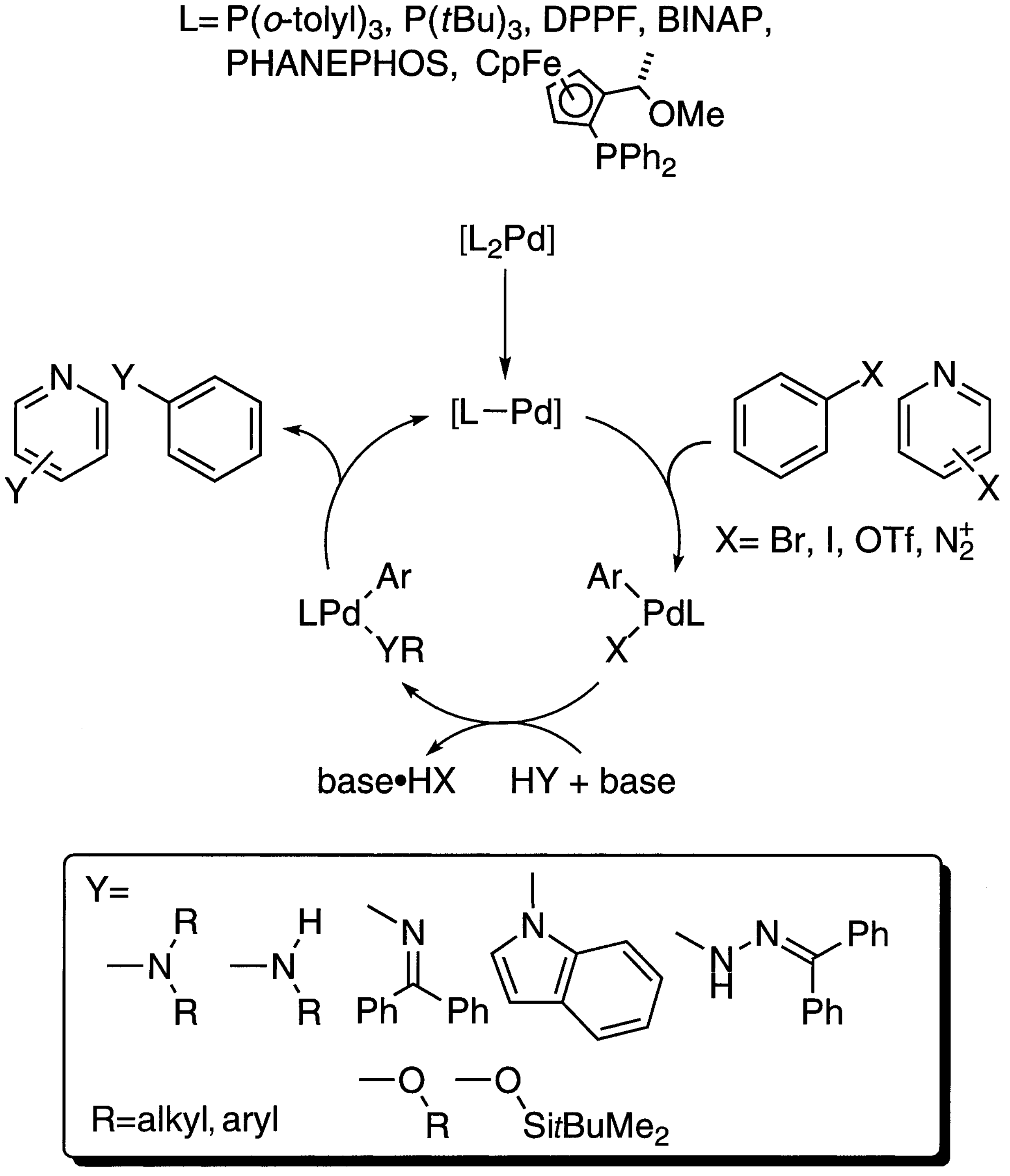
Recent advances in palladium- and nickel-catalyzed chemistry provide new ways to construct C–N and C–O bonds.



Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism

John F. Hartwig*

The transition metal catalyzed synthesis of arylamines by the reaction of aryl halides or triflates (triflate = trifluoromethanesulfonyl) with primary or secondary amines has rapidly become a valuable synthetic tool for a variety of applications. This process can form monoalkyl- or dialkylanilines as well as mixed diaryl- or triarylamines. In addition, the chemistry can be extended to the formation of aryl ethers from aryl halides, although this process is currently less general than the synthesis of arylamines. The mechanism of this reaction involves several novel organometallic reactions. For example, the C–N or C–O bond is formed by reductive elimination of amines or ethers, and the metal–amido complexes that undergo reductive elimination can be formed in the catalytic cycle by N–H activation. Side products are formed by β-hydrogen elimination from amides, examples of which have recently been observed directly. This review covers the development of synthetic methods to form arylamines by this palladium-catalyzed chemistry. In addition to information on syntheses, a description of the pertinent mechanistic data on the overall catalytic cycle, on each elementary reaction in the catalytic cycle, and on competing side reactions is presented. This review covers manuscripts that appeared in press before July 1, 1997 as well as those submitted by the author and co-workers before this date. A brief discussion of papers that appeared between July 1, 1997 and March 1, 1998 is included as an appendix.

Keywords: aminations · arylations · ethers · nickel · palladium

1. Introduction

1.1. Synthetic Considerations

Arylamines and aryl ethers are commonplace. They are part of molecules with medicinally important properties, of molecules with structurally interesting properties, and of materials with important electronic and mechanical properties. An arene–nitrogen or arene–oxygen linkage is included in nitrogen or oxygen heterocycles such as indoles[1, 2] and benzofurans,[3–6] isodityrosine-based natural products such as vancomycin,[7–21] conjugated polymers such as polyanilines,[22–28] readily oxidized triarylamines used in electronic applications such as *N,N'*-diphenyl-*N,N'*-bis(3-methylphenyl)-1,1'-biphenyl-4,4'-diamine (TPD)[29–32] and thermally stable poly(aryl ether)s such as poly(phenylene oxide) (PPO).[33–36]

Despite the simplicity of the arylamine and aryl ether moieties, synthesis of these compounds is often difficult. Procedures involving nitration, reduction, or substitution are incompatible with many functional groups and often involve protection and deprotection steps. Reductive amination, which involves formation of an imine from an arylamine and subsequent reduction of the imine, requires two steps, a preformed C–N bond in an aniline, an excess of the amine, and sluggish reductions.[37–40] On the other hand, copper-mediated (Ullmann) substitutions occur at high temperatures,[41–44] often give products from diarylation, and are typically substrate specific. Addition of amines or alcohols to benzyne intermediates gives regioisomers,[45] and direct nucleophilic substitution of aryl halides typically requires a large excess of reagent, a highly polar solvent, and either high reaction temperatures or highly activated aryl halides.[46, 47] Alternatively, transition metal–arene complexes have been used to accelerate substitution of the aryl halide, but in this case stoichiometric amounts of the transition metal complex are required.[48, 49] Therefore, a new, mild, general catalytic method for replacement of aryl halogen atoms or triflate groups (triflate = trifluoromethanesulfonyl) by amine or alcohol moieties would be an invaluable route to aryl ethers and amines.

Palladium-catalyzed coupling chemistry has proven to be a powerful method for formation of a new C–C bond at an aryl halide or triflate by replacement of the aryl halogen or

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pseudohalogen with a carbon nucleophile.[50–57] A variety of main group and transition metal reagents are used as the source of the carbon nucleophile. Tin and boron compounds are most commonly used, but aluminum, zinc, magnesium, and silicon reagents are also effective in this cross-coupling chemistry. Nickel and palladium complexes are now the most common catalysts. There are a number of reviews on cross-coupling chemistry, several of which are given in the list of references.

1.2. C–X Bond-Forming Coupling Chemistry Related to the Arylation of Amines and Alcohols

There is a substantial body of literature on the palladium- and nickel-catalyzed formation of aryl sulfides, selenides, and phosphanes from aromatic and heteroaromatic halides. A recent review covers the types of transformations that can be conducted and the types of catalysts that are used.[58] In general, either a stannyl sulfide, boryl sulfide, or alkali metal thiolate will react under mild conditions with a variety of aromatic and heteroaromatic halides to form mixed sulfides. Reaction of secondary phosphanes or silylphosphanes and aryl or heteroaryl halides and triflates also occurs with palladium and nickel catalysts, and now provides a route to enantiopure 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) from resolved 1,1′-binaphthol.[59] The soft thiolate and phosphane makes formation of the palladium thiolate or phosphane favorable; ironically their high nucleophilicity also makes reductive elimination of phosphane and sulfide facile, in accordance with results concerning electronic effects on reductive elimination (Section 8.3.1).[60] However, C–S bond cleavage can create problems in the synthesis of sulfides. A mixture of sulfides can result from reaction of an aryl halide with an arenethiol containing a different aromatic group.[61–63]

1.3. Novel Organometallic Chemistry

The reductive elimination to form C–C and C–H bonds[64] is a crucial step in cross-coupling processes as well as many other transition metal catalyzed reactions. Reductive elimination reactions are the subject of an early chapter in any organometallic textbook. Many examples of these reactions have been studied, and a great deal is known about the mechanisms of these processes. Similarly, the cleavage of C–H bonds by oxidative addition, including the C–H bond in methane, is now known.[65] Again, questions remain about how these reactions occur, but a variety of mechanistic studies have revealed key features of these reactions. Even some remarkably mild C–C cleavage reactions have now been observed with soluble transition metal complexes.[66, 67]

In contrast, few examples of reductive elimination reactions that form the C–N bond in amines and the C–O bond in ethers are known. Only in the past several years have complexes been isolated that undergo these reactions.[68–73] These reductive eliminations are the crucial C–N and C–O bond-forming step of the aryl halide and triflate amination and etheration chemistry discussed here. Information on how these reactions occur and what types of complexes favor this reaction have been crucial to the development of new amination and etheration catalysts.[69]

The cleavage of alkylamine N–H bonds by late transition metals is also rare.[74, 75] Reactions that cause cleavage of N–H bonds—by either oxidative addition or exchange of σ-bonded ligands—produce a transition metal – amido complex. In the case of late transition metals, the resulting amido complexes are highly reactive.[76, 77] It appears that the amination of aryl halides can involve an unusual N–H activation process by a palladium alkoxide to form a highly reactive palladium amide.[70] As a result, the discovery of N–H activation processes is crucial to catalysis with amines as substrates, including the amination of aryl halides.

In general, catalytic organometallic chemistry that forms carbon – heteroatom bonds is less developed than that forming C–C bonds and is less well understood. One organometallic oxidation process, the oxidation of ethylene to acetaldehyde (Wacker process),[78] is conducted on a large industrial scale.[78, 79] However, the detailed mechanism of the Wacker process and most other oxidation chemistry is not well understood. The oxidation of hydrocarbons remains an area of active research today, despite many years of studies.[80, 81] Other processes that form carbon – heteroatom bonds by homogeneous catalysis include oxidative carbonylations of amines and alcohols.[79] These carbonylations avoid the formation of phosgene as an intermediate in the synthesis of urethanes and carbonates. Nonoxidative carbonylation includes the reaction between an aryl halide, CO, and an alcohol

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or amine to form esters or amides.[79] These reactions presumably involve attack of alcohol (or amine) at a metal–phenacyl complex. Additional catalytic processes are the amination and hydration of olefins to form the C–X bonds in amines or alcohols (X = N and O, respectively). An efficient, intermolecular hydration or hydroamination of aryl halides is a highly sought process that is currently unknown, despite some interesting intramolecular[82, 83] and several slow intermolecular examples.[84] Other nonoxidative organometallic reactions that form C–N or C–O bonds are rare.

Thus, the selectivities, deactivation mechanisms, and potential transformations of alkoxo and amido intermediates in such reactions are not well understood. It is rare for transition metal–amido and alkoxo complexes to even be clearly identified as intermediates in catalytic chemistry. The hydrogenation of imines and ketones presumably involves such intermediates,[85] but they have not been clearly detected in these reactions.[86] The catalytic reduction of CO on surfaces may involve alkoxides, but well-characterized homogeneous analogues are unusual.[77]

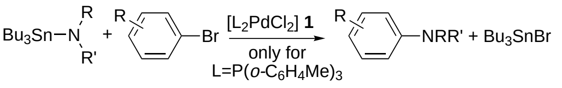
1.4. Organization of the Review

This review will cover the recent developments in palladium- and nickel-catalyzed amination and etheration of aryl halides and triflates. The first sections deal with the useful synthetic methodology that has resulted from recent studies resting upon Kosugi's initial finding[87, 88] that palladium complexes catalyze the formation of arylamines from tin amides and aryl halides. In the next sections recent developments in the formation of aryl ethers from aryl halides and alkoxides are discussed. The final set of sections present a detailed picture of the mechanism of these processes with different catalysts.

2. Background

2.1. Early Palladium-Catalyzed Amination

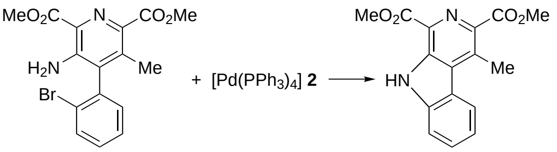
In the 1980s a few results suggested that a general metal-catalyzed method to form arylamines from aryl halides would be possible. In 1983 Kosugi et al. published a short paper on the reaction of tributyltin amides with aryl bromides catalyzed by $[PdCl_2\{P(o\text{-}C_6H_4Me)_3\}_2]$ (**1**) shown in Equation (1).[87, 88]



(1)

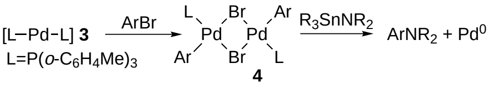
The scope of this reaction appeared to be limited to dialkylamides and electron-neutral aryl halides. For example, the use of aryl halides with nitro, acyl, methoxy, and dimethylamino substituents gave poor yields upon palladium-catalyzed reaction with tributyltin diethylamide. Furthermore, aryl bromides were the only aryl halides that provided any reaction product. Use of vinyl bromides resulted in modest yields of enamines in some cases. Only unhindered dialkyltin amides gave substantial amounts of amination product. The mechanism did not appear to involve radicals or benzyne intermediates.

Boger et al. reported studies on palladium-mediated cyclization to form the CDE ring system of lavendamycin [Eq. (2)].[89–91] These reactions were conducted with stoichiometric amounts of $[Pd(PPh_3)_4]$ (**2**). When used in a 1 mol% quantity, **2** failed to catalyze these reactions, presumably because of the absence of a base. Until almost ten years later, no palladium-catalyzed amination chemistry was reported, and few citations of the early amination chemistry existed.



(2)

Paul, Patt, and Hartwig revealed the reactions involved in the amination chemistry with tin reagents.[92] Although these studies focused on what is now an outdated synthetic method, the classes of stoichiometric reactions that make up the catalytic cycle are general to many current amination procedures. They showed that the active catalyst was $[Pd\{P(o\text{-}C_6H_4Me)_3\}_2]$ (**3**), which oxidatively added aryl halides to give dimeric aryl halide complexes **4**. These aryl halide complexes reacted directly with tin amides to form arylamines [Eq. (3)]. Thus, this chemistry could accurately be viewed as a rough parallel to Stille coupling.



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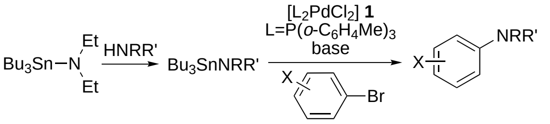
Guram and Buchwald showed that the chemistry could be extended beyond electron-neutral aryl halides.[93] With tin amides derived in situ, this chemistry was extended to aryl halides bearing alkoxycarbonyl, amino, and alkoxo groups [Eq. (4)]. However, reactions that proceeded with 80% yield or greater were still limited to tin amides derived from secondary amines.



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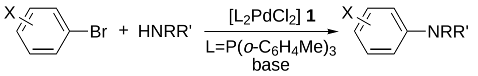
2.2. Initial Synthetic Problems

The initial results concerning aryl halide amination and related results in chemistry forming aryl sulfides and phosphanes strongly suggested that a mild, convenient route to arylamines from aryl halides could be developed. However, a source of the amido group must be less toxic, more thermally stable, and less air-sensitive than tin amides. The types of aryl halide that can undergo this reaction must extend beyond electron-neutral aryl halides, for example to aryl chlorides and iodides and aryl triflates. Of course heteroaromatic amines and halides are also important substrates. Perhaps most important are reactions of primary amines, since the aryl halide amination with primary amines would give secondary alkylarylamines. These substrates are tedious to prepare by classical methods. In addition, it would be highly desirable to extend this type of reaction to the formation of aryl ethers and phenols, since there are no truly mild and convenient methods for this transformation. Finally, the rates and turnover numbers provided by the catalysts must be much higher than those in Kosugi's chemistry and in Boger's stoichiometric cyclization reaction.

3. Initial Tin-Free Aminations of Aryl Halides

3.1. Intermolecular Amination of Aryl Bromides

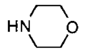
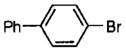
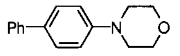
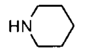
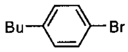
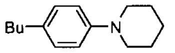
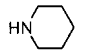
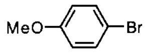
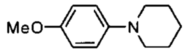
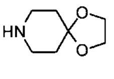
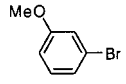
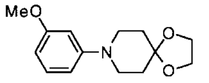
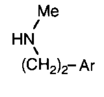
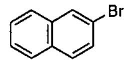
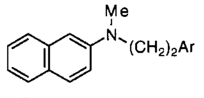
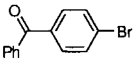
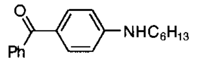
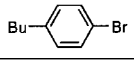
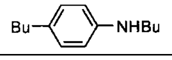
In 1995 the research groups of Hartwig and Buchwald published concurrently their results on tin-free amination of aryl halides.[94, 95] Instead of isolation or generation of a tin amide in situ, the amination reactions were conducted by reaction of an aryl halide with the combination of an amine and either an alkoxide or silylamide base [Eq. (5)]. These reactions were typically carried out between 80 and 100 °C in toluene. The catalysts used initially were **1**, **3**, or a combination of $[Pd_2(dba)_3]$ (**5a**, dba = *trans, trans*-dibenzylideneacetone) and $P(o\text{-}C_6H_4CH_3)_3$. Catalysts used subsequently will be described in Section 4. As shown in Table 1, secondary amines were viable substrates, whereas primary amines gave substantial yields with only electron-poor aryl halides. Little product was obtained from reactions of primary amines with electron-neutral aryl halides. Arenes were the major product instead. Zhao et al. showed that one could arylate piperazine under conditions of excess piperazine[96] to form biologically important aryl piperazines by palladium-catalyzed chemistry.



(5)

X=*o*-, *m*-, or *p*-alkyl, phenacyl, amino, alkoxy
base = NaO*t*Bu or $LiN(SiMe_3)_2$

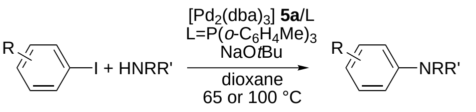
Table 1. Tin-free aminations of aryl halides catalyzed by $[PdCl_2\{P(o\text{-}C_6H_4Me)_3\}_2]$ (**1**).

Amine	Aryl halide	Base[a]	Product	Yield [%]
		NaO*t*Bu		86
		LiN(TMS)$_2$		89
		LiN(TMS)$_2$		89
		NaO*t*Bu		81
		NaO*t*Bu		78
$H_2NC_6H_{13}$		NaO*t*Bu		72
H_2NBu		LiN(TMS)$_2$		<2%

[a] TMS = trimethylsilyl.

3.2. Intermolecular Amination of Aryl Iodides

Complexes other than those containing $P(o\text{-}C_6H_4Me)_3$ ligands have now been shown to catalyze amination of aryl iodides in high yields.[69] However, reaction conditions were initially optimized for amination of aryl iodides with the $P(o\text{-}C_6H_4Me)_3$-based catalysts.[97] It was found that running the reactions in dioxane solvent was important to obtain even modest yields of product. In this solvent, secondary amines are suitable substrates and primary amines couple with *o*-substituted aryl iodides [Eq. (6)]. Primary amines, including aniline, gave poor yields with unhindered aryl iodides. Even electron-deficient, unhindered aryl iodides were poor substrates for primary amines.



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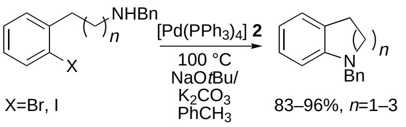
3.3. Intramolecular Amination of Aryl Halides

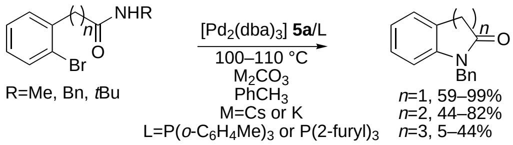
Intramolecular aryl halide aminations to form nitrogen heterocycles were included in the initial reports on tin-free aryl halide aminations.[95] For example, the reactions in Equation (7) occurred in greater than 80 % yield. In this case, the halide could be iodide or bromide, and **2** was a more effective catalyst than was **1**.



(7)

Subsequent to the initial report, Buchwald and co-workers provided an extensive account of the intramolecular amination reactions.[98] K_2CO_3 was an efficient base, but a combination of NaO*t*Bu and K_2CO_3 was most effective. Aryl iodides proved to be the preferred substrate under optimized conditions with **2** as catalyst. Iodide substrates also allowed for the use of triethylamine as base. Screening of a variety of combinations of phosphane ligands and palladium precursors showed that chelating ligands such as $Ph_2P(CH_2)_nPPh_2$ (n = 2–4) or 1,1′-*bis*-(diphenylphosphanyl)ferrocene (DPPF) gave good yields of cyclized product, as did a combination of **5a** and P(2-furyl)$_3$, but none were better than **2**.

Amides and sulfonamides also undergo intramolecular chemistry to form arylamides and arylsulfonamides [Eqs. (8) and (9)]. Cs_2CO_3 was the optimal base for cyclization of acetamides, but K_2CO_3 was the best base for cyclization of benzamides. A combination of **5a** and P(2-furyl)$_3$ was the best



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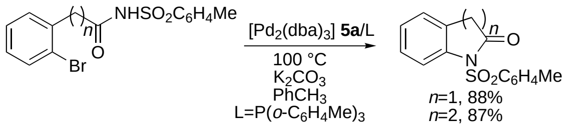


(9)

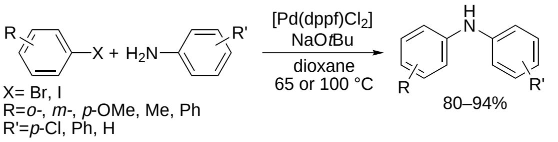
catalyst system for the cyclization of acetamides, and P(o-C_6H_4Me)$_3$ was the optimal ligand for cyclizations of benzamides. For benzamides, reaction times were long; reactions of sulfonamides required either 5 or 14 h depending on ring size, and were conducted with K_2CO_3 and a combination of **5a** and P(o-C_6H_4Me)$_3$ as catalyst. Cyclizations to form five- and six-membered rings gave good yields of heterocyclic product, but they gave poor yields of seven-membered rings.

4. Second-Generation Catalysts with Chelating Phosphanes

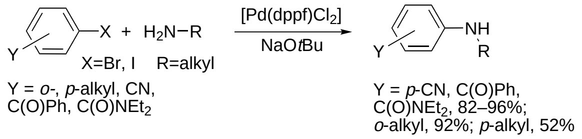
With the exception of intramolecular aminations, all of the reactions described above were catalyzed by palladium complexes containing the sterically hindered P(o-C_6H_4Me)$_3$ ligands. Furthermore, mechanistic studies, which are described in Section 8.6.1, showed that the catalytic cycle involved exclusively mono-phosphane intermediates. However, stoichiometric studies on reductive elimination from PPh_3-ligated palladium amides[68, 99] and on β-hydrogen elimination from related d^8 square-planar iridium amides[100] suggested that palladium complexes with chelating ligands would be particularly effective catalysts for the amination chemistry. In fact, many of the reasons why such complexes should be effective for this amination process parallel the reasons why they are effective for cross-coupling chemistry involving nucleophilic main group alkyl substrates.[101]

In papers published back-to-back in 1996, the research groups of Hartwig and Buchwald reported amination reactions with palladium complexes of DPPF and BINAP as catalysts.[69, 102] These palladium complexes provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary amines, and with anilines. It is ironic that the amination chemistry was first discovered upone use of a particularly labile phosphane, but dramatically improved by the use of chelating ligands.

Palladium complexes with DPPF ligands provided nearly quantitative yields for amination of aryl halides with anilines [Eq. (10)]. Electron-rich, electron-poor, hindered, or unhindered aryl bromides or iodides all participated in the amination chemistry with only a few exceptions. Nitrohaloarenes gave no amination product with aniline substrates. Aryl halides with enolizable carbonyl groups gave poor yields, and esters were converted into the *tert*-butyl ester with *tert*-butoxide as base. These groups have now been shown to be amenable to amination processes that use Cs_2CO_3 as base.[103] Palladium complexes with DPPF ligands also gave good yields of mixed alkylarylamines with a variety of substrates [Eq. (11)]. With electron-poor aryl halides excellent yields of N-alkylanilines were obtained, and with electron-neutral aryl halides yields of 60–92% were achieved, depending on the location of alkyl substituents.[69, 104] For the coupling of unhindered and electron-neutral aryl halides with unhindered primary amines, diarylation can occur. In these cases, running the reactions with excess amine prohibits the formation of diarylation products.[104] For most of these reactions, 5 mol% of catalyst was employed, although 1 mol% can be used in most cases.



(10)

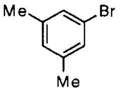
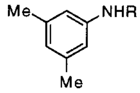
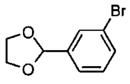
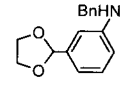
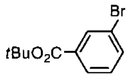
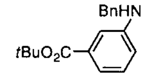
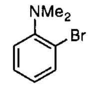
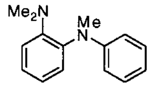
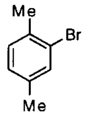
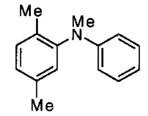


(11)

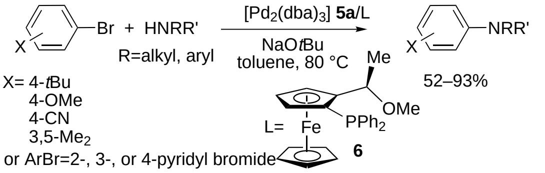
Palladium complexes with BINAP ligands provided higher yields than those with DPPF ligands in the case of electron-neutral aryl halides and alkyl amines, as shown in Table 2. The increased yields resulted in large part from the lack of diarylation products. Slightly less reduction product is formed as well, although the yield of arene is low in both cases. Furthermore, in favorable cases, it was shown that 0.05 mol% of catalyst could be used. Racemic and resolved BINAP gave identical results.

Weakly chelating ligands can be beneficial in some of the amination chemistry. Buchwald and co-workders used the

Table 2. Selected aryl bromide aminations catalyzed by BINAP/[$Pd_2(dba)_3$] (**5a**).

Aryl bromide	Amine	Product	Cat. [mol%]	t[h]	Yield [%]
	RNH_2		0.5	2	88
			0.5	4	79
			0.05	7	79
	H_2NBn		0.5	2	81
	H_2NBn		0.5	3.5	71
	MeNHPh		1.0	39	66
	MeNHPh		0.5	36	94

ligand **6** to improve yields in the amination of aryl halides with acyclic secondary amines [Eq. (12)].[105] It is unclear whether the palladium complexes that are involved in the catalytic cycle resemble the mono-phosphane complexes with P(o-C_6H_4Me)$_3$ ligands or complexes containing chelating ligands such as DPPF or BINAP. The complex isolated from the reaction of the methoxy-substituted phosphane **6**, **5a**, and an aryl halide is a monomer with Pd–O coordination. However, it is difficult to determine if the Pd–O interaction also exists during reactions of the catalytic cycle. Nevertheless, ligand designs based on hemilabile phosphanes[106] should be profitable.

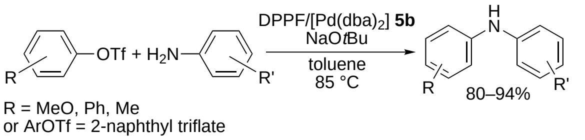


(12)

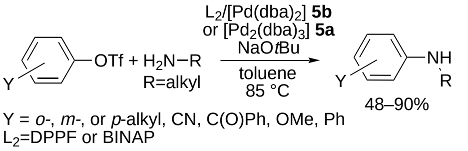
5. New Substrates for the Second-Generation Catalysts

5.1. Aminations of Aryl Triflates

Palladium complexes with chelating ligands are often more effective in C–C bond-forming processes with aryl triflates than are palladium complexes with monodentate ligands such as P(o-C_6H_4Me)$_3$.[107, 108] Similarly, they are not good catalysts for the amination of aryl triflates. However, palladium complexes with the chelating phosphane ligands DPPF and BINAP are effective catalysts for the amination of aryl triflates.[109, 110] Selected aminations of aryl triflates by aniline are shown in Equation (13), and selected aminations of aryl triflates by alkylamines are presented in Equation (14). The reaction conditions employed for the amination of aryl triflates are similar to those for the amination of aryl halides with one exception. Electron-poor aryl triflates were susceptible to cleavage under the basic reaction conditions, presumably because of the stable phenolate that results. This cleavage reaction is likely to be first order with respect to the aryl triflate. In contrast, the catalytic process is likely to be zero order with respect to the aryl triflate, since the catalyst resting state should be an arylpalladium complex.[111] Thus, low concentrations of triflate will minimize the relative rate of cleavage versus amination. Slow addition of the triflate in the case of electron-poor triflates therefore allows amination to occur in high yields with these substrates.[109] Alternatively, the problem of triflate cleavage can be reduced by the use of Cs_2CO_3 as base.[103]



(13)



(14)

The amination of aryl triflates does not require added halide and, in fact, added chloride or iodide inhibited the amination process. Reactions in toluene gave higher yields than those in THF, although good yields were obtained in THF in some cases. The use of [$Pd_n(dba)_m$] ($n = 2$, $m = 3$: **5a**; $n = 1$, $m = 2$: **5b**) or [$Pd(OAc)_2$] (**7**) as precursor, rather than [L_2PdCl_2], was important for this chemistry; [$(dppf)_2PdCl_2$] gave much lower yields than did a combination of **5b** and DPPF.

As was the case for the amination of aryl halides, DPPF was an effective ligand for amination reactions involving anilines or electron poor-aryl triflates. The yields for formation of mixed diarylamines were remarkable. All examples gave yields exceeding 90%.[109] Reactions of electron-neutral aryl halides with alkylamines provided yields in the range of 42–75% with DPPF as ligand. This combination of substrate gave yields in the range of 54–77% with BINAP or 2,2′-bis(di-p-tolylphosphanyl)-1,1′-binapthyl (Tol-BINAP) as ligand. Several examples, particularly the triflate derived from p-methoxyphenol, showed higher yields in reactions employing BINAP as ligand rather than DPPF. The amination of aryl triflates was effective for hindered or unhindered aromatic systems, and for primary or secondary amines.

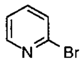
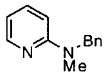
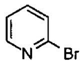
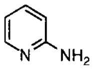
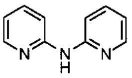
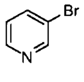
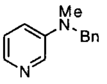
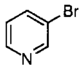
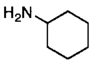
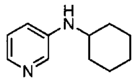
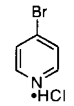
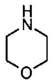
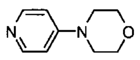
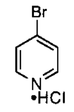
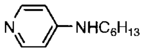
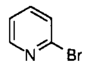
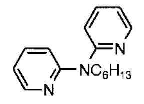
The amination of aryl triflates allows one to use a phenol OH group as a directing group[112] to conduct chemistry *ortho* to a substituent, such as methoxy, that can ultimately act as a leaving group. Furthermore, it is possible to conduct amination reactions with aminophenols; the reaction occurs selectively at the amino group.[113] Thus, the phenol OH group, which can be converted into a triflate or nonaflate group (nonaflate = nonafluorobutanesulfonyl) in the presence of an amino functionality, can act as a convenient source of a leaving group for several applications. In principle, the triflate is recyclable, and one could regenerate triflic anhydride from the sodium triflate by-product. Triflate salts are also less corrosive than alkali halides.

5.2. Amination of Heteroaromatic Halides

Many nitrogen heterocycles are strongly binding ligands for late transition metals. As a result, heteroaromatic halides with basic nitrogen atoms will displace weakly binding ligands such as P(o-C_6H_4Me)$_3$, so that the original catalyst system containing P(o-C_6H_4Me)$_3$ as ligand was ineffective for aminations with heteroaromatic substrates that could bind to palladium. It has been shown in stoichiometric studies that pyridine displaces P(o-C_6H_4Me)$_3$ to form palladium–pyridine complexes.[114] However, chelating phosphanes are not displaced by pyridines. Thus, the advent of amination reactions with use of chelating ligands now allows for the amination of pyridyl halides.[115]

Results from aminations with use of two phosphane ligands and two different precursors are presented in Table 3. The most general palladium precursor is [Pd(OAc)$_2$] (**7**). Again, BINAP was generally effective for amination with either primary or secondary amines. However, unbranched primary amines gave lower yields than did branched amines such as cyclohexylamine. Propane-1,3-diylbis(diphenylphosphane) (dppp), which is less expensive than BINAP, in combination with **5a** or **7**, acted as an effective catalyst system for amination of pyridyl bromides by secondary amines or amines lacking hydrogen atoms α to the nitrogen atom. As was the case for aminations of aryl halides with use of DPPF and BINAP, acyclic secondary amines gave only low yields of the aminopyridines.

Table 3. Palladium-catalyzed amination of pyridyl halides.

Pyridyl halide	Amine	Product	Catalyst	Yield [%]
	BnNHMe		**5a**/DPPP	86
			**5a**/DPPP	87
	BnNHMe		**5a**/(±)BINAP	77
			**5a**/(±)BINAP	82
			**7**/DPPP	91
	$H_2NC_6H_{13}$		**7**/(±)BINAP	67
2 equiv 	$H_2NC_6H_{13}$		**7**/(±)BINAP	71

5.3. Aminations of Solid-Supported Aryl Halides

Two groups have reported results on the solid-phase amination of aryl halides with use of both P(o-C$_6$H$_4$Me)$_3$ and chelating ligands.[116, 117] Since the arylamine group is present in many biologically active materials, the application of amination chemistry in combinatorial chemistry may be important for this approach to drug discovery. It has been shown that Stille and Suzuki reactions are reliable, high-yielding process for substrates loaded on solid supports.[118] Thus, aryl halides are now extremely versatile in solid-phase combinatorial chemistry. They can be used to form new C–C, C–N, and presumably also C–S, C–P, and C–O bonds (see below).

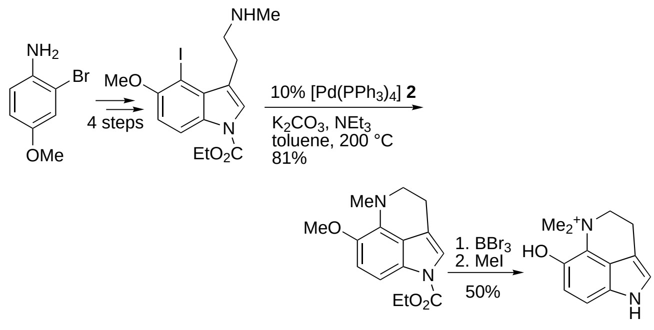
Both Willoughby and Chapman[116] at Merck and Farina and Ward[117] at Boehringer Ingelheim have reported successful amination reactions for aryl halides supported on polystyrene Rink and Rapp TentaGel S RAM resin. The results closely parallel those obtained in the solution phase. Secondary amines are successfully coupled with solid-supported aryl halides in high yields upon use of P(o-C$_6$H$_4$Me)$_3$ as the ligand on palladium. Primary amines required either BINAP or DPPF for successful coupling with the aryl halides, and similar results were obtained with either ligand. Compounds with N–H groups for which no arylation chemistry had been reported in the solution phase were not suitable for chemistry on the solid supports. For example, nitroanilines, aminotriazine, 5-aminouracil, 2,6-diaminoanthraquinone, histidine, 2-aminobenzimidazole, imidazole, and pyrazole gave no products of N–C bond formation in the solid phase with use of palladium complexes containing P(o-C$_6$H$_4$Me)$_3$, DPPF, or BINAP ligands.

6. Applications of the Amination Chemistry

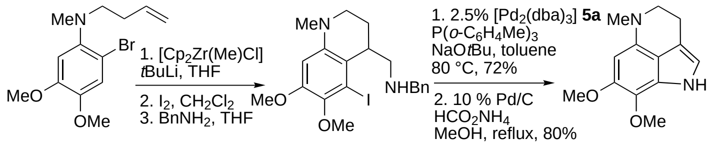
There have not been extensive studies on the applications of the amination chemistry, since the reaction was discovered only a few years ago. However, one application to the total synthesis of biologically active molecules and two applications to the synthesis of materials with potentially interesting electronic properties have been reported.

6.1. Natural-Product Synthesis

Stoichiometric palladium-mediated cyclization was used in natural-product synthesis by Boger et al. a number of years ago, as was noted in the introduction. More recently, Buchwald and co-workers reported the total synthesis or the formal total synthesis of a series of tetrahydropyrroloquinolines by palladium-catalyzed amination.[119] A brief description of the methods employed are shown in Schemes 1 and 2. One approach involves formation of the six-membered ring through palladium-catalyzed intramolecular amination. The cyclization was carried out at high temperatures employing K$_2$CO$_3$ as base. However, the use of NaOtBu, which presumably would have allowed for reaction at lower temperatures, led to cleavage of the carbamate; the cleavage products apparently inhibited catalyst activity.



Scheme 1. Palladium-catalyzed amination in the synthesis of dehydrobufoteinine.

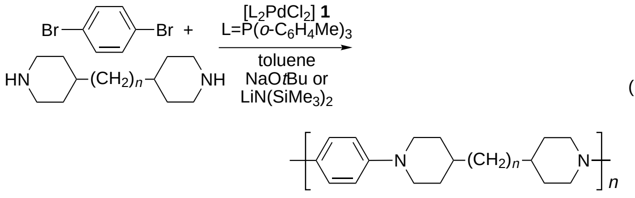


Scheme 2. Palladium-catalyzed amination in the formal total synthesis of makaluvameine C and damirones A and B.

A second approach involved formation of the indole five-membered ring by amination chemistry and the six-membered ring by Zr–benzyne chemistry. This strategy is shown in Scheme 2. In this case, the optimal cyclization conditions could be employed, and the reaction temperature was lower. The product of the cyclization is an intermediate in total syntheses of makaluvamine C and of damirones A and B.

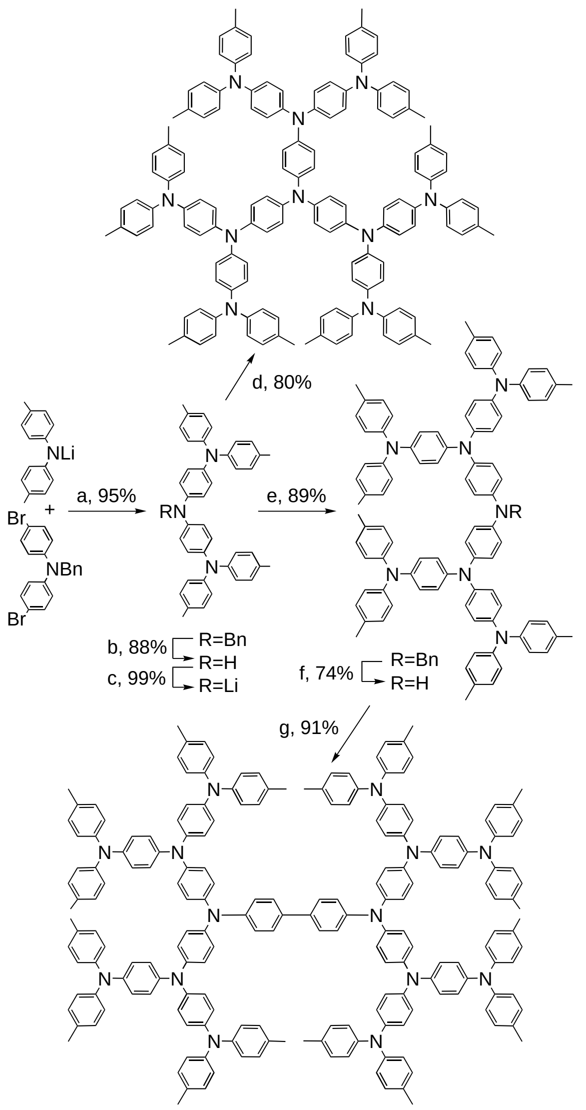
6.2. Applications to Materials Science

Two groups have reported the synthesis of oligomeric or polymeric arylamines by palladium-catalyzed chemistry.[120, 121] One group used the initial amination of aryl halides with dialkylamines to prepare arylamine polymers.[120] This chemistry is a step-growth polymerization. A bifunctional diamine and a dihaloarene were used to generate the polymers as shown in Equation (15). The highest molecular weights achieved were in the range of 5000–6000, indicating an average of 20 monomers in each chain.



(15)

A second group has prepared highly branched triarylamines.[121] The material contains exclusively *p*-phenylenediamine linkages and triarylamine units. The triarylamines were constructed with a combination of benzyl-protected 4,4′-dibromodiarylamines and lithium diarylamides. The formation of the triarylamine linkage from aryl bromides and lithium diarylamides occurred in greater than 90% yields under mild conditions with **3** as catalyst. The final products of the reaction sequences in Scheme 3 are discrete oligomers of a *p*-phenylene amine with the highest molecular weight. These materials were characterized by conventional spectroscopic means as well as microanalysis. Each carbon atom could be observed by ^{13}C NMR spectrometry, and a molecular ion was observed by mass spectrometry. The electrochemical behavior of the dendrimer at the top of Scheme 3 was complex and showed a large number of reversible redox waves in the cyclovoltammogram. The radical cation was generated in solution, was stable, and was observed by ESR spectroscopy. This material also shows a high glass-transition temperature.



Scheme 3. Palladium-catalyzed synthesis of triarylamine dendrimers. a) **3**, L; b) H_2, Pd/C; c) BuLi; d) $N(p\text{-}C_6H_4Br)_3$, **3**, L; e) $BnN(p\text{-}C_6H_4Br)_2$, **3**, L; f) H_2, Pd/C; g) **3**, L, NaO*t*Bu, $(p\text{-}C_6H_4Br)_2$. $L = P(o\text{-}C_6H_4Me)_3$.

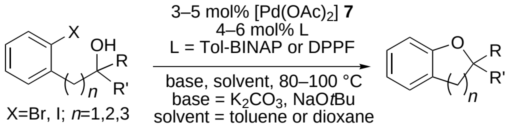
7. Synthesis of Aryl Ethers from Aryl Halides

Our group has shown that reductive elimination reactions that form C–X bonds are faster with more nucleophilic amides and thiolates (Section 8.3). Given this information and the lower nucleophilicity of alkoxides than amides or thiolates, it seems likely that formation of aryl ethers by reductive elimination would be difficult to accomplish. In fact, the first formations of aryl ethers by use of palladium catalysts were observed only with substrates that could undergo intramolecular formation of arene–oxygen bonds.[122] We have also shown that reductive eliminations are faster when electron-poor aryl groups are bound to palladium. Thus, electron poor-aryl halides might be activated enough toward reductive elimination that they would react to form aryl ethers in the presence of palladium catalysts, alkoxide, and base. Indeed, the first examples of intermolecular formation of aryl ethers involved electron-poor aryl halides as substrates.[70]

Further work must be conducted to make this process as general as the formation of arylamines from aryl halides.

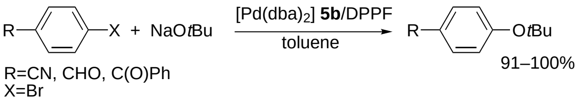
7.1. Intramolecular Palladium-Catalyzed Synthesis of Aryl Ethers

Intramolecular formation of oxygen heterocycles was reported by Buchwald et al.[122] His group showed that 3–5 mol% of [Pd(OAc)$_2$] and either Tol-BINAP or DPPF catalyzed the cyclization of *o*-haloaryl-substituted alcohols [Eq. (16)]. These reactions occur with the highest yields for tertiary alcohols, but also take place for secondary alcohols. They can produce either five-, six-, or seven-membered rings. It is believed that the reaction occurs by an oxidative addition of the aryl halide, subsequent generation of the palladium oxametallacycle, and C–O bond-forming reductive elimination. Although aryl halide intermediates were generated independently and were shown to be kinetically competent to be intermediates, the oxametallacycles could not be observed or isolated.



(16)

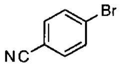
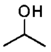
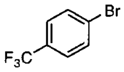
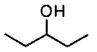
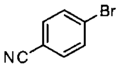
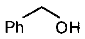
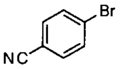
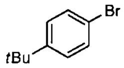
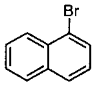
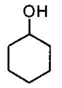
The first intermolecular etheration of aryl halides is shown in Equation (17) and was reported by Mann and Hartwig.[70] In these studies, a combination of DPPF and **5b** was used as catalyst for the addition of NaO*t*Bu to 4-bromobenzophenone, 4-bromobenzaldehyde, and 4-bromobenzonitrile. The yields for these reactions are now greater than 90%.[123] Reaction of *n*-butanol gave more reduction product than etheration product. The *tert*-butyl ethers produced by this chemistry are susceptible to deprotection to generatee phenol by simple addition of acid directly to the reaction mixture after completion of the etheration.



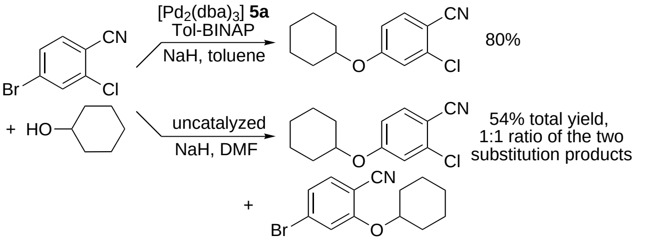
(17)

Buchwald et al. reported similar chemistry (Table 4) employing a larger range of alkoxides and showed that BINAP provided improved generality.[124] Nevertheless, this chemistry remains limited to electron-poor aryl halides. Electron-neutral aryl halides give modest yields for formation of aryl *tert*-butyl ethers. Buchwald also compared the catalyzed and uncatalyzed reactions that can occur in highly polar solvents such as DMF. In some cases, the uncatalyzed reactions in DMF gave yields similar to those for the catalyzed chemistry in nonpolar solvents. However, in several cases the yields were higher for the catalyzed reactions. Furthermore, one could use the higher reactivity of aryl bromides toward palladium and the higher reactivity of aryl chlorides for direct nucleophilic substitutions to conduct selective formation of aryl ethers. The use of palladium catalysts selectively converted a bromochloroarene into the chloro aryl ether [Eq. (18a)], while the direct nucleophilic substitution converted the bromochloroarene into a mixture of bromo aryl and chloro aryl ethers [Eq. (18b)].

Table 4. Palladium-catalyzed and uncatalyzed formation of aryl ethers from aryl halides and a combination of alcohols and NaH.

Aryl halide	Alcohol	T[°C]	Yield[%] with cat.[a]	Yield[%] without cat.[b]
		50	80	76
		70	50	48
		70	71	78
	MeOH	70	81	65
	NaO*t*Bu	100	53	<10
		70	65	<5

[a] In toluene. [b] In DMF.

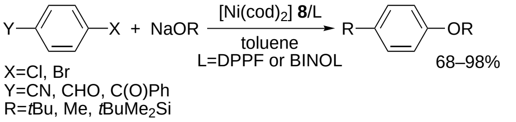


(18a)

(18b)

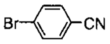
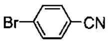
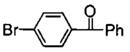
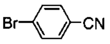
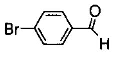
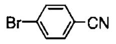
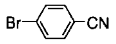
7.2. Nickel-Catalyzed Etheration

Nickel complexes have been employed successfully in the formation of protected phenols [Eq. (19)].[123] Selected examples are presented in Table 5. A combination of [Ni(cod)$_2$] (**8**, cod = 1,5-cyclooctadiene) and either DPPF or BINAP successfully formed *tert*-butyl, methyl, and silyl aryl ethers. A combination of **8** and BINAP gave methyl aryl ethers in high yields. A combination of **8** and DPPF provided higher yields than palladium catalysts for the formation of *tert*-butyldimethylsilyl aryl ethers from aryl halides and NaOTBDMS (TBDMS = *tert*-butyldimethylsilyl), and they did so at lower temperatures. However, a combination of BINAP or DPPF and palladium-catalyst precursors gave higher yields than did nickel complexes for the formation of *tert*-butyl aryl ethers. Of course, the methyl ethers are readily deprotected by a variety of reagents including Lewis acids, while the silyl ethers are



(19)

Table 5. Nickel- and palladium-catalyzed formation of aryl ethers from aryl halides.

Catalyst	Amount [mol %]	Aryl halide	NaOR	T[°C]	Yield [%]
8/DPPF	15		NaO*t*Bu	95	84[a]
8/Tol-BINAP	15		NaOMe	95	84[a]
8/DPPF	15		NaOMe	95	76[b]
8/DPPF	15		NaOTBDMS	95	96[a], 67[b]
8/DPPF	15		NaOTBDMS	95	98[a]
5b/Tol-BINAP	10		NaOTBDMS	120	75[a]
5b/DPPF	10		NaOTBDMS	120	49[a]

[a] Yields determined by gas chromatography (average of at least two runs). [b] Yields are for pure, isolated product (average of at least two runs).

conveniently deprotected by fluoride. As was the case for the palladium chemistry reported above, the nickel catalysts were effective for reactions of electron-poor aryl halides, but less than 5% yield was achieved for aryl ethers formed from electron-neutral or electron-rich aryl halides. As discussed at the end of Section 7.1, some of the chemistry that forms aryl ethers can occur in an uncatalyzed fashion in highly polar solvents such as DMF. However, the metal-catalyzed chemistry allows for the etheration reactions to occur within shorter reaction times under mild conditions in nonpolar solvents that need not be rigorously dry.

8. Mechanism of Aryl Halide Amination and Etheration

The previous sections described synthetic methods involving palladium- and nickel-catalyzed additions of alcohols and amines to aryl halides and triflates. The development of procedures and catalysts used in these processes has occurred hand in hand with mechanistic analysis of the amination and etheration chemistry. The following sections discuss our current understanding about why these procedures and catalysts are effective and how this understanding led to some of the breakthroughs in synthetic methods presented above.

8.1. Identification and Chemistry of [Pd{P(o-C_6H_4Me)$_3$}$_2$]

The original amination chemistry required the use of the bulky monodentate ligand P(o-C_6H_4Me)$_3$. Although this ligand has been used in a wide range of cross-coupling processes, as well as Heck reactions, few palladium complexes of this ligand had been isolated. [Pd{P(o-C_6H_4Me)$_3$}$_2$] (**3**) was reported in a patent,[125] but the characterization described was with IR spectroscopy. Paul, Patt, and Hartwig reported a reliable synthesis of this complex as analytically pure yellow crystals by addition of P(o-C_6H_4Me)$_3$ to **5b** [Eq. (20)].[92, 114] Although none of the product could be detected in the reaction solution, addition of ether or pentane to the benzene reaction solution led to precipitation of **3**. This synthesis, therefore, relies on rapid equilibria and the low solubility of **3**. The complex is a rare example of a 14-electron two-coordinate transition metal complex.[126–128] It is air-stable as a solid.

$$\underset{\mathbf{5b}}{[\mathrm{Pd(dba)_2}]} + \mathrm{P}(o\text{-}\mathrm{C_6H_4Me})_3 \xrightarrow[\text{2. Et}_2\text{O}]{\text{1. benzene}} \underset{\mathbf{3}}{[(o\text{-}\mathrm{C_6H_4Me})_3\mathrm{P{-}Pd{-}P}(o\text{-}\mathrm{C_6H_4Me})_3]} \quad (20)$$

8.1.1. *Structural Features of [Pd{P(o-C_6H_4Me)$_3$}$_2$]*

A crystal structure analysis of **3** (Figure 1) showed a perfectly linear geometry.[114] The o-tolyl hydrogen atoms are located closer to the metal center than those of similar two-coordinate complexes.[126–128] However, the absence of unusual IR signals for ν_{CH} or upfield chemical shifts in the ^1H NMR spectrum suggested that an agostic stabilization of **3** was not occurring. Moreover, a derivative of **3** with one deuterium at each methyl group[129] showed no isotopic perturbation of the NMR chemical shifts,[130, 131] indicating that any agostic interaction would have to be weaker than those detected previously.[132, 133]

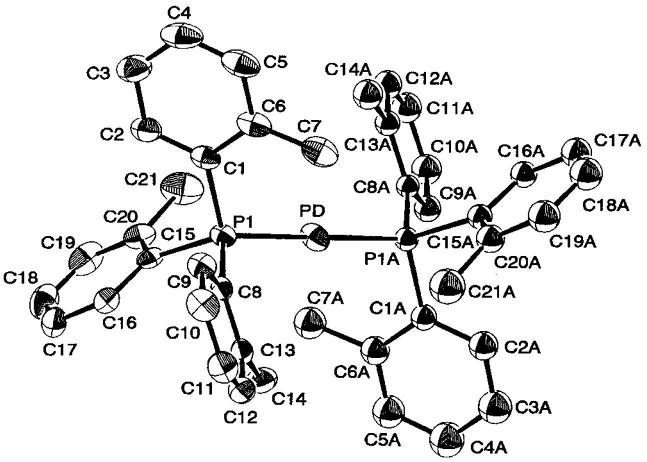
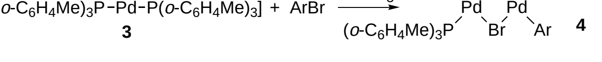


Figure 1. ORTEP drawing of the structure of [Pd{P(o-C_6H_4Me)$_3$}$_2$]. Hydrogen atoms have been omitted for clarity.

8.1.2. *Oxidative Addition to [Pd{P(o-C_6H_4Me)$_3$}$_2$] and Its Mechanism*

Complex **3** underwent oxidative addition of aryl halides to provide the novel dimeric aryl halide complexes **4** [Eq. (21)].[92, 114] It is unusual for phosphane-ligated aryl halide complexes formed by oxidative addition to be dimeric. These oxidative addition products were isolated and structur-

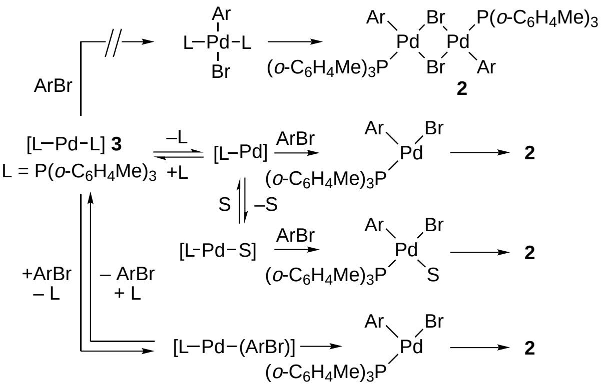


(21)

ally characterized. They remain dimeric in solution, as determined by molecular-weight measurements in solution, but react as the monomers, as described below.

The mechanism of the oxidative addition was surprising.[134] It has been well established that aryl halides undergo oxidative addition to L_2Pd fragments.[135–138] Thus, one would expect oxidative addition of the aryl halide to occur directly to **3** and ligand dissociation and dimerization to take place subsequently. Instead, the addition of aryl halide to **3** occurs after phosphane dissociation, as shown by an inverse first-order dependence of the reaction rate on phosphane concentration and the absence of any tris-phosphane complex in solution.[134]

Three mechanisms consistent with phosphane dissociation before oxidative addition are shown in Scheme 4. In one case, a one-coordinate 12-electron intermediate adds the aryl halide. A second mechanism involves formation of a solvated one-coordinate 12-electron intermediate ligand dissociation and then addition of aryl halide to this solvated species. In a third pathway reversible displacement of a phosphane ligand by aryl halide takes place to generate an aryl halide complex with the carbon–halogen bond intact. Reaction rates in benzene, toluene, and *p*-xylene were all essentially identical, despite their different abilities to coordinate a transition metal. Thus, it is unlikely that a complex with solvent directly bound to the metal is an intermediate. It was not possible to distinguish between the other two intermediates, but a mono-phosphane complex clearly lies on the reaction pathway for this addition process and on the catalytic cycle for reactions involving **3**.



Scheme 4. Potential mechanisms for oxidative addition of aryl halides to **3**. S = solvent.

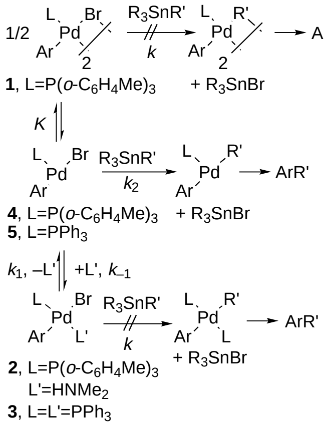
Oxidative addition to a mono-phosphane–palladium complex is unusual, but is a reasonable pathway if one bears in mind that reductive eliminations often occur from mono-phosphane–palladium complexes.[139, 140] These reductive eliminations from mono-phosphane–Pd^{II} species would form a mono-phosphane–Pd^0 complex as the initial metal product; these Pd^0 products are similar to the intermediate in the oxidative addition of aryl halide deduced from kinetic studies.

8.2. Transmetalation Processes

In the case of C–C bond-forming cross-coupling, as well as amination and etheration, transmetalation processes convert the palladium–aryl halide complexes into the intermediate that undergoes reductive elimination of the final organic product.[50, 51, 139–141] There has been scattered evidence that this reaction involves mono-phosphane intermediates,[142] but much of this data was based on catalytic processes, rather than direct, stoichiometric observation of the transmetalation process. Further, no information was available on transmetalations involving tin amides or thiolates.

8.2.1. *Mechanism of Transmetalation with Tin Amides*

The thermodynamics and relative reaction rates for individual steps of the transmetalation and reductive elimination varied depending on the type of tin reagent. However, the mechanisms for the reactions of tin amides, tin thiolates, or trialkylaryltin reagents all involved analogous mono-phosphane–palladium intermediates (Scheme 5).[143] The dimeric $[Pd\{P(o\text{-}C_6H_4Me)_3\}(p\text{-}C_6H_4Me)(Br)]_2$ (**4a**) was cleaved reversibly to form a 14-electron mono-phosphane complex before reaction with Bu_3SnPh. The monomeric $[Pd(PPh_3)_2(p\text{-}C_6H_4Me)(Br)]$ (**9**) underwent reversible dissociation of phosphane before reacting with Bu_3SnPh or $Bu_3SnS\mathit{t}Bu$. The transmetalation process with tin thiolates was endothermic and reversible. Similarly, reaction of Bu_3SnNEt_2 with **4a** reversibly formed the monomeric, mono-phosphane amido intermediate $[Pd\{P(o\text{-}C_6H_4Me)_3\}(p\text{-}C_6H_4Me)(NEt_2)]$. The reversibility of these reactions was determined by the inverse reaction order in product Bu_3SnBr. As a result of the requirement for monophosphane intermediates, palladium complexes with chelating ligands were not effective in the amination chemistry involving tin amides.[93]

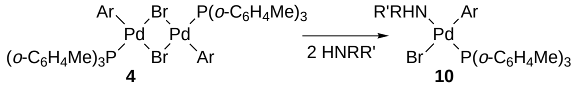


Scheme 5. Potential mechanism for transmetalation between tin reagents and palladium–aryl halide complexes. R = Me, Bu; R' = Ph, S*t*Bu, SAr, NMe_2.

8.2.2. *Mechanism of Palladium–Amide Complex Formation from Amines*

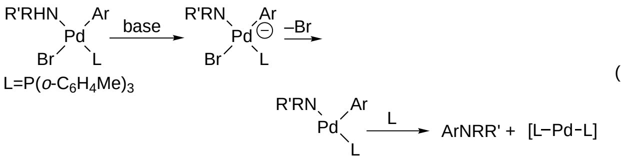
The mechanism by which palladium–aryl halide complexes are transformed into palladium–aryl amido complexes by the combination of amine and base is clearly very different from that of transmetalation with tin, and is more relevant to the most convenient method for conducting the amination chemistry. One pathway for generation of the amido complex from amine and base would be reaction of the metal complex with the small concentration of amine that is present in the reaction mixtures. This pathway seems unlikely considering the two directly observed alternative pathways discussed below and the absence of benzyne and radical nucleophilic aromatic substitution products that would be generated from a reactive alkali amide.

Paul, Patt, and Hartwig showed that the dimeric aryl halide complexes **4** react with a variety of amines to form monometallic, amine-ligated aryl halide complexes [Pd{P(o-C_6H_4Me)$_3$}(amine)(Ar)(Br)] [**10**, Eq. (22)].[114] Buchwald and Widenhoeffer published similar results subsequently and showed that primary amines can even displace the phosphane ligand.[144–146] These amine complexes are important in the catalytic cycle because the acidity of the N–H bond is enhanced when coordinated to the metal. Amine-ligated aryl halide complexes can be formed in a similar fashion from [Pd(PPh_3)$_4$] in cases where the amine can coordinate intramolecularly.[68, 99]

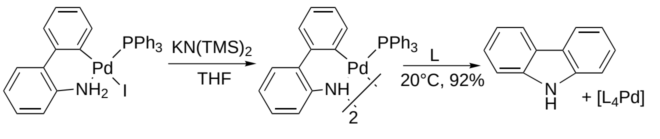


(22)

The amine-ligated aryl halide complexes react with alkoxide or silylamide bases to form arylamines [Eq. (23)].[147] The reaction of [Pd{P(o-C_6H_4Me)$_3$}($HNEt_2$)(p-C_6H_4Bu)(Br)] (**10a**) and LiN($SiMe_3$)$_2$ occurred immediately at room temperature to form the arylamine in greater than 90% yield. Low-temperature reactions conducted in an NMR tube allowed direct observation of the anionic haloamido complex [Pd{P(o-C_6H_4Me)$_3$}(NEt_2)(Ar)(Br)]$^-$.[147] The neutral metallacycle [{Pd(PPh_3)(η^2-$NC_6H_4C_6H_4$)}$_2$] was formed after deprotonation of the azametallacycle [Pd(PPh_3)(η^2-$NHC_6H_4C_6H_4$)(I)] [Eq. (24)].[68, 99] One experimentally supported mechanism for generation of the amido aryl intermediate is coordination of amine to form a square-planar 16-electron complex that reacts with base.



(23)

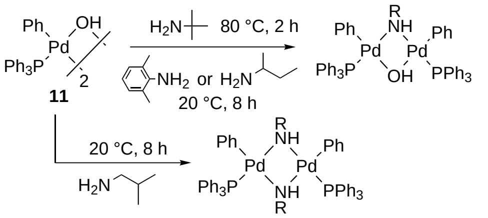


(24)

LiN($SiMe_3$)$_2$ and alkoxides have similar basicities in organic solvents[148] and are both suitable for the tin-free amination chemistry. LiOtBu is generally unreactive as a base in the amination processes, while KOtBu tends to generate black solutions with inactive catalyst.[94] With the exception of intramolecular chemistry at relatively high reaction temperatures,[98] bases weaker than alkoxides tend to be ineffective for reactions employing P(o-C_6H_4Me)$_3$ or PPh_3 as ligand because the electron-rich metal center they create is only weakly Lewis acidic.

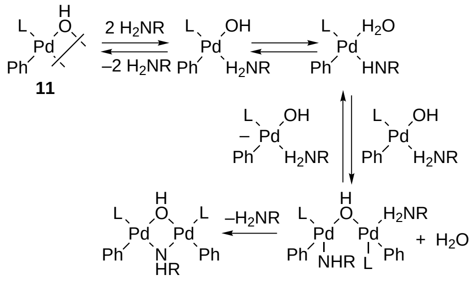
An alternative pathway would involve reaction of a palladium–amido aryl complex with alkoxide or silylamide base to form an intermediate alkoxide or amide that might react with amine to form the required amido aryl intermediate. This pathway seems to occur for aryl halide aminations catalyzed by complexes with chelating ligands. The inorganic chemistry involved in this transformation is unusual, since the reaction between an alkoxide complex and an alkylamine to form an amido complex had not been observed previous to the work described below.

The reaction of [{Pd(PPh_3)(Ph)(μ-OH)}$_2$] (**11**) with primary alkylamines to generate palladium–amido complexes and water [Eq. (25a,b)][75, 149] was an initial indication that the conversion of an alkoxide into an amide could be occurring during the catalytic cycle. These reactions are reversible, but the equilibrium favors the amido complex. The kinetic behavior of the reaction was counterintuitive. The reaction of **11** with *sec*-butylamine was second order with respect to the amine, even though a single amido group was formed during the reaction [Eq. (25a)]. Extensive kinetic studies supported the mechanism in Scheme 6 involving reversible reaction of two amines to cleave the hydroxo dimer. After cleavage of the dimer, *internal* proton transfer within the square-planar complexes would occur, which is in contrast to the coordination and *external* deprotonation observed for the P(o-C_6H_4Me)$_3$ complexes.



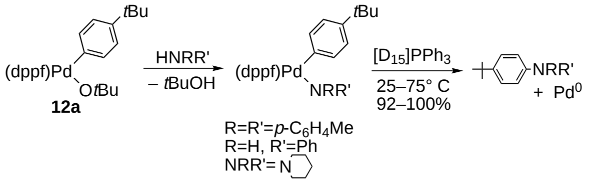
(25a)

(25b)



Scheme 6. Mechanism for the reaction of a palladium hydroxide with amine.

The potential of amines to convert alkoxo complexes into amido complexes in analogous systems with chelating ligands was evaluated recently.[70] [Pd(dppf)(p-C_6H_4tBu)(OtBu)] (**12a**) reacted with diphenylamine, aniline, or piperidine as shown in Equation (26) to give the product of amine arylation in high yields.[70] Since no alkali metal is present in the system, the palladium amide is formed by a mechanism that cannot involve external deprotonation by alkali metal base.



(26)

In the actual catalytic process, it is possible that coordination of amine and deprotonation are faster than substitution and N–H bond cleavage. However, stoichiometric reactions of [Pd(dppf)(p-C_6H_4tBu)(Br)] (**13**) with amine and alkoxide base rapidly gave rise to **12a**, indicating that substitution is faster than coordination and deprotonation. This alkoxide forms the arylamine product by reaction with amine.[150] The exact mechanism for N–H bond cleavages by palladium complexes containing chelating ligands is not clear at this time, but palladium–amido complexes are certainly thermodynamically accessible by reaction of a palladium alkoxide with free amine.

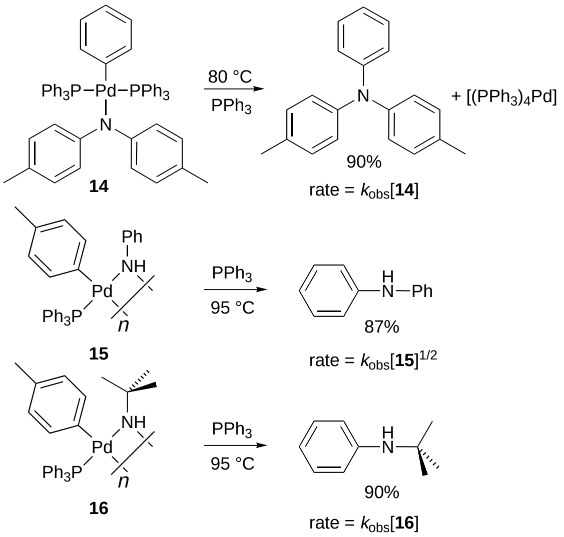
8.3. Reductive Eliminations of Amines and Ethers

Reductive elimination of amines and ethers is the key bond-forming step in the catalytic amination and etheration processes. These reactions were unknown a couple of years ago. There are now several examples, and the factors that control the rates of this process are beginning to be understood. The identity of the intermediates in some of these reductive elimination reactions has recently been uncovered. In some cases the reactions appear concerted. In other cases, particularly related reactions that involve eliminations from nickel complexes to form alkyl–nitrogen bonds, the reductive elimination may involve radical processes.

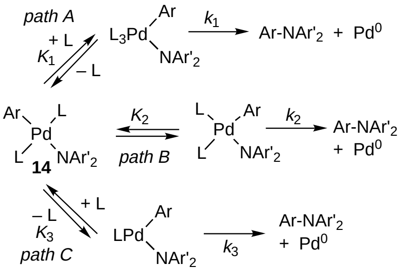
8.3.1. Reductive Elimination of Amines from Palladium Complexes

The best understood examples of reductive eliminations that form the C–N bond in amines involve palladium complexes. Both Boncella et al.[71] and Hartwig et al.[68, 69, 99] have observed these reactions from palladium–amido aryl complexes. Our group has studied the mechanism of this process in detail.[68, 99] Although monomeric and dimeric amido complexes have been isolated, the monomeric species undergoes reductive elimination. For complexes with monodentate ligands, kinetic studies indicated that the actual C–N bond formation occurs simultaneously from both three- and four-coordinate intermediates. With chelating phosphanes, the chemistry is, therefore, likely to occur from the four-coordinate complexes observed in solution. The reductive elimination of arylamines is favored by increasing nucleophilicity of the amido group and increasing electrophilicity of the aryl group.

The mechanisms of the reductive eliminations in Scheme 7 were studied.[68, 99] Potential pathways for the reaction of **14** are shown in Scheme 8. The reductive eliminations from the monomeric diarylamido aryl complex **14** illustrate two important points of the elimination reactions. First, these reactions were first-order, demonstrating that the actual C–N bond formation occurred from a monomeric complex. Second, the observed rate constant for the elimination reaction contained two terms [Eq. (27)]. One of these terms was



Scheme 7. Reductive elimination of arylamines from PPh_3-ligated Pd^{II}–amide complexes.



Scheme 8. Potential mechanisms for reductive elimination of arylamines from PPh_3-ligated Pd^{II}–amide complexes.

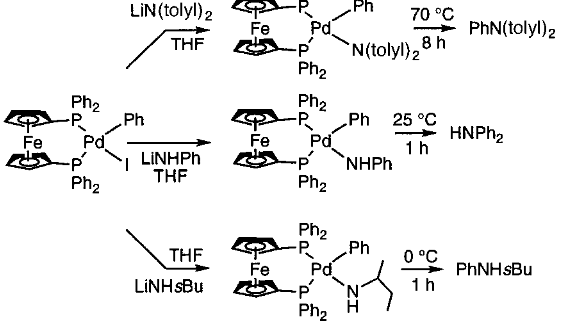
$$-\frac{d[\mathbf{14}]}{dt} = k_{\mathrm{obs}}[\mathbf{14}]$$

$$\text{where } k_{\mathrm{obs}} = K_2k_2 + \frac{K_3\,k_3}{[\mathrm{PPh_3}]} \qquad (27)$$

inverse first order with respect to PPh_3 and the other was zero order with respect to PPh_3. These results were consistent with two competing mechanisms, path B and path C in Scheme 8, occurring simultaneously. One of these mechanisms involves initial, reversible phosphane dissociation followed by C–N bond formation in the resulting 14-electron, three-coordinate intermediate. The second mechanism involves reductive elimination from a 16-electron four-coordinate intermediate, presumably after *trans* to *cis* isomerization.

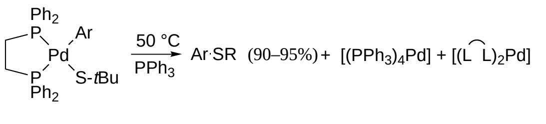
The dimeric amido complexes underwent reductive elimination after cleavage to form two monomeric, three-coordinate, 14-electron amido complexes. In the case of the anilido dimer **15**, a half-order rate dependence in the palladium complexes showed that the reductive elimination occurred after reversible cleavage of the dimer to form two monomers. In the case of the *tert*-butylamido complex **16** rapid reductive elimination occurred after irreversible dimer cleavage. This conclusion was supported by reaction rates that were first order with respect to the palladium dimer and by the lack of crossover during the reductive elimination reactions containing two doubly labeled dimers.

The observation that the reductive elimination process involved a pathway through four-coordinate, presumably cis, monomeric amido aryl complexes led to the preparation of palladium–amido complexes with chelating ligands.[69] Results with these complexes confirmed this conclusion and led to the development in our lab of second-generation catalysts based on palladium complexes with chelating ligands.[151] The palladium–amido aryl complexes with DPPF ligand in Scheme 9 underwent reductive elimination of arylamines in high yields.[69, 99] The rates for these reactions were first order with respect to palladium and zero order with respect to the trapping ligand. Thus, the data on the reductive elimination reactions is consistent with a direct, concerted formation of the C–N bond from the four-coordinate *cis*-DPPF complex.



Scheme 9. Reductive elimination of arylamines from DPPF-ligated palladium–amido complexes.

Because the reductive elimination from DPPF-ligated palladium complexes did not involve geometric rearrangements or changes in coordination number before the rate-determining step, the DPPF complexes allowed for an assessment of the electronic properties of the transition state in this reaction. The relative rates for elimination from amido groups was alkylamido > arylamido > diarylamido. This trend implies that the more nucleophilic the amido group, the faster the elimination process. Variation of the aryl group showed similar results to an extensive study of the electronic aspects of C–S bond-forming eliminations of sulfides [Eq. (28)].[60]



$$\mathrm{(P^\frown P)Pd(Ar)(S\text{-}}t\mathrm{Bu)} \xrightarrow[\mathrm{PPh_3}]{50\,^\circ\mathrm{C}} \mathrm{Ar{\cdot}SR}\ (90\text{–}95\%) + [(\mathrm{PPh_3})_4\mathrm{Pd}] + [(\mathrm{L^\frown L})_2\mathrm{Pd}] \qquad (28)$$

The data for electronic effects on sulfide and amine eliminations presented in Figure 2 were similar. They point out that electron-withdrawing groups accelerated the reductive elimination process and that substituents with large σ_R values for the resonance effect affected the reaction rates more than substituents with large σ_I values for the inductive effect. Resonance effects were stronger than inductive effects, perhaps due to arene coordination during the reaction. In a more rough sense, the amido group acts as a nucleophile and the aryl group as the electrophile.

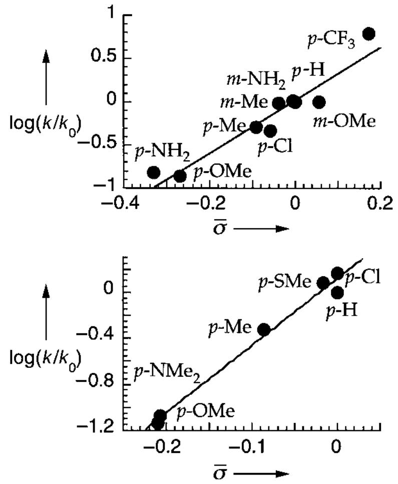
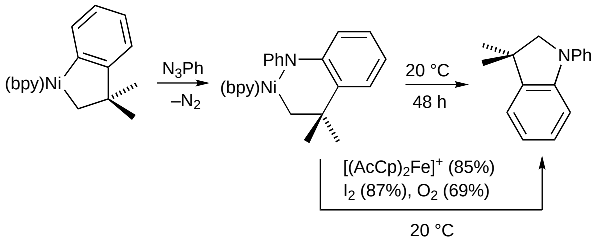


Figure 2. Analysis of electronic effects on the reductive elimination of aryl sulfides (top; $\rho_R/\rho_I = 3$, $\rho_R = 2.3$, $\rho_I = 0.77$) and arylamines (bottom; $\rho_{R^-}/\rho_I = 2$, $\rho_{R^-} = 3.9$, $\rho_I = 1.9$) by considering a combination of the substitution constants σ_I and σ_R^0.

8.3.2. Reductive Elimination of Amines from Nickel Complexes

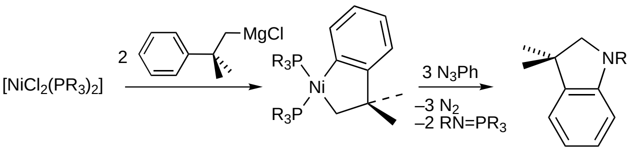
Koo and Hillhouse have shown that the reductive elimination of amines can also occur from nickel complexes.[72] This research group has prepared nickel–arylamido alkyl complexes by insertion of the NAr fragment from aryl azides into Ni–C bonds.[152] A variety of the amido alkyl complexes undergo reductive elimination to form alkylarylamines as shown in Scheme 10. This transformation differs from the palladium chemistry by forming a C–N bond between an amido group and an alkyl rather than an aryl group. Furthermore, most of these reductive elimination reactions



Scheme 10. Oxidatively induced reductive eliminations of amines from $\mathrm{Ni^{II}}$–amido complexes generated in situ. Cp = cyclopentadienyl.

occurred only after initial oxidation by I_2, O_2, or $[Cp_2Fe]^+$, although one example of thermally induced elimination from the bpy–nickel fragment (bpy = 2,2′-bipyridine) was observed. In the case of acyclic amido aryl complexes, the yields were lower for the reductive elimination process. This result, coupled with the information that single-electron oxidation triggers the elimination process, led Hillhouse to propose an alkyl or aminyl radical as an intermediate in these reactions.[72]

A subsequent report from Hillhouse's lab focused on phosphane-ligated nickel complexes. He showed that consumption of phosphane by the azide led to rapid nonoxidatively induced eliminations to form nitrogen heterocycles (Scheme 11).[153] Thus, the phosphane-ligated nickel centers may react by different pathways than the bpy-ligated complexes.

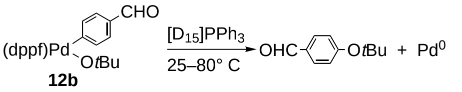


Scheme 11. Reductive elimination of indolines from Ni^{II} amides generated in situ.

8.3.3. Reductive Elimination of Ethers from Palladium Complexes

The reductive elimination of ethers from palladium complexes was recently reported by Mann and Hartwig, and these reactions were the first examples of C–O bond-forming reductive eliminations of aryl ethers.[70] The ability of transition metal complexes to perform this reaction is crucial to generalization of the catalytic conversion of aryl halides into aryl ethers.

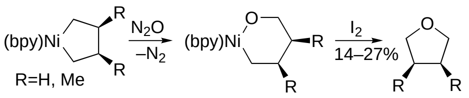
The reductive elimination chemistry reported by Mann and Hartwig is shown in Equation (29). The scope of this reaction can be understood in terms of the electronic effects on amine and sulfide eliminations. The alkoxo ligand is less nucleophilic than an amide or thiolate. As a result, its participation in high-yielding reductive elimination reactions is so far limited to electrophilic aryl groups. Thus, the DPPF-ligated alkoxo aryl complex with an electron donating substituent, even a weak one, does not undergo reductive elimination of ether in significant yields. However, the alkoxo aryl complex **12b**, in which the aryl group contains a substituent that is an electron acceptor in a resonance fashion, does give high yields of alkoxo aryl complex under thermal reaction conditions.



(29)

8.3.4. Reductive Elimination of Ethers from Nickel Complexes

Oxidation induces reductive elimination of ethers from cyclic alkoxo alkyl complexes of nickel in a similar fashion to the oxidatively induced reductive elimination of amines from bpy–nickel amido alkyl complexes.[73] Hillhouse's group has prepared oxametallacycles of nickel by insertion of the oxygen atom of N_2O into nickel–alkyl compounds.[154] Oxidation of these complexes by I_2, O_2, and $[Cp_2Fe]^+$ led to the reductive elimination of oxygen heterocycles, albeit in fairly low yields [Eq. (30)].[73] The yields are only mildly dependent on substitution of the metallacycle. Acyclic alkoxo alkyl complexes did not undergo oxidatively induced reductive elimination to form acyclic ethers. The reduced nucleophilicity of the alkoxo group relative to the amido group may also be important in the mechanistically distinct chemistry of the bpy–nickel complexes, or the greater M–O bond dissociation energy relative to that of M–N[149, 155] may disfavor the proposed radical intermediates.



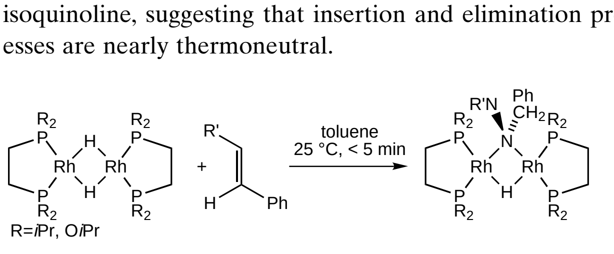
(30)

8.4. Competing *β*-Hydrogen Elimination

The amination chemistry depends on the absence of irreversible *β*-hydrogen elimination from the amido complexes before reductive elimination of amine. The conversion of aryl halides into aryl ethers similarly depends on reductive elimination being faster than *β*-hydrogen elimination from an alkoxide. At the early stages of the development of the amination chemistry, it was remarkable that the unknown reductive elimination of arylamines could be faster than the presumed rapid[76, 77] *β*-hydrogen elimination from late transition metal amides. In fact, directly observed *β*-hydrogen elimination from late transition metal–amido complexes was rare, and no examples occurred irreversibly from a simple monomeric amido species.[86] At this point, it is clear that C–N bond-forming reductive elimination of amines and ethers can be rapid, and that *β*-hydrogen elimination can be slow.

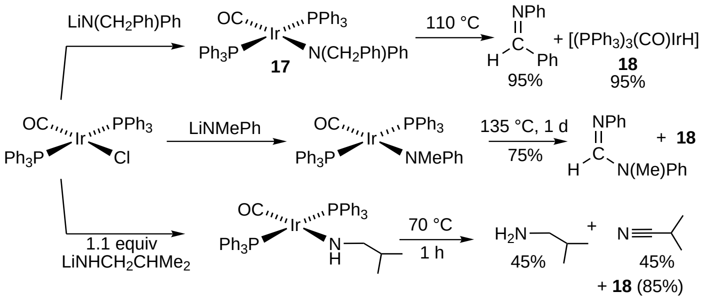
8.4.1. β-Hydrogen Elimination from Amides

β-Hydrogen elimination from amido complexes is a process that was assumed to be rapid, but that had not been observed directly with monomeric amido complexes until recently. Fryzuk et al. have studied the related insertion of imines into a dimeric, bridging hydride of Rh^I [Eq. (31)].[86] Their results showed that imine insertion was reversible upon use of isoquinoline, suggesting that insertion and elimination processes are nearly thermoneutral.



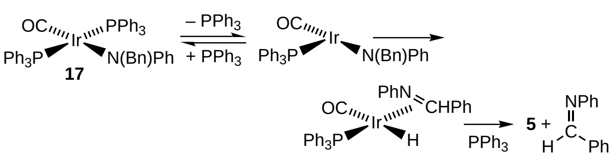
(31)

Recently, Hartwig prepared 16-electron, square-planar amido complexes that undergo irreversible *β*-hydrogen elimination.[100] This observation allowed the beginning of a mechanistic understanding of this process, but also highlighted the unfounded assumption that this β-hydrogen elimination process is typically rapid. Three different monomeric amido complexes with β-hydrogen atoms were prepared from Vaska's complex (Scheme 12). All three complexes underwent high-yielding β-hydrogen elimination processes, two of which gave unexpected products from imine disproportionation. In the case of elimination from the *N*-benzyl anilide **17** the reaction produced iridium hydride **18** and imine in nearly quantitative yields. β-Hydrogen elimination from the anilides required temperatures of 100 °C or above, and elimination from the alkylamide proceeded at 70 °C. In contrast, Schwartz et al. showed that the analogous alkyl complexes underwent β-hydrogen elimination below room temperature.[156, 157]



Scheme 12. β-Hydrogen elimination from Ir^I–amido complexes.

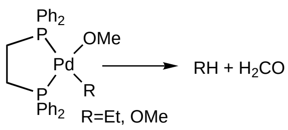
The mechanism for β-hydrogen elimination from **17**, which forms a stable imine product, involved monomeric amido complexes. The intermediate that underwent C–H bond cleavage was a 14-electron, three-coordinate complex that formed by reversible phosphane dissociation [Eq. (32)].



(32)

Importantly, there was no detectable competing β-hydrogen elimination from a 16-electron, four-coordinate complex. The mechanism for β-hydrogen elimination from a 14-electron intermediate parallels that for β-hydrogen elimination from square-planar alkyl complexes.[158, 159] β-Hydrogen elimination from the alkylamido complex and from the *N*-methyl anilide were less well defined, and firm conclusions on the coordination number of the complex that loses the β-hydrogen atom requires further study.

β-Hydrogen elimination from alkoxo complexes has been observed previously on two different types of systems, but these studies led to ambiguous mechanistic conclusions. The presence of a chelating phosphane on the complexes in Equation (33) prevented determination of the coordination number of the species undergoing β-elimination, and the value of 1.33 obtained for the order with respect to MeOH for the reaction in Equation (34) was difficult to explain.



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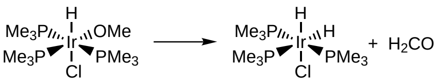


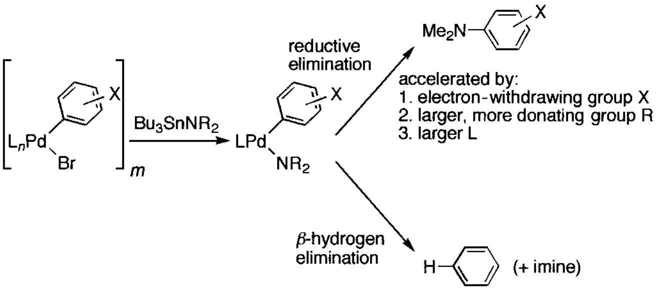
(34)

Unpublished studies on β-hydrogen elimination from Vaska-type alkoxo complexes that are analogous to the amides in Scheme 12 suggest a mechanism for β-hydrogen elimination from alkoxo complexes that is distinct from that for β-hydrogen elimination from amides.[160] The rates for β-hydrogen eliminations from the alkoxides are also faster than in the case of the amides.

8.5. Selectivity: Reductive Elimination versus β-Hydrogen Elimination

Two studies have been conducted on the effect of steric and electronic properties of ligands on the relative rates for reductive elimination of amine and β-hydrogen elimination from amides. One investigation focused on the amination chemistry catalyzed by palladium complexes with $P(o\text{-}C_6H_4Me)_3$ ligands,[161] while the second dealt with the chemistry catalyzed by complexes containing chelating ligands.[104]

Studies of aryl halide amination with secondary aminostannanes and palladium catalysts bearing $P(o\text{-}C_6H_4Me)_3$ ligands is summarized in Scheme 13. They revealed four factors that control the relative degrees to which aryl halide hydrodehalogenation and amination occur. First, a certain amount of arene was formed by the reduction of Pd^{II} dihalides to the active Pd^0 catalyst; the mechanism for this reduction was not explored. Second, electron-withdrawing groups on the aryl ring gave more amination and less hydrodehalogenation than those with electron-donating groups. This result is consistent with the faster reductive elimination of amines with electron-poor aromatic groups discussed above. *N*-Alkyl arylamides provided more hydrodehalogenation, consistent with arylamides undergoing reductive elimination of amines more slowly than the dialkylamides. Further, deuterium-labeling experiments showed that the majority of the dehalogenation product formed after catalyst initiation resulted from β-hydrogen elimination from the amido group.



Scheme 13. Factors controlling the selectivity for amination versus hydrodehalogenation of aryl halides.

The final point concerned the steric effects of the phosphane aryl groups on the relative amounts of arene and arylamine produced. Careful monitoring of the products from both stoichiometric and catalytic reactions employing palladium complexes containing $P(o\text{-}C_6H_4Me)_3$, $P(o\text{-}C_6H_4Me)_2Ph$, $P(o\text{-}C_6H_4Me)Ph_2$, and PPh_3 ligands showed monotonically decreasing ratios of amine to arene as the size of the ligand decreased. Since arene formation by hydrodehalogenation occurred predominantly by β-hydrogen elimination, it is clear that larger phosphane ligands enhance the reductive elimination of amines at the expense of β-hydrogen elimination processes. Reductive elimination of amine decreases the metal's coordination number, while β-hydrogen elimination from an amide either increases the metal's coordination number because of formation of a coordinated imine along with the hydride or maintains the same coordination number if imine is extruded without coordination. Large groups on the phosphane ligand will enhance the rate of the reaction that decreases the coordination number, and will, therefore, increase the rate for reductive elimination[162] of amines relative to that for β-hydrogen elimination.

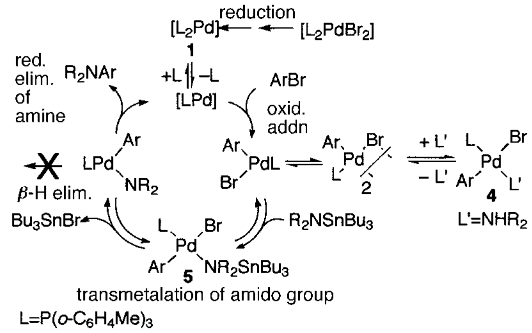
Results obtained with chelating ligands that display varied steric properties contrasted those with monodentate ligands.[104] Large, chelating phosphane ligands such as bis-1,1′-(di-o-tolylphosphanyl)ferrocene gave more hydrodehalogenation product than did DPPF. Reactions employing electron-poor DPPF derivatives, which should generate a more electron-poor metal that favors reductive elimination of amine, produced more arene than did those employing electron-rich DPPF derivatives. Furthermore, ligands with large bite angles gave more arene than those with small bite angles, which is in contrast to what would be expected from previous studies that showed an increase in rate of C–C bond-forming reductive elimination with increasing bite angle.[163] Although the origin of the unusual results with chelating phosphanes in the amination chemistry are not fully understood at this time, it is clear that chemistry other than reductive elimination of amine and β-hydrogen elimination from an amide is occurring. The arene produced from reactions of amines that are deuterated at the position α to the nitrogen atom or at the N–H group was primarily protiated when the catalysts contained any of several chelating phosphane ligands. The source of hydrogen is currently unclear, but much of the arene generated in reactions employing DPPF or BINAP does not form by a simple β-hydrogen elimination and C–H bond-forming reductive elimination sequence.

8.6. Overall Catalytic Cycle with Specific Intermediates

At this time, one can put together the results on reductive elimination and oxidative additions to make a justified prediction about the mechanism for the amination chemistry catalyzed by palladium complexes containing both monodentate and chelating ligands. The catalytic cycles differ in the coordination number of the palladium complexes involved and the factors that control amination or etheration versus aryl halide reduction. We have shown that the catalytic cycle for the amination of aryl halides catalyzed by palladium complexes with $P(o\text{-}C_6H_4Me)_3$ ligands exclusively contains mono-phosphane intermediates. In contrast, the chemistry catalyzed by palladium complexes with DPPF or BINAP ligands involves bis-phosphane complexes as a result of ligand chelation and the fact that reductive elimination can occur without ligand dissociation.

8.6.1. Mechanism for Amination Catalyzed by Palladium Complexes with $P(o\text{-}C_6H_4Me)_3$ Ligands

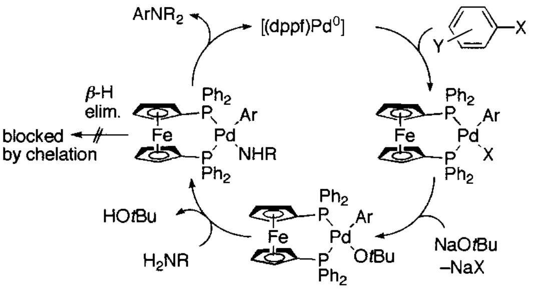
Scheme 14 shows an experimentally supported mechanism for amination catalyzed by $P(o\text{-}C_6H_4Me)_3$ complexes. The Pd^0 complex is a 14-electron two-coordinate species that loses one of the phosphane ligands before oxidative addition of the aryl halide. This conclusion was supported by kinetic studies on the stoichiometric oxidative addition of aryl halides to **3**. This process generates an aryl halide complex that is isolated as a dimer, but which reacts in the catalytic cycle as a monomer. During reactions involving amines in the presence of base, amine cleaves the dimeric aryl halide complexes to form a mono-phosphane, amine-ligated aryl halide complex. Stoichiometric reactions of these amine complexes with base show that the coordinated amine is deprotonated by base to generate a three-coordinate amido species that undergoes rapid reductive elimination. In addition to these stoichiometric studies, studies on the rates of kinetically well-behaved catalytic reactions involving tin amides showed that monomeric, mono-phosphane complexes of palladium were the intermediates of the actual catalytic cycle. Furthermore, the kinetic studies revealed an inhibition by tin bromide by-product, and this product inhibition allowed for kinetic detection of the monomeric, mono-phosphane amido aryl intermediate. In the case of monodentate ligands, the use of large phosphanes accelerates the overall rate by favoring the formation of mono-phosphane complexes, and leads to high yields by accelerating reductive elimination relative to β-hydrogen elimination.



Scheme 14. Overall mechanism for aryl halide amination catalyzed by palladium complexes with $P(o\text{-}C_6H_4Me)_3$ ligands.

8.6.2. Mechanism for Amination Catalyzed by Palladium Complexes with Chelating Ligands

Scheme 15 shows a mechanism for the amination of aryl halides catalyzed by DPPF–palladium complexes which is presumably similar to that for reactions catalyzed by



Scheme 15. Overall mechanism for aryl halide amination catalyzed by palladium complexes with DPPF ligands.

BINAP–palladium complexes. In this case, the resting state of the catalyst, the relative rates and reversibility of the various steps, and the reaction orders with respect to the different components for the overall reaction are not known. Furthermore, a variety of ligand transformations can occur over the course of the reaction. However, existing data do provide a reasonable mechanism for the catalytic process, assuming that ligand transformations do not disrupt the chelating properties of the ligand.[164] In the case of palladium complexes with chelating ligands, the Pd^0 complex that undergoes oxidative addition of aryl halide most likely contains one chelating ligand. This reaction would lead to a [PdL$_2$(Ar)(X)] complex.[163] The amido aryl complex that would result from reaction of the aryl halide complex with amine and base is also a bis-phosphane complex.[70] Mechanistic studies on the reductive elimination of amine from amido aryl complexes show that these complexes would undergo reductive elimination directly from the 16-electron, four-coordinate complex, in contrast to reductive elimination from the mono-phosphane, 14-electron, three-coordinate amido complex containing P(o-C$_6$H$_4$Me)$_3$ ligands. For reactions involving chelating phosphanes, the selectivity for reductive elimination rather than β-hydrogen elimination results from chelation blocking phosphane dissociation and accompanying pathways for β-hydrogen elimination from 14-electron, three-coordinate species. Although many mechanistic questions have not been answered at this point, these results provided a general, experimentally supported pathway for reactions catalyzed by complexes with monodentate and chelating phosphane ligands.

9. Summary

The amination of aryl halides and triflates catalyzed by palladium complexes is suitable for use in complex synthetic problems. Many substrates will produce high yields of mixed arylamines with one of the existing catalyst systems. Nevertheless, there are also many combinations of substrates for which the amination chemistry must be substantially improved. For the most part, these reactions involve nitrogen centers, such as those in pyrroles, indoles, amides, histidines, and other heterocyclic groups that are less basic than standard alkylamines, or they involve arenes that are electron-rich. Furthermore, it is important to develop increasingly mild reaction conditions and to increase the number of turnovers.

The palladium-catalyzed synthesis of aryl ethers from aryl halides is more limited at this time, but could become a synthetic method that may ultimately provide a general route to aryl ethers. Currently, alkoxides will react with electron-deficient aryl halides in good yields in nonpolar solvents to generate ether products upon use of either palladium or nickel catalysts. Diaryl ethers have recently been formed from palladium-catalyzed substitutions of aryl halides with phenols, but again this process is limited to electron-deficient aryl halides. This combination of substrates is clearly important since these ethers are not produced conveniently under mild conditions by classical methods, and, as discussed in the introduction, since they are important structural types in thermally stable polymers and biologically active natural products.

10. Appendix

Synthetic improvements, new mechanistic information, further applications, and new classes of amination reactions are constantly appearing. Several papers that describe important synthetic results have been published since the submission of this manuscript. Thus, they are included in this appendix for readers interested in the most recent developments.

Nishiyama et al. reported the use of tri-*tert*-butylphosphane for the amination of piperazine at low catylyst loadings.[165] Rossen, Pye, and co-workers described the amination of a dibromocyclophane for kinetic resolution.[166] They also showed that 4,12-bis(diphenylphosphanyl)[2.2]paracyclophane (PHANPHOS) is a more effective ligand than BINAP for amination of some aryl halides.

Buchwald's group has reported the amination of aryl chlorides with nickel complexes,[167] Tanaka's group the palladium-catalyzed amination of aryl chlorides with use of tricyclohexylphosphane,[168] and Beller and Herrmann the amination of electron-poor aryl chlorides with a palladacycle.[169] Senanayake et al. described the amination of a 2-chloro-1,3-diazole derivative for the synthesis of H$_1$-antihistaminic norastemizole.[170]

Buchwald and co-workers have published the use of Cs$_2$CO$_3$ in combination with Kumada's ligand to give improved functional group compatibility for the amination of aryl halides,[171] and the use of Cs$_2$CO$_3$ for the amination of aryl triflates[172] to alleviate competing triflate cleavage. His group has also reported the use of benzophenone imine as a surrogate for ammonia.[173] Darses et al. described the room-temperature amination of arene diazonium salts,[174] and Buchwald et al. reported the room temperature amination of aryl halides with use of crown ether additives.[175]

In 1996 Ma and Yao had reported a synthesis of chiral N-aryl-α-amino acids by Pd/Cu-catalyzed couplings of chiral α-amino acids with aryl halides,[176] and Buchwald and co-workers recently evaluated the enantiomeric integrity of products obtained from the palladium-catalyzed arylation of optically active amines in the absence of copper.[177] Beletskaya et al. reported the amination of polyamines,[178] and

Buchwald's group prepared end-functionalized oligomers of poly(*p*-aniline).[179]

Buchwald's group published mechanistic studies on the reductive elimination of aryl ethers from aryl alkoxo complexes generated in situ, but not isolated,[180] and Hillhouse and co-workers reported data on the selectivity for reductive elimination versus β-hydrogen elimination from nickel–alkoxo complexes.[181]

Hartwig's group reported the polymerization of *N*-arylbromoanilines, as well as the copolymerization of dihaloarenes and diamines for formation of donor–acceptor polymers.[182] They extended aryl ether formation to the preparation of diaryl ethers from aryl halides and phenols; increased yields were obtained upon use of electron-poor phosphane ligands.[183] They also reported the arylation of pyrroles, indoles, carbazoles, and benzophenone imine with DPPF-ligated palladium complexes, along with information that allows for a comparison of the relative rates for reductive eliminations of arylamines, *N*-aryl azoles, and *N*-aryl imines.[184] Finally, they have demonstrated the arylation of hydrazones and have isolated hydrazonato complexes that allow for direct oberservation of the reductive elimination of *N*-aryl hydrazones in high yields.[185]

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