

Discovery and Understanding of Transition-Metal-Catalyzed Aromatic Substitution Reactions

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Abstract: This article presents studies on the development of cross-coupling reactions of aryl halides and sulfonates with amines, alkoxides, and various enolates. Emphasis is placed on the process of developing new catalysts with mechanistic information gained in the author's laboratory.

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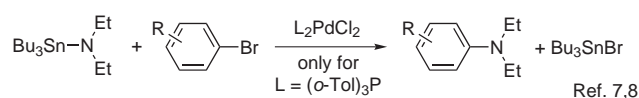
Key words: cross-coupling, palladium, amination, arylation, mechanism

1 Introduction

Nucleophilic aromatic substitution is a fundamental organic transformation. However, the scope of the direct reaction is narrow and the temperature for reaction of unactivated substrates is high. Mild, direct nucleophilic aromatic substitution requires highly electron-deficient aryl halides. Thus, alternative uncatalyzed methods have been studied to develop a net aromatic substitution process, such as reactions through aryne intermediates¹ or reactions occurring by radical nucleophilic substitution.^{2,3} Although these reactions are useful in some contexts, the scope of these stepwise, uncatalyzed methods is also narrow and the tolerance for accompanying functional groups is poor.

My group has sought transition-metal catalysts for nucleophilic aromatic substitution reactions that occur with both heteroatom nucleophiles and common enolate nucleophiles.^{4–6} As a result of these efforts, we have developed mild methods to prepare aromatic amines, ethers, sulfides, and α -aryl carbonyl compounds with phosphine-ligated palladium catalysts. Our work on metal-catalyzed aromatic substitution, or 'cross-coupling', stemmed from work by Kameyama, Kosugi and Migita from the early 1980's.^{7,8} These authors reported the coupling of electron-neutral aryl bromides with tin

amides derived from secondary amines in the presence of a palladium catalyst containing a sterically hindered aromatic phosphine (Equation 1). Although the scope of this prior work was also narrow, it demonstrated that palladium complexes could catalyze aromatic carbon–nitrogen bond formation.



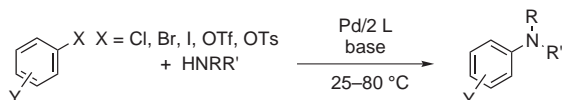
Equation 1

We were interested in developing methods that would expand the scope of this process and that would occur without tin reagents. Although we did not anticipate that the process would be as general and widely used as it has become, we did hope that these advances would create a process that is convenient enough to be useful for organic synthesis. We hoped to uncover catalysts that would be more active for the amination process and that could expand the scope to encompass primary amines, nitrogen nucleophiles other than amines, and related nucleophiles, such as alkoxides.

We were also interested in uncovering the elementary reactions of this catalytic process, including the step of the catalytic cycle that forms the carbon–nitrogen bond in the product. If the C–N coupling process followed a mechanism that was analogous to that for conventional C–C cross-coupling, then the carbon–nitrogen bond would be formed by a type of reductive elimination that was unknown when we started our work.^{9,10} We sought to use this type of mechanistic information on the catalytic process to design or select catalysts that would give rise to the desired increase in activity and scope of the process.

Due to the efforts of students and postdocs in my group, as well as work by many other groups, including the extensive work of Steve Buchwald's group at MIT,^{11,12} the scope of this reaction is now extremely broad. Equation 2 summarizes the types of catalysts now employed in the amination process and an overall view of the scope of the C–N coupling. With these catalysts, the amination reactions can be conducted with low loadings of catalyst, and can now be conducted with aromatic bromides, chlorides, triflates, in some cases with aryl iodides, and most recently with aryl tosylates. Both primary and secondary amines undergo this reaction, although the optimal catalyst for

these two classes of amines is often different. The reaction has been adopted for many types of applications, such as the synthesis of aromatic amines and nitrogen heterocycles for biological and medicinal applications, synthesis of sophisticated materials for electronic applications, and synthesis of anionic nitrogen ligands for applications in both asymmetric catalysis and the synthesis of polyolefins.



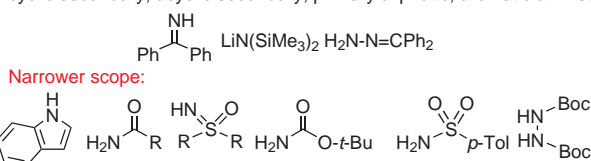
L = hindered monodentate ligands

$P(o\text{-Tol})_3$, $P(t\text{-Bu})_3$, $\text{Ph}_3\text{FCP}(t\text{-Bu})_2$ (Q-phos), heterocyclic carbenes, $(\text{Biaryl})\text{PR}_2$, $^-\text{OP}(t\text{-Bu})_2$, Solvias metallacycle, Verkade's phosphatranes or chelating bidentate ligands

DPPF, BINAP, Josiphos ligands, Xantphos

Broad scope:

cyclic secondary, acyclic secondary, primary aliphatic, aromatic amines



Equation 2

Biographical Sketch



John F. Hartwig was born in 1964 outside of Chicago, and was raised in upstate New York. He received a B.A. in 1986 from Princeton University, and a Ph.D. in 1990 from the University of California, Berkeley under the collaborative direction of Robert Bergman and Richard Andersen. After an American Cancer Society postdoctoral fellowship with Stephen Lippard, he began an appointment at Yale University in 1992, where he is now the Irénée P. duPont Professor of Chemistry. He and his wife Anne Baranger have recently accepted positions at the University of Illinois, where they will move during 2006 with their two daughters Pauline and Amelia. Professor Hartwig's research focuses on the discovery and understanding of new reactions catalyzed by

2 Early Reaction Development

The first synthetic advance was published concurrently by Steve Buchwald's group and by us^{13,14} and showed that the reaction could be conducted with amine nucleophiles in the presence of an alkoxide or silylamide base with the catalyst originally used by Kosugi and Migita for the coupling of tin amides. A wide variety of catalysts have now been evaluated for this reaction, and the current scope of this reaction is summarized in a broad sense in Equation 2. In addition to amines, some other nitrogen nucleophiles that are useful in synthetic applications undergo the coupling process with broad scope. For example, the reaction of ammonia equivalents, such as benzophenone imine^{15,16} and lithium hexamethyldisilylamide (LiHMDS),^{17,18} occur in good yield with many aromatic halides. Reactions of benzophenone imines and an alkoxide base are milder than those with the more strongly basic LiHMDS and can be conducted with ortho-substituted aryl halides, but the hydrolysis of the aromatic silylamide products is more facile. Benzophenone hydrazone also reacts with aryl halides with broad scope, and the products from these reactions are precursors to a variety of nitrogen heterocycles.^{19–22}

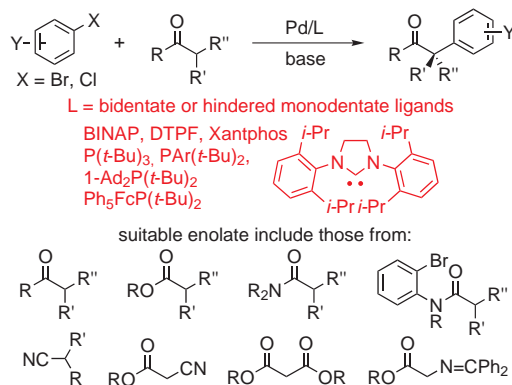
transition-metal complexes. He has developed a selective catalytic functionalization of alkanes, a method for formation of arylamines and aryl ethers from aryl halides or sulfonates, a method for the direct conversion of carbonyl compounds to α -aryl carbonyl derivatives, a system for the catalytic addition of amines to vinylarenes and dienes, and highly selective catalysts for the regio- and enantioselective amination of allylic carbonates. With each system, his group has conducted extensive mechanistic investigations. He has revealed several new classes of reductive eliminations, has isolated discrete compounds that functionalize alkanes, and has reported unusual three-coordinate arylpalladium complexes that are intermediates in cross-coupling.

In addition to the Thieme–IUPAC Prize in Synthetic Organic Chemistry, Professor Hartwig received the Leo Hendrik Baekeland Award in 2003, the A.C. Cope Scholar Award in 1998, the Camille Dreyfus Teacher-Scholar Award in 1997, a Union Carbide Innovative Recognition Award in 1995 and 1996, the National Science Foundation Young Investigator Award in 1994, and both Dupont and Dreyfus Foundation New Faculty Awards in 1992. He was the 1998 R.C. Fuson lecturer at the University of Illinois, the first AstraZeneca lecturer in Stockholm, and the 2001 Carl Ziegler lecturer at Mülheim. Most recently, he was named the 2006 recipient of the ACS Award in Organometallic Chemistry.

Several other nitrogen nucleophiles that participate in the coupling process are listed at the bottom of Equation 2. The scope of the coupling of these nucleophiles tends to be narrower, the amount of catalyst required for good yields tends to be higher, and the temperatures required for full conversion tend to be higher than those of reactions of amines. Although these substrates have diverse structures, their common feature is a nitrogen that is less basic and less nucleophilic. Thus, the transition-metal-catalyzed coupling process occurs with much broader scope than the uncatalyzed aromatic substitution but the reaction does remain somewhat sensitive to the electronic properties of the nitrogen nucleophile.

Consistent with this trend, the couplings to form carbon–oxygen bonds from aryl halides and alkoxides is challenging. Initially my group and Steve Buchwald's group published the coupling of alkoxides with electron-poor aromatic halides with catalysts containing aromatic bisphosphines such as BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] and DPPF [1,1-bis(diphenylphosphino)ferrocene].^{23–27} More recently, this process has been reported with aryl halides that are electron-neutral and lack activating groups.^{28–35} These etherifications have been accomplished with phosphine ligands that are extremely hindered. For example, we have reported the conversion of aryl halides to diaryl ethers and *tert*-butyl ethers with a ligand called Q-phos that contains five phenyl groups on one cyclopentadienyl ring of a di-*tert*-butylphosphino ferrocene unit.²⁹ Buchwald has reported the coupling of aryl halides with aryloxides and alkoxides,^{31,35} including those with hydrogens α to oxygen, with catalysts generated from biaryldialkyl phosphine ligands.

We have also developed the coupling of carbon nucleophiles that can be generated readily by deprotonation of a carbonyl compound or a nitrile. After obtaining a serendipitous preliminary result, we appreciated that the similar pK_a values of carbonyl compounds and amines could allow ketones, esters, amides and nitriles to undergo coupling with aryl halides under conditions that are analogous to those of the coupling of amines, and we began to develop the α -arylation of carbonyl compounds.^{36,37} Now, ketones, esters, amides, nitriles, 1,3-dicarbonyl compounds and cyano esters react with aryl halides and triflates in the presence of an appropriate base and palladium catalyst.⁶ Buchwald reported early examples of this reaction with BINAP as ligand³⁷ and we reported examples with a sterically hindered version of 1,1'-bis(di-*o*-tolylphosphino)ferrocene (DTPF).³⁶ Improved catalysts have been reported by various groups,^{38–40} including ours,⁴¹ with sterically hindered alkyl phosphines. Complexes generated from this class of ligands catalyze the reactions of the carbonyl compounds and nitriles shown at the bottom of Equation 3.

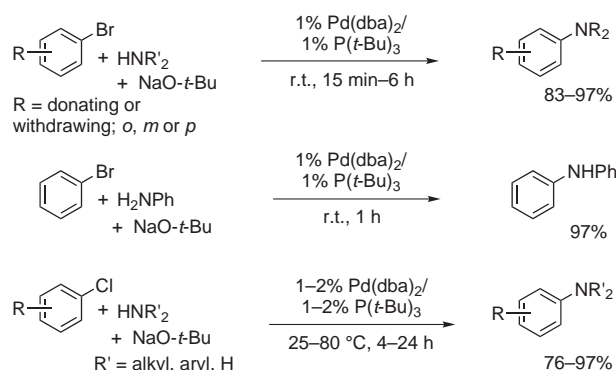


Equation 3

3 New Catalyst Developments

Substantial effort in my group has focused on using mechanistic principles to uncover improved catalysts for these coupling reactions. This approach led us to begin using bisphosphines, such as DPPF, for the catalytic process.⁴² In 1998, researchers at Tosoh Company in Japan reported that P(*t*-Bu)₃ catalyzed the amination of aryl halides with relatively high turnover numbers in refluxing xylenes.⁴³ As we began to explore the mechanism of this reaction, we quickly found that reactions conducted with a 1:1 ratio of P(*t*-Bu)₃ to Pd(dba)₂ occurred rapidly at room temperature.⁴⁴

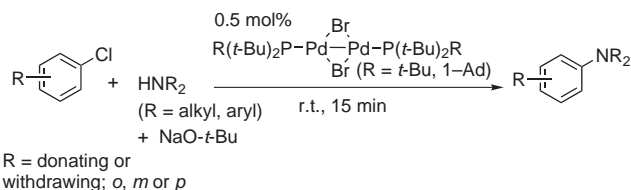
Scheme 1 summarizes our contribution to the amination of aryl halides with this ligand system. Reactions of secondary alkylamines, primary aromatic amines, or secondary aromatic amines occurred in good yields at room temperature with a variety of bromoarenes. Likewise, the reaction of aryl chlorides occurred under conditions that were milder than those with most catalysts reported previously, and the reaction with aniline was even accomplished at room temperature. However, this catalyst system is not particularly effective for the reactions of primary aliphatic amines.



Scheme 1

Considering that this catalyst contained a 1:1 ratio of P(*t*-Bu)₃ to palladium, a complex that already contains a 1:1 ratio of palladium to P(*t*-Bu)₃ that can rapidly undergo

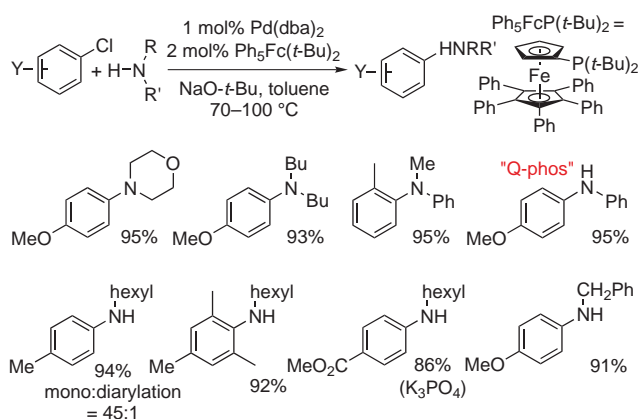
reduction to palladium(0) could lead to even faster reactions. Indeed, the dimeric palladium(I) complex in Equation 4 is spectacularly reactive for the amination of aryl chlorides and bromides.⁴⁵ The adamantyl di-*tert*-butylphosphine complex is more stable toward air and catalyzes these processes with slightly higher yields than the $P(t\text{-Bu})_3$ analogue. Yet, both of these complexes lead to the coupling of secondary aliphatic amines and arylamines with aryl chlorides within 15 min at room temperature with 0.5 mol% of the dimer. Of course, aryl bromides react as fast as aryl chlorides. Like reactions of primary amines catalyzed by the 1:1 ratio of $P(t\text{-Bu})_3$ and $Pd(dba)_2$, reactions of primary amines catalyzed by this dimer occurred in low yields.



Equation 4

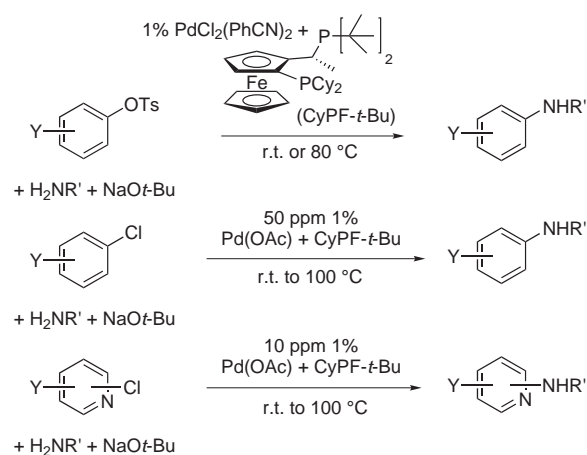
My group has also developed an extremely hindered ferrocenyl ligand that generates catalysts that react with broad scope for a variety of cross-coupling reactions.³⁰ Equation 5 presents the coupling of amines with aryl chlorides in the presence of catalysts containing this pentaphenylferrocenyl di-*tert*-butyl phosphine, which we call Q-phos after Quinetta Shelby who first prepared it. Complexes of this ligand react slightly slower than those of the tri-*tert*-alkylphosphines for the amination of aryl chlorides. However, complexes of this ligand catalyze the coupling of a broad scope of amines and aryl chlorides in high yields. As shown in Equation 5, complexes of this ligand catalyze the coupling of cyclic or acyclic secondary amines, including the difficult coupling of an acyclic secondary amine with an electron-rich aryl chloride. In addition, this complex catalyzes the coupling of both aromatic and aliphatic primary amines. The coupling of an unhindered aryl chloride with an unhindered amine without an excess of the primary amine is a difficult reaction to conduct with high selectivity because the product secondary amine can undergo arylation to generate a diaryl alkylamine. However, complexes ligated by Q-phos catalyze the selective monoarylation of a primary amine in high yield.

Finally, my group has uncovered palladium catalysts with a hindered bisphosphine that addresses many of the limitations on the reactions of aryl halides and sulfonates with primary amines. For reasons that will be discussed later in this manuscript, complexes with sterically hindered bidentate ligands are highly effective for the coupling of primary amines with aryl chlorides, heteroaryl chlorides, and aryl tosylates. With a large bite angle, rigid backbone and sterically demanding alkyl substituents, the Josiphos ligand containing one dicyclohexylphosphino and one di-*tert*-butylphosphino group generates a catalyst that in-



Equation 5

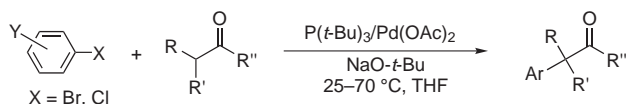
duces the coupling of primary amines with aryl and heteroaryl chlorides with remarkably high turnover numbers⁴⁶ and with aryl tosylates under unusually mild conditions.⁴⁷ A short summary of the reactions of aryl tosylates are shown in Scheme 2. Reactions of aryl and heteroaryl chlorides will be presented in detail at the close of this Account.



Scheme 2

Many of the factors that create an active catalyst for the amination of aryl halides also create an active catalyst for the α -arylation of carbonyl compounds. For example, the coupling of ketone enolates with aryl chlorides and bromides occurs under mild conditions in the presence of catalysts generated from a 1:1 ratio of $P(t\text{-Bu})_3$ and $Pd(OAc)_2$ (Equation 6).⁴¹ Aryl bromides of varying electronic and steric properties couple with acetophenone derivatives and two equivalents of base to generate at room temperature the monoarylation product. Reactions with one equivalent of base occur in high yield at the methylene positions of cyclic ketones, such as cyclohexanone, at the methylene positions of acyclic ketones, such as propiophenone, and at the methine positions of ketones, such as isobutyrophenone. When two types of enolizable hydrogens are present in the ketone, the reaction occurs

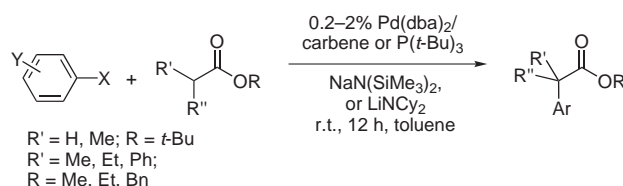
selectively at the less hindered of the two enolizable positions. Although our initially published work reported only a 3:1 ratio for arylation at the methylene position of ethyl isopropyl ketone, a change in solvent from THF to toluene led to a 12:1 ratio of these products. Further, changing the ligand from tri-*tert*-butyl phosphine to the sterically hindered, saturated *N*-heterocyclic carbene led to coupling of phenyl chloride with the same ketone to generate a single product at room temperature in 91% isolated yield. Reactions of aryl chlorides with the same types of ketones occurred with a 1:1 ratio of Pd(OAc)₂ and P(*t*-Bu)₃ in high yield after roughly 12 hours of reaction time at 70 °C.



Equation 6

The coupling of aryl halides with the enolates of esters is challenging because these enolates are less stable than those of ketones.^{48,49} Even reactions of aryl halides with the lithium enolates of *tert*-butyl acetate and *tert*-butyl propionate, which Rathke showed to be more stable than the enolates of less hindered esters,⁴⁹ occurred in modest yields with catalysts that required elevated temperatures. However, the high reactivity of catalysts generated from P(*t*-Bu)₃ and *N*-heterocyclic carbenes allows the catalytic coupling to occur much faster than the decomposition of the ester enolates.^{17,50} As summarized in Equation 7, The reaction of *tert*-butyl acetate and *tert*-butyl propionate with aryl bromides possessing a variety of electronic properties occurred in high yields. Reactions of *tert*-butyl acetate occurred fastest and in the highest yields with lithium dicyclohexylamide as base and a 1:1 combination of P(*t*-Bu)₃ and Pd(*dba*)₂ as catalyst.⁵⁰ Reactions of *tert*-butyl propionate occurred in the highest yields with the *N*-heterocyclic carbene as ligand.^{17,50} Reactions of methyl, ethyl, and benzyl esters that are disubstituted in the α -position occurred in high yields with LiNCy₂ as base and P(*t*-Bu)₃ and Pd(*dba*)₂ as catalyst.⁵⁰ Not only did the scope

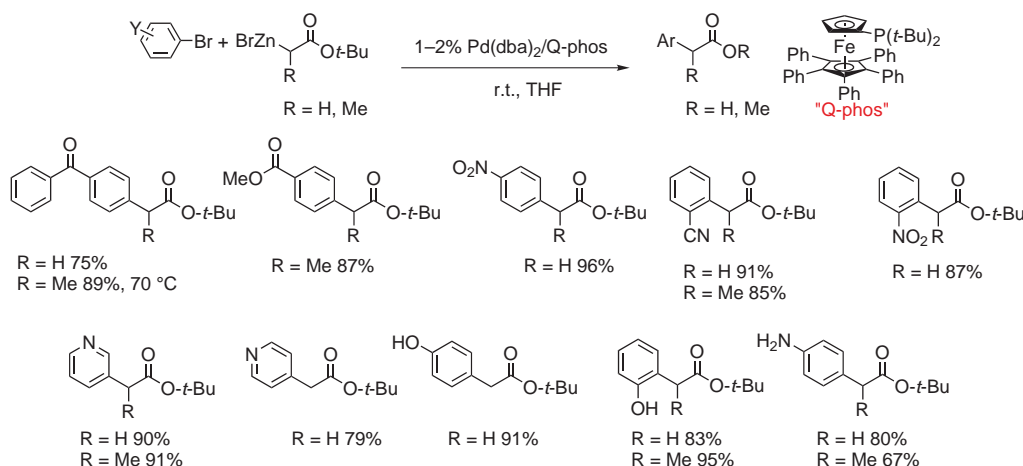
of these reactions encompass aryl halides with a range of electronic properties, but the reactions of pyridyl halides with α,α -disubstituted esters occurred in high yield. For reasons we do not yet understand, the reactions of pyridyl halides with alkali metal enolates of acetates and propionates did not occur.



Equation 7

Although the scope of these reactions encompasses aryl halides with a range of electronic properties, the basicity of the enolates limits the type of functional groups that are tolerated by this α -arylation chemistry. For example, reactions of substrates with electrophilic functionality, such as carbonyl, cyano and nitro groups, as well as substrates with enolizable hydrogens, did not occur in synthetically useful yields. Thus, we sought reactions of zinc and silicon enolates to improve functional group tolerance.

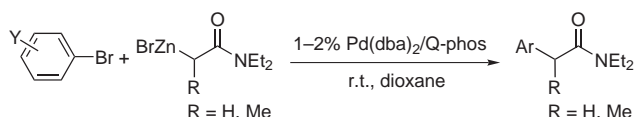
The use of zinc enolates has provided one solution to the problem of functional group tolerance in the reactions of enolates with aryl halides, as summarized in Equation 8.⁵¹ The reaction of a Reformatsky reagent, either isolated or generated in situ from the α -bromo ester and activated zinc metal, occurred with aryl halides possessing an array of functionality that was not tolerated by the reactions of alkali metal enolates. For example, the reactions of bromobenzophenone, bromo-4-methylbenzoate, 4-bromonitrobenzene and bromobenzonitriles all occurred in good yield with the zinc enolate generated from α -bromo *tert*-butyl acetate and *tert*-butyl propionate. These reactions occurred in the highest yields with the lowest catalyst loadings when the palladium catalyst was generated from Pd(*dba*)₂ and Q-phos.



Equation 8

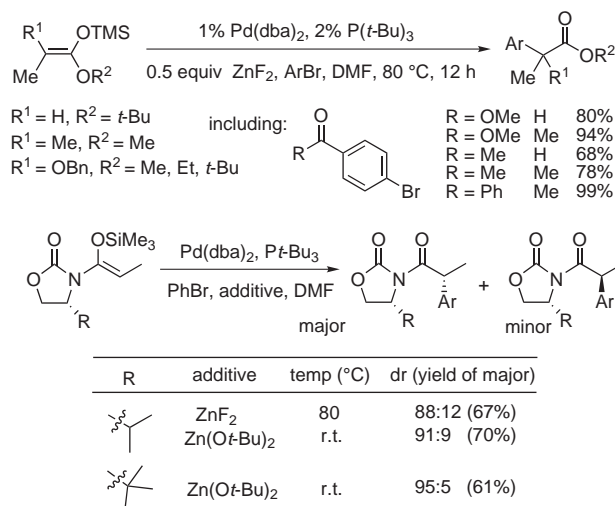
As shown in Equation 8, the scope of the α -arylation of ester enolates also included aryl halides with protic functionality and bromopyridines. The enolate of *tert*-butyl acetate reacted with 3- and 4-bromopyridines in good yields, and the enolate of *tert*-butylpropionate reacted with 3-bromopyridine in good yield. The zinc enolate of *tert*-butyl acetate and *tert*-butylpropionate also reacted with 2- and 4-bromophenol and 4-bromoaniline. These reactions were accomplished with either two equivalents of the enolates or one equivalent of KH, followed by one equivalent of the enolate.

The coupling of aryl halides with the alkali metal enolates of amides occurred in synthetically useful yields in some cases, but the scope and typical reaction yields were much narrower than those of the reactions of alkali metal enolates of ketones and esters.⁵² Thus, we have recently reinvestigated the α -arylation of amides, and have found that the reactions of zinc enolates of amides occur in higher yields (Equation 9).⁵¹ Although we do not have a precise explanation for the lower yields and narrow scope for the reactivity of the alkali metal enolates of amides, the high basicity of the reaction medium and the relative pK_a values of acetamides and α -aryl acetamides lead to decomposition of the catalyst and to competing formation of products from diarylation. In contrast, the reactions of the zinc enolates of acetamides occur in high yields with broad functional-group tolerance and without formation of products from diarylation. Thus, the zinc enolate of diethyl acetamide and diethyl propionamide (Equation 9) occurred in good yields, not only with an electron-neutral aryl bromide such as 4-bromo-*tert*-butyl benzene, but with aryl bromides that failed to react with the lithium enolates of amides, such as bromobenzoates, bromonitroarenes, and bromobenzonitriles.



Equation 9

Clearly, silicon enolates could react with even higher functional group tolerance than zinc enolates, and the enolates could be formed directly from the carbonyl compound. Xiaoxiang Liu surmised that addition of zinc fluoride would transform the silicon enolates to zinc enolates, which might react as just described. The origin of the effect of the zinc fluoride or zinc *tert*-butoxide additive is likely to be different than that originally proposed, but this combination of silicon enolate and zinc additive did react with aryl halides in the presence of palladium and P(*t*-Bu)₃ as catalyst, as summarized in Scheme 3.^{51,53} Unlike the reactions of alkali metal enolates, these reactions occurred in highest yields in a polar solvent such as DMF at 80 °C over 12 h. In addition to improving the tolerance of functional groups on the aryl halide, this procedure allowed the α -arylation of α -alkoxy esters that failed to couple, as their alkali metal enolates, with aryl halides.



Scheme 3

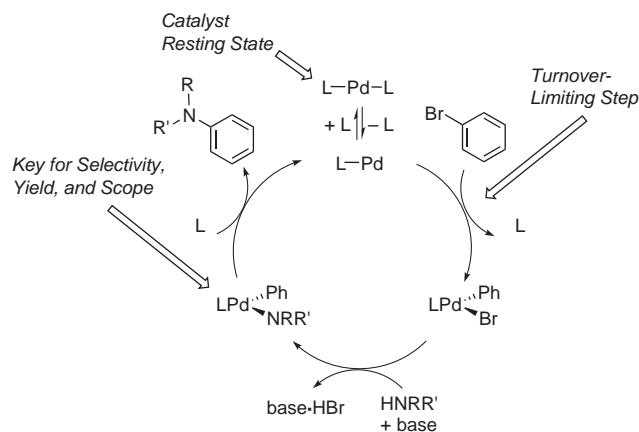
The stereochemistry of the carbon α to the carbonyl group in products generated from the silicon enolates are stable to the reaction conditions because of the low basicity of these enolates.⁵³ As shown at the bottom of Scheme 3, the silyl ketimine that bears an Evans auxiliary reacted with aryl halides diastereoselectively in the presence of the palladium catalyst. Further, the ratio of diastereomers results from a kinetic selectivity. The ratio of diastereomers was constant throughout the reaction, and no epimerization of the pure diastereomer of a related compound, which was added to the reaction as a probe of the basicity of the medium, occurred. Further, trimethylsilyl enolates of the reagents developed by Ley react with aryl halides to generate products of very high diastereomeric purity.

4 Mechanism of the Cross-Coupling Processes

Catalytic cross-coupling processes typically occur in three stages: oxidative addition of an aryl halide to a palladium(0) complex, reaction of the aryl halide complex with a nucleophile to generate an intermediate with the nucleophile bound to palladium, and reductive elimination to couple the aryl group and the nucleophile and to regenerate the palladium(0) complex. Each of these three stages is a multi-step process often involving ligand dissociation prior to the elementary oxidative addition, transmetalation and reductive elimination steps.

Scheme 4 highlights several features of this general mechanism that should be considered when rationalizing reactivity or when designing or selecting ligands for cross-coupling. First, the rates of reactions of aryl chlorides and of most reactions of aryl bromides are controlled by the rate of oxidative addition. Thus, the phosphine-ligated palladium(0) complex is the catalyst resting state,⁵⁴ and efforts to accelerate the rates of the cross-coupling chemistry must focus on increasing the rate of oxidative addition. However, the yields and scope of the reaction are generally controlled by the reductive elimination. The reductive elimination step must be faster than side reac-

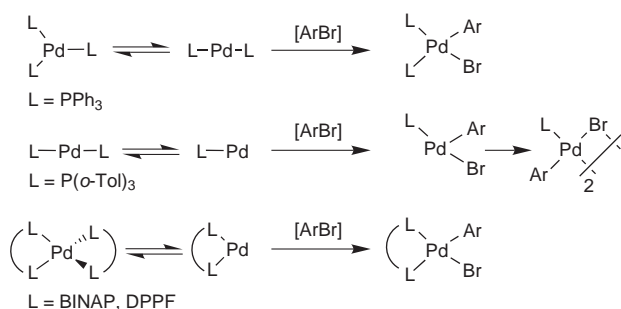
tions such as β -hydrogen elimination, protonolysis of the metal amide, alkoxide or enolate intermediate or disproportionation of the aryl palladium complexes to form biaryl complexes that undergo reductively elimination of biaryl. We have studied the mechanism of each of the three stages of the catalytic amination of aryl halides and α -arylation of carbonyl compounds.



Scheme 4

5 Mechanism of Oxidative Addition

Scheme 5 summarizes the mechanism of oxidative addition of aryl halides to several phosphine-ligated Pd(0) complexes. Fauvarque and Amatore^{55,56} independently showed that oxidative addition of aryl halides to triphenylphosphine-ligated palladium(0) occurs after dissociation of ligand from $(\text{PPh}_3)_3\text{Pd}$ to generate linear $(\text{PPh}_3)_2\text{Pd}$. This intermediate then undergoes the cleavage of the carbon-halogen bond to generate $(\text{PPh}_3)_2\text{Pd}(\text{Ar})(\text{X})$. We showed that palladium(0) complexes with extremely hindered phosphines, such as $\text{P}(o\text{-Tol})_3$ or Q-phos, which are stable in their two-coordinate geometry, undergo oxidative addition of aryl halides after dissociation of phosphine.^{57,58} The three-coordinate product from this oxidative addition then dimerizes to form the stable product when the ligand is $\text{P}(o\text{-Tol})_3$.



Scheme 5

We have also shown that the major pathway for oxidative addition to palladium(0) complexes of bis-phosphines, such as BINAP and DPPF, occurs by full dissociation of

the chelating ligand to generate a bent two-coordinate complex prior to oxidative addition.⁵⁹ A minor pathway for addition to $[\text{Pd}(\text{BINAP})_2]$ and presumably $[\text{Pd}(\text{DPPF})_2]$ occurs by reaction of the aryl halide with $[\text{Pd}(\kappa^2\text{-bisphosphine})(\kappa^1\text{-bisphosphine})]$, most likely by displacement of the κ^1 -ligand by the aryl halide to generate $[\text{Pd}(\text{BINAP})(\text{ArX})]$ or $[\text{Pd}(\text{DPPF})(\text{ArX})]$ that precedes oxidative addition. The bent two-coordinate palladium(0) complexes are less stable than the linear species and, in the bent conformation, project orbitals that are appropriate to interact with the incoming aryl halides.

Others have suggested that the amine coordinates to the palladium(0) species and that the amine complex undergoes oxidative addition faster than the two-coordinate palladium(0) species.⁶⁰ If so, then the order in which the nucleophile and aryl electrophile react in the amination of aryl halides would be different from the order in which they react in other types of cross-coupling, and previous conclusions about the species that add haloarenes would require reconsideration. This assertion was based on kinetic modeling of rate data obtained by calorimetry on reactions conducted with a catalyst generated in situ. During the past few years, we have shown that the rate of oxidative addition to $[\text{Pd}(\text{BINAP})_2]$ is much less than first order in amine,⁶¹ and that the catalytic reaction shows no positive order in amine.⁶² More than two years after the original submission of these data, the results of this work have been published.^{61,62} The apparent order in amine measured under the conditions of the catalytic system resulted from catalyst decomposition.

The effect of steric hindrance on the oxidative addition of aryl halides is summarized in the energy diagram in Figure 1. The unsaturated reactive intermediate lies uphill from the starting palladium(0) complex, but reaction of this intermediate with the aryl halide generates a stable arylpalladium halide complex. The largest difference between the starting palladium(0) species and the reactive intermediate is the coordination number. Thus the presence of more hindered ligands on the palladium(0) complex will increase the energy of the ground state more than they will increase the energy of the low-coordinate palladium(0) intermediate. As a result, the difference in energy between the ground state and the reactive intermediate will be smaller when more hindered ligands are bound to the palladium(0) than when less hindered ligands are bound to the palladium(0).

Two examples presented in Scheme 6 demonstrate the dramatic acceleration of the rate of oxidative addition by complexes of hindered monodentate ligands. First, the oxidative additions of aryl bromides to palladium(0) ligated by tri-*tert*-butylphosphine are much faster than additions to those with less hindered ligands.^{63,64} For example the oxidative addition of phenyl bromide to a combination of $\text{Pd}(\text{dba})_2$ and $\text{P}(t\text{-Bu})_3$ occurs at room temperature within minutes, whereas the oxidative addition of phenyl bromide to the bisphosphine-ligated palladium(0) requires 70 °C and several hours.⁶⁵ The products from oxidative addition of phenyl bromide to

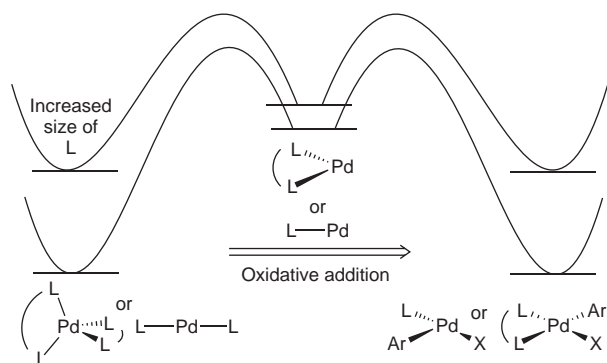


Figure 1

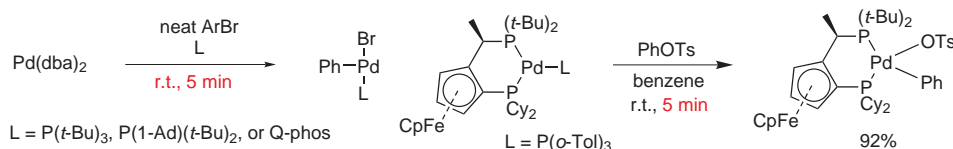
the combination of $\text{Pd}(\text{dba})_2$ and $\text{P}(t\text{-Bu})_3$ have unusual coordination geometries with only three heavy atoms bound to the metal.^{63,64}

Second, reactions of phenyl tosylate with the palladium(0) complexes of a very hindered Josiphos ligand with one *tert*-butylphosphino and one dicyclohexylphosphino group (CyPF-*t*-Bu) occur within minutes at room temperature.^{47,66} Considering that no oxidative additions of aryl tosylates have been published previously and previous palladium-catalyzed couplings of aryl tosylates have required activated substrates or high temperatures, the room-temperature oxidative addition of phenyl tosylate by the palladium(0) complex is remarkable.

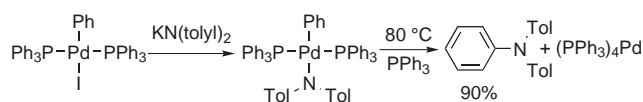
6 Reductive Elimination of Amines

As noted in Scheme 4, reductive elimination controls the scope and yields of the catalytic amination of aryl halides. When my group began studying the coupling of amines with aryl halides, no examples of reductive elimination of amines from a transition metal complex were known. Yet, today, this reaction occurs with many types of anionic nitrogen ligands and with a broad scope of aryl and vinyl groups.

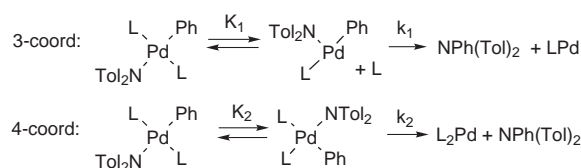
Initially, we studied the reductive elimination of arylamine from arylpalladium amido complexes ligated by triphenylphosphine (Scheme 7). As one representative example, arylpalladium diarylamido compounds underwent reductive elimination of triarylamines in good yields at 80 °C.^{67,68} Kinetic studies of the reaction of this complex and related anilido and alkylamido complexes showed that reductive elimination occurred by two concurrent pathways: fast reductive elimination from a three-coordinate arylpalladium amido complex and slower reductive elimination from a *cis* four-coordinate complex.



Scheme 6



Kinetic Studies Show Two Concurrent Mechanisms

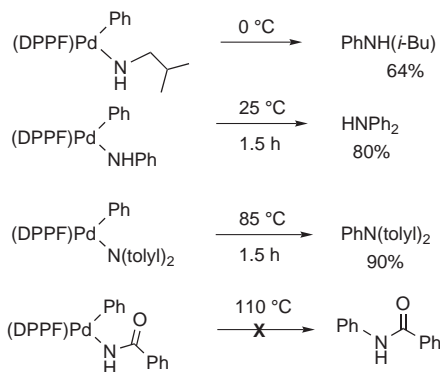


Scheme 7

To confirm the kinetic data that implied that reductive elimination occurred from four-coordinate complexes, we prepared a series of arylpalladium complexes ligated by bisphosphines. The DPPF complexes underwent reductive elimination of aryl amines in good yields⁴² and, for this reason, we began to investigate coupling of amines with aryl halides catalyzed by palladium complexes bearing chelating phosphines. The studies on the reductive eliminations to form C–N bonds summarized in Scheme 8 revealed several principles.

First, the clean formation of amine confirmed that C–N bond-forming reductive elimination can occur from a four-coordinate palladium complex. Second, the relative rates of reactions of complexes with different amido groups showed that reductive elimination was faster from complexes with more electron-donating groups on nitrogen than from complexes with more electron-withdrawing groups on nitrogen.^{42,68} For example, the reductive elimination of *N*-alkylarylamines from an alkyl amido complex occurred over several hours at 0 °C, whereas the reductive elimination of triaryl amine from a ditolylamido complex required several hours at 65 °C and the reductive elimination of the benzamidate complex did not occur under any conditions. Third, reductive elimination was faster from complexes with more electron-poor aryl groups bound to palladium.⁶⁸ Taken together with the studies of the electronic effects of substituents at nitrogen, these studies showed that the pairing of an electron-rich nitrogen ligand and an electron-poor aryl group leads to the fastest reductive elimination. Although the reason for this effect is likely to be complex, one can consider that this trend could result from a favorable pairing of a nucleophilic nitrogen ligand and an electrophilic aryl group. Finally, arylpalladium amido complexes with chelating ligands undergo reductive elimination faster than they undergo β -hydrogen elimination.^{42,68} We showed that β -hydrogen elimination from square-planar amido complexes occurs after the generation of a three-coordinate amido

complexes.^{69,70} Thus, complexes with chelating bidentate ligands undergo slow β -hydrogen elimination, but undergo reasonably facile reductive elimination. This retardation of the rate of β -hydrogen elimination leads to better selectivity in the catalytic process for formation of aryl amines over the formation of arenes by the combination of β -hydrogen elimination of the amide to generate a palladium hydride and reductive elimination of arene.

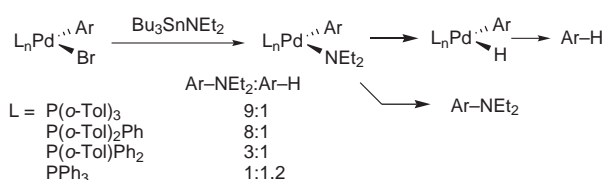


Scheme 8

Results presented in the early sections of this paper show that the scope of the coupling to form C–N and C–O bonds is broader with catalysts containing sterically hindered phosphines than with complexes containing less hindered ligands. The origin of this effect can be interpreted in terms of the energy diagram in Figure 1. The reductive elimination reaction begins with a four- or three-coordinate palladium complex and generates the combination of amine and a two- or one-coordinate intermediate that is likely to be higher in energy than the starting arylpalladium amide complex. Trapping of the unsaturated palladium(0) intermediate with phosphine would then generate a stable palladium(0) species. Sterically hindered ligands on the metal center will, again, increase the energy of the reactant more than they increase the energy of the low-coordinate reactive intermediate. Therefore, reductive elimination occurs faster from complexes with more hindered ligands.

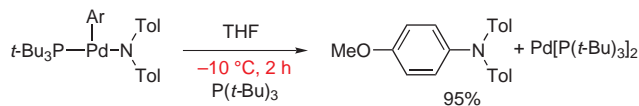
Sterically hindered ligands also enhance the relative rates for reductive elimination over β -hydrogen elimination.⁷¹ Reductive elimination reduces the coordination number of the metal, but β -hydrogen elimination either increases the coordination number or leaves the coordination number unchanged. Thus, sterically hindered ligands will accelerate reductive elimination, but will retard β -hydrogen elimination. As a result, catalysts with hindered ligands will react with better selectivity for the formation of amines versus the formation of arenes. This trend is illustrated by the selectivity of catalysts containing arylphosphines of varied size, summarized in Scheme 9.

The reaction in Equation 10 illustrates the magnitude of the effect of sterically hindered phosphines on the rate of reductive elimination. The three-coordinate arylpalladium ditolylamido complex with $P(t\text{-Bu})_3$ as ligand underwent



Scheme 9

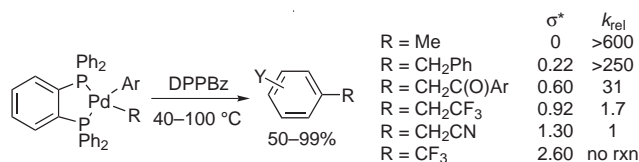
reductive elimination of triarylamine over about two hours at $-10\text{ }^\circ\text{C}$.⁷² Analogous complexes ligated by DPPF or by triphenylphosphine required temperatures in the range of $80\text{ }^\circ\text{C}$ to undergo reductive elimination on the same time scale.



compare to $80\text{ }^\circ\text{C}$, 2 h for DPPF complexes

Equation 10

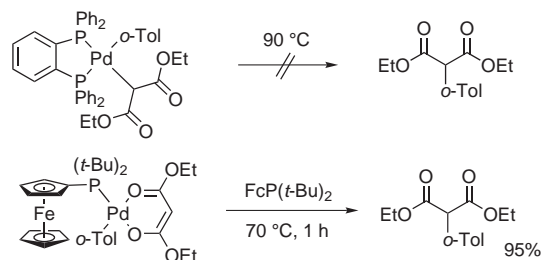
We have conducted related studies on the reductive elimination from a series of arylpalladium alkyl complexes containing alkyl groups with varied electronic properties (Equation 11).^{73,74} These reactions are much less sensitive to electronic effects than the reductive elimination to form carbon–oxygen or carbon–nitrogen bonds. For example, the aryl palladium complexes of enolates derived from amides, esters and ketones underwent reductive elimination with rates that were indistinguishable. These studies show that the reductive elimination to form a carbon–carbon bond involves a transition state that is less polar than the reductive elimination to form a carbon–nitrogen or carbon–oxygen bond. We also showed that the stability of the main group metal enolates more likely controls the yields of these reactions than the chemistry of the palladium enolates. Moreover, we showed that the selectivity for reaction at the less hindered position of a ketone with two different types of enolizable hydrogens is derived from the greater thermodynamic stability of the complex of the less hindered enolate. Because the rates of reductive elimination from the two enolates are similar, the ratio of products is controlled predominantly by the thermodynamic stability of the enolate complexes.



Equation 11

Although less sensitive to electronic effects than the C–N or C–O bond-forming reductive eliminations, the rates of C–C bond-forming reductive eliminations can be large enough to control the scope of the catalytic arylation of enolates and the anions of nitriles. For example, arylpalladium complexes of the anions of nitriles undergo

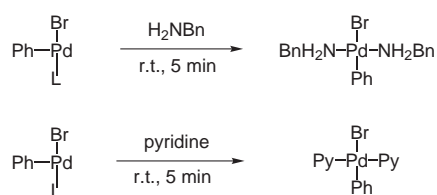
reductive elimination more slowly than arylpalladium complexes of enolates because the cyano group is more electron-withdrawing than an acyl group. Moreover, complexes with two electron-withdrawing groups on the α -carbon, such as the complexes of the anion of a malonate, require hindered ligands on the metal to undergo reductive elimination (see Scheme 10). In broad terms, the rate of reductive elimination from complexes with a functional group on the α -carbon can be predicted from the Taft substituent parameter of the functional group.⁷⁴



Scheme 10

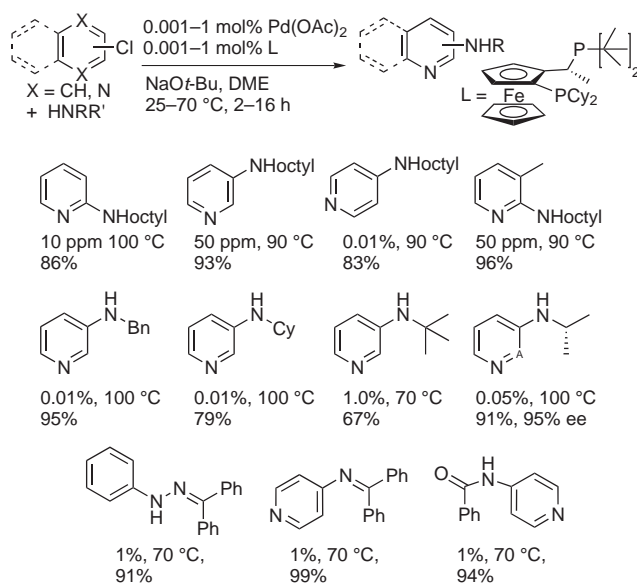
7 Stable Palladium Catalysts for Coupling of Primary Amines: Identification and Reduction of One Process that May Limit Turnover Numbers

The low coordination number of the palladium complexes with sterically hindered ligands leads to high reactivity, but this low coordination number may also be an Achilles heel. We have shown that $\{Pd[P(t-Bu)_3](Ar)(Br)\}$, which would be an intermediate in the coupling of aryl bromides with catalysts containing $P(t-Bu)_3$ as ligand, reacts with pyridine and with amines to displace the phosphine ligand and generate four-coordinate palladium complexes with two pyridine or amine ligands (Scheme 11). These pyridine and amine complexes are inactive for the coupling of aryl chlorides.



Scheme 11

Based on this information, we proposed that sterically hindered, bidentate phosphines would generate highly active catalysts for the coupling of aryl chlorides, bromides and tosylates but would resist deactivation by the replacement of the ligand by amines or basic nitrogen heterocycles. Indeed, the combination of palladium acetate and CyPF-*t*-Bu generates a spectacularly reactive catalyst for the coupling of primary nitrogen nucleophiles with aryl and heteroaryl halides.⁴⁶ Three sets of recently reported reactions are summarized in Equations 12–14.⁴⁶

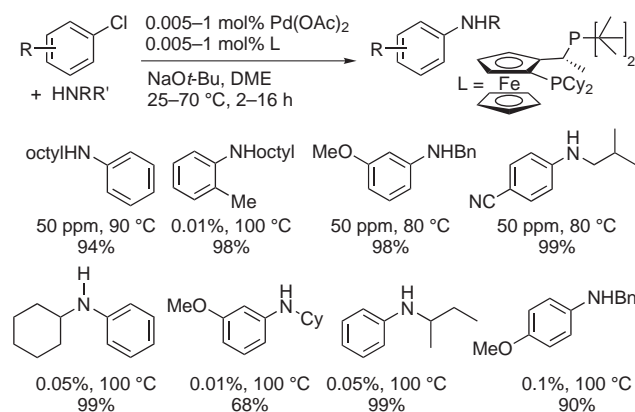


Equation 12

Our initial efforts were directed at finding a catalyst for mild coupling of heteroaryl halides. Reactions of primary amines such as octylamine, benzylamine, isobutylamine, cyclohexylamine and *tert*-butylamine occurred with 2-, 3-, and 4-chloropyridine in high yields as shown in Equation 12. In many cases these reactions occurred with catalyst loadings as low as 10–50 ppm for a 1:1 ratio of palladium and ligand. Although we have not yet determined the minimum amount of catalyst necessary for reactions of pyridyl chlorides with other types of nitrogen nucleophiles, we have shown that other primary nitrogen nucleophiles, such as benzophenone hydrazone, benzophenone imine, and benzamide react with halopyridines to give the coupled products in high yields.

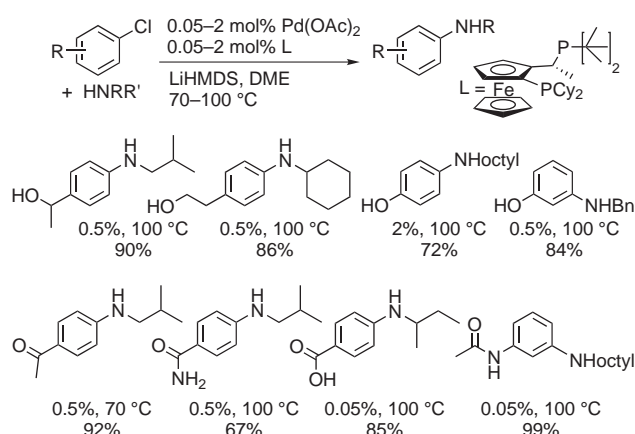
This catalyst is also highly reactive for the coupling of chloroarenes. The reactions of primary amines with unactivated chloroarenes occurred with low loadings of a 1:1 ratio of $Pd(OAc)_2$ and CyPF-*t*-Bu under mild conditions, as summarized in Equation 13. For example, the prototypical reaction of octylamine with phenyl chloride occurred in high yield with only 50 ppm catalyst. This yield and catalyst loading correspond to nearly 19,000 turnovers, and this value is about two orders of magnitude higher than the reaction of a primary amine with an aryl chloride in the presence of any other catalyst. The reactions of aliphatic amines that are branched α to nitrogen, and the reactions of benzylamine, also formed the coupled product in good yield with much less catalyst than has been used previously.

Finally, we have shown that this combination of metal and ligand will catalyze the reactions of primary amines with aryl halides containing the diverse array of functional groups shown in Equation 14. These reactions were conducted under the conditions with $LiN(SiMe_3)_2$ as base to deprotonate protic groups.^{75,76} For example, the reactions of aryl halides bearing pendant primary or secondary alcohols, halophenols, aryl halides with enolizable



Equation 13

hydrogens, aryl halides with unprotected primary amides, aryl chlorides with free carboxylic acids, and chloro *N*-arylacetamides all reacted with primary amines in high yields.



Equation 14

8 Guidelines for Catalyst Selection

This mechanistic information provides a basis to understand the scope and the types of catalyst that are most effective for reactions of the different aryl halides with oxygen, nitrogen, or carbon enolate nucleophiles. For example, mild reactions of unactivated aryl chlorides occur with catalysts containing phosphines with sterically hindered alkyl substituents, but reactions of aryl bromides occur with catalysts containing triarylphosphines. Further, different types of catalyst are most active for the reactions of secondary amines and primary amines. The additional steric hindrance of secondary amines accelerates the rate of reductive elimination versus β -hydrogen elimination, and many complexes with sterically hindered monodentate ligands catalyze the coupling of aryl halides with secondary amines. However, primary amines generate amido complexes that undergo reductive elimination slower than those generated from secondary amines. Thus, β -hydrogen elimination more often competes with reductive elimination during coupling of aryl halides with

primary amines. Further, primary amines bind more tightly to palladium(II) than do secondary amines, and the primary amines can poison catalysts with labile phosphines by displacement of the ligand. Thus, catalysts containing bidentate ligands can be more reactive toward coupling of primary amines than catalysts containing monodentate ligands, and complexes of the most sterically hindered version of the Josiphos ligands, CyPF-*t*-Bu, catalyze the coupling of aryl bromides, chlorides and tosylates with primary nitrogen nucleophiles in high yields and with extremely high turnover numbers in many cases.

Although the origin of electronic effects can be rationalized in many ways, reductive eliminations from complexes containing less electron-donating groups bound to palladium are slower than reductive eliminations from complexes with more electron-donating groups bound to palladium. Catalysts containing sterically hindered monodentate phosphines, which accelerate the rate of reductive elimination, expand the scope of coupling reactions of the less electron-rich substrates by accelerating the rate of reductive elimination enough to make this desired step faster than competing reactions that lead to undesired side products.

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