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Approaches to catalyst discovery. New carbon–heteroatom and carbon–carbon bond formation*

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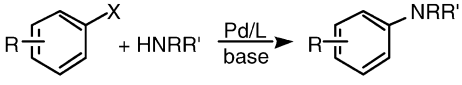
Abstract: Studies on the palladium-catalyzed formation of aryl amines, aryl ethers and a-aryl carbonyl compounds from aryl halides are reported. These studies range from synthetic methodology, to detailed mechanistic analysis, to new methods one can use to screen for catalytic covalent bond formation. Improved methods for formation of aryl ethers and room temperature amination chemistry have resulted from a mechanistic understanding of the reaction.

Over the past 20 years, palladium-catalyzed methods for aromatic substitution have provided useful routes to biaryl, alkynyl-aryl and vinyl-aryl compounds [1,2], The palladium-catalyzed formation of aromatic carbon-heteroatom bonds has become a useful synthetic tool in the past few years [3]. The new direct formation of α-aryl carbonyl compounds provides a method to form sp^3-aromatic carbon-carbon bonds [4–7], The purpose of this presentation is to provide examples of C–N, C–O and C–C bond formation that have been developed recently in the author's laboratory and to provide mechanistic information that allows one to understand why one type of catalyst is more effective than another for a particular class of transformation (Scheme 1).



(1)

R= *o, m or p*- donating	HNRR'=amine,	base=NaO- *t*-Bu	L=P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, DPPF
or withdrawing group	Ph_2C=NH,	KN($SiMe_3$)$_2$	BINAP, BPEphos, Kumada's ligands,
X=Cl, Br, I, OTf, OTs	Ph_2C=NNH_2, azole	Pd=Pd_n(dba)$_m$, Pd(OAc)$_2$	Phanephos, biarylPR$_2$

Our initial work was motivated by Kosugi and Migita's publications describing the coupling of tin amides with aryl halides using palladium catalysts containing tri-*o*-tolylphosphine as ligand [8,9], Although these reactions were limited in scope and possessed problems from the toxicity and environmental instability of tin amides, the potential for palladium complexes to catalyze aromatic carbon-nitrogen bond formation in a synthetically valuable fashion was suggested. A summary of the current group of palladium-catalyzed aromatic aminations published by several laboratories is provided in Eqn 1. The first synthetic advance in this area was the use of amines in the presence of base, instead of tin amides, to conduct this chemistry [10,11]. Originally, these reactions employed palladium catalysts ligated by tri-*o*-tolylphosphine, but there are several other systems that are now useful for reactions of secondary amines with aryl halides [12,13]. In contrast, the coupling of primary amines with aryl halides typically requires a catalyst containing a different type of ligand: a tightly chelated bis-phosphine [14,15]. With such catalysts, reactions of aryl halides with primary alkylamines and arylamines provided mixed

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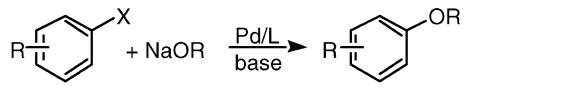
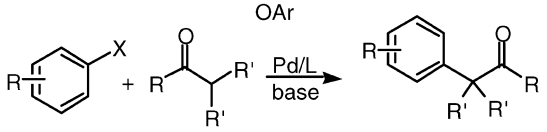
secondary amines. The use of chelating ligands has also allowed for the coupling of diphenylhydrazone [16,17] and benzophenone imine in a general fashion to provide *N*-aryl hydrazones and protected anilines [18,19]. Although slower, reactions of aryl halides with indoles were also observed in good yields [18]. The analogous reactions of alcohols, silanols and phenols to form ethers (Eqn 2) was less general until recently [20–24]. The catalyst systems containing arylphosphine ligands provided aryl ethers from highly activated aryl halides, but not from unactivated aryl halides. Finally, reactions of ketones and malonates with aryl halides or the intramolecular reaction of amides containing pendant aryl halides occur in the presence of alkoxide base and palladium catalysts to form α-aryl ketones [4–7], aryl malonates [5], and oxindoles [25] (Eqn 3).



R= withdrawing group
X=Cl, Br

NaOR=O-*t*-Bu
OSi(*t*-Bu)Me$_2$
OAr

L=DPPF, BINAP



R= *o, m or p*- donating or withdrawing group
X=Cl, Br, I, OTf, OTs

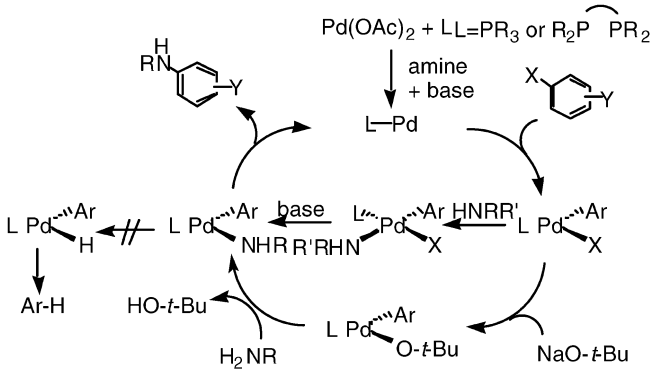
R=alkyl, aryl, NR$_2$, OEt
R'=alkyl, aryl, C(O)OEt

base=NaO-*t*-Bu
KN(SiMe$_3$)$_2$
Pd=Pd$_n$(dba)$_m$, Pd(OAc)$_2$

L=P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$
DPPF, BINAP, biarylPR$_2$

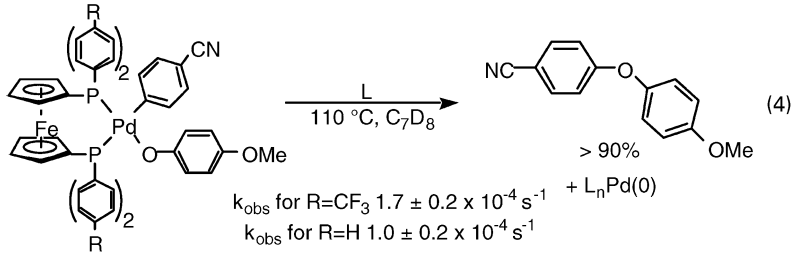
Scheme 1 summarizes a variety of mechanistic studies on the amination chemistry and highlights two important issues. First, the Pd(0) complex is the resting state. Thus, rate acceleration relies upon increasing the rate of the oxidative addition portion of the catalytic cycle. [26]. Second, β-hydrogen elimination is an important side reaction [27,28]. This reaction is slower for complexes containing secondary amido ligands than for those containing primary amides when compared to their respective rates for reductive elimination. This difference in rate explains why a change in catalyst was necessary to conduct aminations with primary instead of secondary amines.

Several concepts that are important for this catalytic process emerged from studying the stoichiometric chemistry of arylpalladium amido and Vaska-type iridium amido complexes. First, reductive elimination can occur from either a four-coordinate bisphosphine or three-coordinate monophosphine arylpalladium amido complex [29]. Eliminations from the three-coordinate compounds are faster. Second, β-hydrogen elimination occurs from a three-coordinate intermediate [30]. Therefore, β-hydrogen elimination occurs slowly from arylpalladium complexes containing chelating phosphines while reductive elimination can still occur from these four-coordinate species. This mechanistic information is similar to that observed with palladium and platinum alkyl complexes [31], despite the potential π-donor character of the amido ligand and increased ionic character of the amido-metal bond. Third, reductive elimination is faster from



Scheme 1

complexes with more nucleophilic heteroatom ligands and more electrophilic aromatic ligands [29,32–34]. This information explains the difficulty in observing the formation of aryl ethers. Complexes with the more weakly nucleophilic alkoxide ligand undergo reductive elimination more slowly than those with amido ligands. Therefore, a strongly activated aryl group was initially necessary to observe reductive elimination of aryl ethers (Eqn 4).



(4)

Another change of catalyst structure was, therefore, required to increase the scope of the reductive elimination process to include a more general formation of ethers and *N*-aryl azoles, as well as the formation of *N*-aryl carbamates and related compounds. In the optimal case, this same change in ligand structure would also accelerate the initial oxidative addition because oxidative addition is the turnover limiting step of most, but not all, amination chemistry. A common method to accelerate reductive elimination is to reduce the electron density at the metal center. Thus, we prepared the arylpalladium phenoxide complexes in Eqn 4 containing DPPF and a DPPF analog that contained *p*-CF_3 groups on the ligand. This complex did undergo reductive elimination when an activated palladium-bound aryl group was present, but the rate was faster by a factor of only two.

A different strategy was required. Figure 1 shows a qualitative energy diagram for oxidative addition (left to right) and reductive elimination (right to left) involving Pd(0) and Pd(II) complexes. The mechanisms for these reactions have either been reported or are under study currently. Clearly, the method to accelerate both addition and elimination is to decrease the difference in energy between the Pd(0) reactive intermediate and the two ground states. Because the reactive intermediate has a lower coordination number than the more stable Pd(0) and Pd(II) complexes, we used steric effects to raise the energy of the ground states relative to that of the low-coordinate number Pd(0) reactive intermediate.

We prepared or selected from the pool of commercially available ligands sterically hindered bis-phosphines to accelerate amination and perhaps observe more general etherification reactions. Indeed, we now could observe amination chemistry at room temperature using *bis*-(di-*t*-butylphosphino)ferrocene (D^{t}BPF) and could observe amination of aryl chlorides or even aryl tosylates [26]. Perhaps most important, we could begin to observe formation of alkyl aryl and diarylethers when the aryl halide was unactivated. For example, reaction of sodium *t*-butoxide and 4-BrC_6H_4-*t*-Bu catalyzed by a mixture of $Pd(OAc)_2$ and D^{t}BPF gave roughly 90% yield of ether, and reactions catalyzed by the hindered

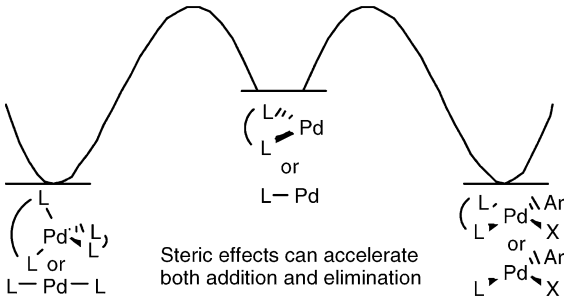
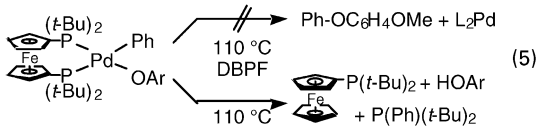


Fig. 1 A qualitative energy diagram for oxidative addition and reductive elimination reactions with Pd complexes.

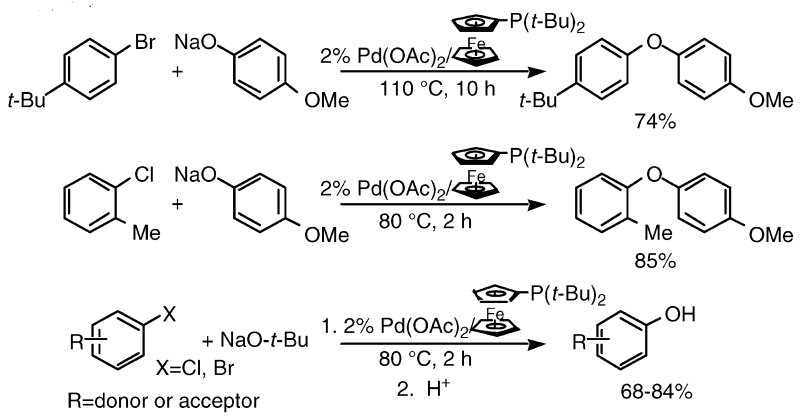
monophosphine P(*t*-Bu)$_3$ occurred in quantitative yields [35]. Reactions of *p*-MeOC$_6$H$_4$ONa with the same aryl halide gave roughly 45% yield when using D^{t}BPF as ligand, only 20% yield when using P(*t*-Bu)$_3$, and no product when using DPPF, BINAP, or P(*o*-tolyl)$_3$. Unfortunately, these reaction times were as long as 7 days. Nevertheless, we sought the isolation of complexes containing DB^{t}PF that would undergo reductive elimination of diarylether when the aryl group bound to palladium was unactivated. These studies showed how to prepare catalysts that were synthetically valuable for formation of aryl ethers. We were surprised to find that heating of (D^{t}BPF)Pd(Ph)(OC$_6$H$_4$-4-OMe) gave no ether product (Eqn 5).



(5)

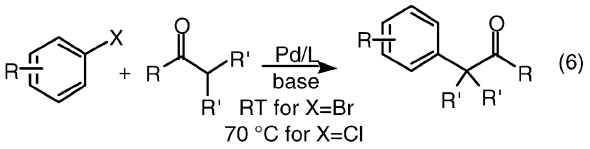
Instead, formation of PhP(*t*-Bu)$_2$ and FcP(*t*-Bu)$_2$ (Fc = ferrocenyl) was observed by GC/MS. We prepared these two ligands and tested them for the formation of aryl ethers. Indeed, a combination of FcP(*t*-Bu)$_2$ and Pd(dba)$_2$ catalyzed the formation of *t*-butyl aryl ethers in high yields (selected examples in Scheme 2). The corresponding phenols were generated by addition of acid to the resulting reaction mixture. Moreover, FcP(*t*-Bu)$_2$ and Pd(dba)$_2$ catalyzed the formation of diaryl ethers from aryl halides and phenols or phenoxides in good yields with sterically hindered or sterically unhindered unactivated aryl halides. To understand the chemistry of potential intermediates in these reactions, we prepared arylpalladium phenoxide complexes containing the FcP(*t*-Bu)$_2$ ligand. They undergo reductive elimination of diaryl ethers (25% yield), the first examples of these reactions with unactivated aryl groups on palladium. The reductive eliminations occur in quantitative yield when P(*t*-Bu)$_3$ is added in excess [35]. The relationship between this chemistry and that of the catalytic cycle is currently under investigation.

Remarkable improvements on C-N bond-forming reactions discussed above have been made by employing *t*-butylphosphine ligands and the appropriate ratio of ligand:catalyst precursor. First, use of a 1:1 ratio of commercially available P(*t*-Bu)$_3$ and Pd(dba)$_2$ provided rapid α-arylations of ketones (Eqn 6) [5]. These reactions occurred with aryl bromides at room temperatures in most cases and at only 50–70 °C with chloroarenes. In one case, we have observed 20 000 turnover numbers in 6–12 h of reaction time. Second, complexes formed from the same ligand:catalyst ratio catalyzed room-temperature aminations of aryl bromides with secondary alkylamines, secondary arylamines, and primary arylamines (Eqn 7) [36].

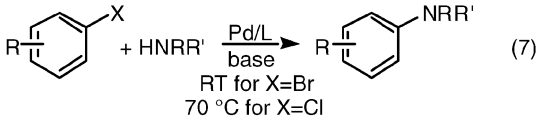


Scheme 2

Reactions with chloroarenes occurred at only 25–70 °C. Further, arylations of indoles occurred in only 6–8 h at 100 °C, and the first reaction of aryl halides with carbamates to prepare conveniently protected anilines occurred in good yields at 100 °C (Eqn 7).



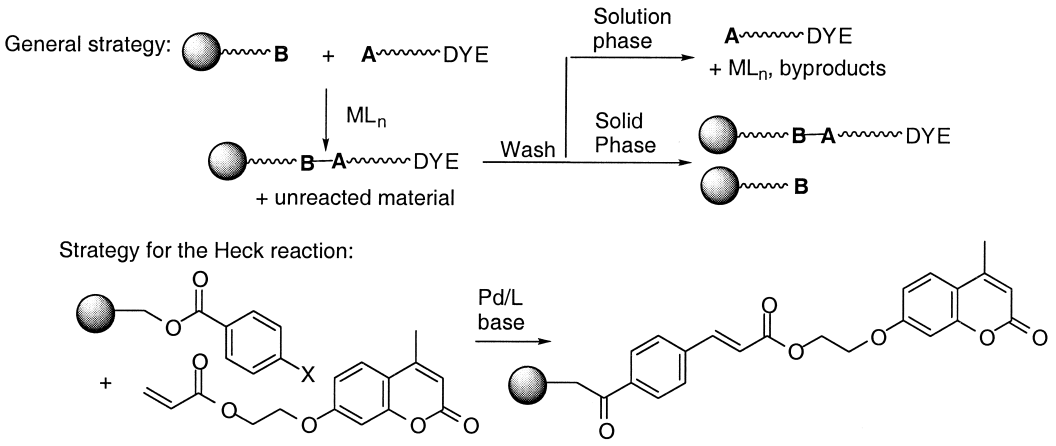
R= *o, m or p*- donating or withdrawing group; X=Cl, Br | R=alkyl, aryl, OEt; R'=alkyl, aryl, C(O)OEt | base=NaO-*t*-Bu; Pd=$Pd_n(dba)_m$, $Pd(OAc)_2$ | L=$P(t\text{-}Bu)_3$with 1:1 ratio of L/Pd



R= *o, m or p*- donating or withdrawing group; X=Cl, Br | HNRR'=2° amine, or arylamine | base=NaO-*t*-Bu; Pd=$Pd(dba)_2$ | L=$P(t\text{-}Bu)_3$, 1:1 with Pd

Several years ago the mechanistic analysis of palladium-catalyzed aryl amination suggested that chelating ligands should improve the relative rates for reductive elimination vs. β-hydrogen elimination. However, this analysis did not provide detailed information on which chelating ligand would be most effective. In addition, our studies on reductive elimination of amines and oxidative addition of aryl halides indicated the same reactive intermediate was involved in both processes, and the analysis in Fig. 1 suggested that sterically hindered phosphines would accelerate both addition and elimination steps of the cycle. However, it is unclear how large the ligands should be. The effectiveness of $FcP(t\text{-}Bu)_2$ would have been hard to predict. Thus, we have sought methods to screen catalysts for coupling reactions, and we hope these techniques can be used to assay for a variety of catalytic processes.

We have used fluorescent tags on one substrate and either a complementary tag or solid support on another to provide a rapid assay for covalent bond formation. One strategy using solid support is shown in Scheme 3 [37]. Using this strategy, we evaluated for the Heck reaction palladium catalysts containing the phosphine ligands we had prepared or purchased for our studies on carbon-heteroatom bond formation. An aryl halide was attached to Wang resin using standard, published methods. An acrylate with a tethered coumarin dye was prepared by simple synthetic methods. The reactions producing the most fluorescent beads contain the most active catalysts. The reactions were evaluated by isolating the beads using



Scheme 3

filtration or centrifugation and by visualizing them with a hand-held UV lamp typically used for TLC. We repeated this chemistry using an aryl chloride as substrate and catalysts containing both ligands selected by the assay for Heck reactions of aryl bromides and those that were structurally related. This screen showed that FcP(*t*-Bu)$_2$ was the most active catalysts for Heck reactions of aryl chlorides that do not contain bromide additives and that are conducted at 110 °C, instead of higher temperatures that are more typical for Heck reactions with aryl chloride substrates.

In summary, a variety of carbon-heteroatom bond-forming cross-coupling processes have been developed using a strategy of understanding mechanistic details of the reaction and using this information to select more active catalyst systems. To address the detailed structural questions that are difficult to address by mechanistic analysis, we have begun to develop colorimetric methods to detect the formation of covalent bonds by catalytic processes.

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