. Beletskaya, A. G. Bessermertnykh, and R. Guilard, *Tetrahedron Lett.*, **1997**, *38*, 2287.
[71] Y. P. Hong, C. H. Senanayake, T. J. Xiang, C. P. Vandenbossche, G. J. Tanoury, R. P. Bakale, and S. A. Wald, *Tetrahedron Lett.*, **1998**, *39*, 3121.
[72] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, and A. Tijani, *J. Am. Chem. Soc.*, **1994**, *116*, 4062.
[73] H. Blaser and F. Spindler, *Chimia*, **1997**, *51*, 297.
[74] Y. Kubota, S. Nakada, and Y. Sugi, *Synlett*, **1998**, 183.
[75] S. I. Hauck, K. V. Lakshmi, and J. F. Hartwig, *Org. Lett.*, **1999**, *1*, 2057.
[76] N. Spetseris, R. E. Ward, and T. Y. Meyer, *Macromolecules*, **1998**, *31*, 3158.
[77] T. Kanbara, K. Izumi, Y. Nakadani, T. Narise, and K. Hasegawa, *Chem. Lett.*, **1997**, 1185.
[78] R. A. Singer, J. P. Sadighi, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 213.
[79] J. P. Sadighi, R. A. Singer, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 4960.
[80] J. P. Sadighi, M. C. Harris, and S. L. Buchwald, *Tetrahedron Lett.*, **1998**, *39*, 5327.
[81] S. Vyskocil, M. Smrcina, and P. Kocovsky, *Tetrahedron Lett.*, **1998**, *39*, 9289.
[82] S. Wagaw, B. H. Yang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 6621.
[83] J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 2090.
[84] S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, and D. G. Putman, *Tetrahedron Lett.*, **1998**, *39*, 1313.

[85] G. Mann, M. S. Driver, and J. F. Hartwig, *J. Am. Chem. Soc.*, **1998**, *120*, 827.

[86] J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer, and S. L. Buchwald, *Tetrahedron Lett.*, **1997**, *38*, 6367.

[87] C. Bolm and J. P. Hildebrand, *Tetrahedron Lett.*, **1998**, *39*, 5731.

[88] J. P. Wolfe, R. A. Rennels, and S. L. Buchwald, *Tetrahedron*, **1996**, *52*, 7525.

[89] W. Shakespeare, *Tetrahedron Lett.* **1999**, *40*, 2035.

[90] S.-K. Kang, H.-W. Lee, W.-K. Choi, R.-K. Hong, and J.-S. Kim, *Synth. Commun.*, **1996**, *26*, 4219.

[91] D. V. Davydov and I. P. Beletskaya, *Russ. Chem. Bull.*, **1995**, *44*, 1141.

[92] I. P. Beletskaya, D. V. Davydov, and M. Morenomanas, *Tetrahedron Lett.*, **1998**, *39*, 5617.

[93] I. P. Beletskaya, D. V. Davydov, and M. Morenomanas, *Tetrahedron Lett.*, **1998**, *39*, 5621.

[94] D. Ma and J. Yao, *Tetrahedron: Asymmetry*, **1996**, *7*, 3075.

[95] D. W. Ma, Y. D. Zhang, J. C. Yao, S. H. Wu, and F. G. Tao, *J. Am. Chem. Soc.*, **1998**, *120*, 12459.

[96] A. Abouabdellah and R. Dodd, *Tetrahedron Lett.*, **1998**, *39*, 2119.

[97] F. Kerrigan, C. Martin, and G. H. Thomas, *Tetrahedron Lett.*, **1998**, *39*, 2219.

[98] S. Zhao, A. K. Miller, J. Berger, and L. A. Flippin, *Tetrahedron Lett.*, **1996**, *37*, 4463.

[99] S. Morita, K. Kitano, J. Matsubara, T. Ohtani, Y. Kawano, K. Otsubo, and M. Uchida, *Tetrahedron*, **1998**, *54*, 4811.

[100] S. L. Macneil, M. Gray, L. E. Briggs, J. J. Li, and V. Snieckus, *Synlett*, **1998**, 419.

[101] A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*, **1996**, *118*, 1028.

[102] Y. P. Hong, G. J. Tanoury, H. S. Wilkinson, R. P. Bakale, S. A. Wald, and C. H. Senanayake, *Tetrahedron Lett.*, **1997**, *38*, 5663.

[103] G. J. Tanoury, C. H. Senanayake, R. Hett, A. M. Kuhn, D. W. Kessler, and S. A. Wald, *Tetrahedron Lett.*, **1998**, *39*, 6845.

[104] N. Chida, T. Suzuki, S. Tanaka, and I. Yamada, *Tetrahedron Lett.*, **1999**, *40*, 2573.

[105] C. A. Willoughby and K. T. Chapman, *Tetrahedron Lett.*, **1996**, *37*, 7181.

[106] Y. D. Ward and V. Farina, *Tetrahedron Lett.*, **1996**, *37*, 6993.

[107] A. G. MacDiarmid and A. J. Epstein, in *Science and Applications of Conducting Polymers*, W. R. Salaneck, D. T. Clark, and E. J. Samuelsen, Eds., Adam Hilger, New York, 1991, 117 pp.

[108] A. G. MacDiarmid and A. J. Epstein, *Faraday Discuss. Chem. Soc.*, **1989**, *88*, 317.

[109] A. G. MacDiarmid, J. C. Chiang, A. F. Richter, and A. J. Epstein, *Synth. Met.*, **1987**, *18*, 285.

[110] A. Ito, K. Ota, K. Tanaka, T. Yamabe, and K. Yoshizawa, *Macromolecules*, **1995**, *28*, 5618.

[111] K. Yoshizawa, K. Tanaka, and T. Yamabe, *Chem. Lett.*, **1990**, 1311.

[112] K. Yoshizawa, K. Tanaka, T. Yamabe, and J. Yamauchi, *J. Chem. Phys.*, **1992**, *96*, 5516.

[113] T. Ishida and H. Iwamura, *Chem. Lett.*, **1991**, 317.

[114] M. Stolka, J. F. Yanus, and D. M. Pai, *J. Phys. Chem.*, **1984**, *88*, 4707.

[115] S. Thayumanavan, S. Barlow, S. R. Marder, P. Lee, J. Anderson, N. R. Armstrong, G. E. Jabbour, Y. Kawabe, M. M. Morrell, S. E. Shaheen, B. Kippelen, and N. Peyghambarian, *Abs. Am. Chem. Soc.*,**1997**, *214*, 97.

[116] M. M. Wienk and R. A. J. Janssen, *J. Am. Chem. Soc.*, **1997**, *119*, 4492.

[117] K. R. Stickley and S. C. Blackstock, *J. Am. Chem. Soc.*, **1994**, *116*, 11576.

[118] M. M. Wienk and R. A. J. Janssen, *J. Chem. Soc. Chem. Commun.*, **1996**, 267.

[119] K. R. Stickley, T. D. Selby, and S. C. Blackstock, *J. Org. Chem.*, **1997**, *62*, 448.

[120] K. R. Stickley and S. C. Blackstock, *Mol. Cryst. Liq. Cryst. Sci. Technol. A*, **1995**, *271*, A81.

[121] K. R. Stickley and S. C. Blackstock, *Tetrahedron Lett.*, **1995**, *36*, 1585.

[122] T. Kanbara, A. Honma, and K. Hasegawa, *Chem. Lett.*, **1996**, 1135.

[123] T. Kanbara, K. Izumi, T. Narise, and K. Hasegawa, *Polym. J.*, **1998**, *30*, 66.

[124] F. E. Goodson and J. F. Hartwig, *Macromolecules*, **1998**, *31*, 1700.

[125] F. E. Goodson, S. I. Hauck, and J. F. Hartwig, *J. Am. Chem. Soc.*, **1999**, *121*, 7527.

[126] F. E. Goodson, T. I. Wallow, and B. M. Novak, *Macromolecules*, **1998**, *31*, 2047.

[127] F. E. Goodson, T. I. Wallow, and B. M. Novak, *J. Am. Chem. Soc.*, **1997**, *119*, 12441.

[128] T. Kanbara, M. Oshima, T. Imayasu, and K. Hasegawa, *Macromolecules*, **1998**, *31*, 8725.

[129] T. Kanbara, M. Oshima, and K. Hasegawa, *J. Polym. Sci. Polym. Chem.*, **1998**, *36*, 2155.

[130] B. Witulski, S. Senft, and A. Thum, *Synlett*, **1998**, 504.

[131] I. P. Beletskaya, A. G. Bessmertnykh, R. A. Mishechkin, and R. Guilard, *Russ. Chem. Bull.*, **1998**, *47*, 1416.

[132] A. Mendiratta, S. Barlow, M. W. Day, and S. R. Marder, *Organometallics*, **1999**, *18*, 454.

[133] B. Witulski, Y. Zimmermann, V. Darcos, J. P. Desvergne, D. M. Bassani, and H. Bouas-Laurent, *Tetrahedron Lett.*, **1998**, *39*, 4807.

[134] J. Ipaktschi and A. Sharifi, *Monatsh. Chem.*, **1998**, *129*, 915.

[135] G. E. Greco, A. I. Popa, and R. R. Schrock, *Organometallics*, **1998**, *17*, 5591.

[136] I. Cabanal-Duvillard and P. Mangeney, *Tetrahedron Lett.*, **1999**, *40*, 3877.

[137] S. Vyskocil, M. Smrcina, and P. Kocovsky, *Collect. Czech. Chem. Commun.*, **1998**, *63*, 515.

[138] S. Vyskocil, S. Jaracz, M. Smrcina, M. Sticha, V. Hanus, M. Polasek, and P. Kocovsky, *J. Org. Chem.*, **1998**, *63*, 7727.

[139] R. A. Singer and S. L. Buchwald, *Tetrahedron Lett.*, **1999**, *40*, 1095.

[140] J. F. Hartwig, *J. Am. Chem. Soc.*, **1996**, *118*, 7010.

[141] J. F. Hartwig, unpublished results.

[142] C. Amatore, E. Carre, A. Jutand, and M. A. M′Barki, *Organometallics*, **1995**, *14*, 1818.

[143] C. Amatore and F. Pfluger, *Organometallics*, **1990**, *9*, 2276.

[144] J. F. Hartwig and F. Paul, *J. Am. Chem. Soc.*, **1995**, *117*, 5373.

[145] L. M. Alcazar-Roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-Sands, and I. A. Guzei, *J. Am. Chem. Soc.*, **2000**, *122*, 4618.

[146] L. Alcazar-Roman and J. F. Hartwig, unpublished results.

[147] G. Mann, D. Baranano, J. F. Hartwig, A. L. Rheingold, and I. A. Guzei, *J. Am. Chem. Soc.*, **1998**, *120*, 9205.

[148] D. Barañano and, J. F. Hartwig, *J. Am. Chem. Soc.*, **1995**, *117*, 2937.

[149] R. A. Widenhoefer and S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, *120*, 6504.

[150] G. Mann, C. Incarvito, A. L. Rheingold, and J. F. Hartwig, *J. Am. Chem. Soc.*, **1999**, *121*, 3224.

[151] J. Louie, F. Paul, and J. F. Hartwig, *Organometallics*, **1996**, *15*, 2794.

[152] J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, in Principles and Applications of Organotransition Metal chemistry 2nd ed., University Science Books, Mill Valley, CAD **1987**, 279–354.

[153] G. Mann and J. F. Hartwig, unpublished results.

[154] M. D. Fryzuk and W. E. Piers, *Organometallics*, **1990**, *9*, 986.

[155] J. F. Hartwig, S. Richards, D. Barañano, and F. Paul, *J. Am. Chem. Soc.*, **1996**, *118*, 3626.

[156] H. Heaney, *Chem. Rev.*, **1962**, *62*, 81–97.

[157] R. Rossi and R. H. de Rossi, *Aromatic Substitution by the $S_{RN}1$ Mechanism*, Vol. 178, American Chemical Society, Washington, DC, **1983**.

[158] F. Paul, J. Patt, and J. F. Hartwig, *Organometallics*, **1995**, *14*, 3030.

[159] R. A. Widenhoefer and S. L. Buchwald, *Organometallics*, **1996**, *15*, 3534.

[160] R. A. Widenhoefer, H. A. Zhong, and S. L. Buchwald, *Organometallics*, **1996**, *15*, 2745.

[161] R. A. Widenhoefer and S. L. Buchwald, *Organometallics*, **1996**, *15*, 2755.
[162] G. Mann and J. Hartwig, *J. Am. Chem. Soc.*, **1996**, *118*, 13109.
[163] T. Hirao, T. Masunaga, T. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, **1980**, *21*, 3595.
[164] T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro, and T. Agawa, *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 909.
[165] T. Hirao, T. Masunaga, Y. Ohshiro, and T. Agawa, *Synthesis*, **1981**, 56.
[166] Y. Xu, Z. Li, J. Xia, H. Guo, and Y. Huang, *Synthesis*, **1983**, 377.
[167] H. Xu, H. Wei, J. Zhang, and G. Huang, *Tetrahedron Lett.*, **1989**, *30*, 949.
[168] J. Zhang, Y. Xu, G. Huang, and H. Guo, *Tetrahedron Lett.*, **1988**, *29*, 1955.
[169] Y. Xu, J. Xia, and H. Guo, *Synthesis*, **1986**, 691.
[170] Y. Xu, Z. Li, J. Xia, H. Guo, and Y. Huang, *Synthesis*, **1984**, 781.
[171] Y. Xu and J. Zhang, *J. Chem. Soc. Chem. Commun.*, **1986**, 1606.
[172] D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, **1979**, *101*, 4981.
[173] L. Kurz, G. Lee, D. Morgans, Jr., M. J. Waldyke, and T. Ward, *Tetrahedron Lett.*, **1990**, *31*, 6321.
[174] Y. Uozumi, A. Tanahashi, S. Lee, and T. Hayashi, *J. Org. Chem.*, **1993**, *58*, 1945.
[175] S. Vyskocil, M. Smrcina, and P. Kocovsky, *Tetrahedron Lett.*, **1998**, *39*, 9289.
[176] S. Vyskocil, M. Smrcina, V. Hanus, M. Polasek, and P. Kocovsky, *J. Org. Chem.*, **1998**, *63*, 7738.
[177] S. Y. Cho and M. Shibasaki, *Tetrahedron Lett.*, **1998**, *39*, 1773.
[178] H. Doucet and J. M. Brown, *Tetrahedron: Asymmetry*, **1997**, *8*, 3775.
[179] G. Martorell, X. Garcias, M. Janura, and J. M. Saa, *J. Org. Chem.*, **1998**, *63*, 3463.
[180] V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, *J. Organomet. Chem.*, **1980**, *202*, C58.
[181] P. Lefloch, D. Carmichael, L. Ricard, and F. Mathey, *J. Am. Chem. Soc.*, **1993**, *115*, 10665.
[182] I. P. Beletskaya, Y. A. Veits, V. A. Leksunkin, and V. L. Foss, *Bull. Russ. Acad. Sci. Div. Chem. Sci.*, **1992**, *41*, 1272.
[183] Y. A. Veits, N. B. Karlstedt, and I. P. Beletskaya, *Russ. J. Org. Chem.*, **1994**, *30*, 70.
[184] D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **1994**, *59*, 7180.
[185] M. McCarthy and P. J. Guiry, *Tetrahedron*, **1999**, *55*, 3061.
[186] A. Kojima, C. D. J. Boden, and M. Shibasaki, *Tetrahedron Lett.*, **1997**, *38*, 3459.
[187] M. A. Kazankova, E. A. Chirkov, A. N. Kochetkov, I. V. Efimova, and I. P. Beletskaya, *Tetrahedron Lett.*, **1999**, *40*, 573.
[188] O. Herd, A. Hebler, M. Hingst, M. Tepper, and O. Stelzer, *J. Organomet. Chem.*, **1996**, *522*, 69.
[189] A. Casalnuovo and J. C. Calabrese, *J. Am. Chem. Soc.*, **1990**, *112*, 4324.
[190] S. R. Gilbertson and G. W. Starkey, *J. Org. Chem.*, **1996**, *61*, 2922.
[191] S. R. Gilbertson, G. Chen, and M. McLoughlin, *J. Am. Chem. Soc.*, **1994**, *116*, 4481.
[192] T. Oshiki and T. Imamoto, *J. Am. Chem. Soc.*, **1992**, *114*, 3975.
[193] H. Brisset, Y. Gourdel, P. Pellon, and M. Le Core, *Tetrahedron Lett.*, **1993**, *34*, 4523.
[194] B. H. Lipshutz, D. J. Buzard, and C. S. Yun, *Tetrahedron Lett.*, **1999**, *40*, 201.
[195] D. J. Ager, M. B. East, A. Eisenstadt, and S. A. Laneman, *Chem. Commun.*, **1997**, 2359.
[196] M. D. Fryzuk, K. Joshi, R. K. Chadha, and S. J. Rettig, *J. Am. Chem. Soc*., **1991**, *113*, 8724.
[197] D. K. Wicht, S. N. Paisner, B. M. Lew, D. S. Glueck, G. P. A. Yap, L. M. Liable-Sands, A. L. Rheingold, C. M. Haar, and S. P. Nolan, *Organometallics*, **1998**, *17*, 652.
[198] A. C. Gaumont, M. B. Hursthouse, S. J. Coles, and J. M. Brown, *Chem. Commun.* **1999**, 63.