Amination Reactions of Aryl Halides with Nitrogen-Containing Reagents Mediated by Palladium/Imidazolium Salt Systems

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Nucleophilic N-heterocyclic carbenes have been conveniently used as catalyst modifiers in amination reactions involving aryl chlorides, aryl bromides, and aryl iodides with various nitrogen-containing substrates. The scope of a coupling process using a Pd(0) or Pd(II) source and an imidazolium salt in the presence of a base, KO^{t}Bu or NaOH, was tested using various substrates. The $Pd_2(dba)_3$/IPr·HCl (**1**, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) system presents the highest activity with respect to electron-neutral and electron-rich aryl chlorides. The ligand is also effective for the synthesis of benzophenone imines, which can be easily converted to the corresponding primary amines by acid hydrolysis. Less reactive indoles were converted to *N*-aryl-substituted indoles using as supporting ligand the more donating SIPr·HCl (**5**, SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene). The $Pd(OAc)_2$/SIPr·HCl/NaOH system is efficient for the N-arylation of diverse indoles with aryl bromides. The general protocol developed has been applied successfully to the synthesis of a key intermediate in the synthesis of an important new antibiotic. Mechanistically, palladium-to-ligand ratio studies strongly support an active species bearing one nucleophilic carbene ligand.

Introduction

Palladium-catalyzed synthesis of N-substituted anilines using aryl halides or halide equivalents has proven to be a very useful and versatile method in organic synthesis.[1] The *N*-aryl moiety represents an important motif in natural products[2a] and pharmaceutical and medicinal compounds,[2b] as well as in polymers and materials.[3−6] Early development of *N*-aryl synthesis proved to be quite difficult and limited in generality.[7] Consequently, transition-metal-assisted amination of aryl halides has developed in the past few years as a most viable and direct method leading to the synthesis of a large variety of substituted amines.[8] Studies by Hartwig and Buchwald on catalytic amination have shown that metal−supporting ligation plays a crucial role in dictating the efficiency of the catalytic system.[8] To this end, bulky monodentate phosphine or bidentate PX (X = P, N, O) ligands are usually employed.[8,9] Ligand properties make possible the activation of inexpensive aryl chlorides as partners in amination reaction.[9] However, despite their effectiveness in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis,[10] tertiary phosphines are often air-sensitive and are subject to P−C bond degradation at elevated temperatures. As a consequence, the use of higher phosphine concentration in such catalytic processes is often required.[11]

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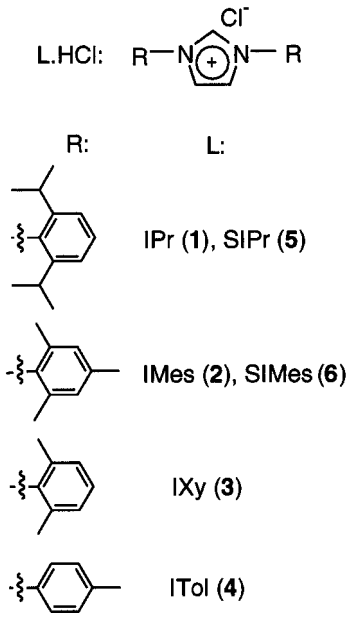
With the isolation of free N-heterocyclic carbenes in 1991 by Arduengo et al.[12] and the use of these compounds as ancillary ligation in homogeneous catalysis, this area of catalysis represents a rapidly developing field. Early studies have shown that nucleophilic N-heterocyclic carbenes[13] represent a very versatile class of ligands, mimicking tertiary phosphines, as they act as two-electron donors and their steric and electronic properties can be modulated by appropriate substitution on the heterocyclic nitrogen atoms.[14] A solution calorimetric study of nucleophilic carbenes aimed at determining steric and electronic properties of a series of these ligands allowed us to better understand/quantify these effects.[15] The nucleophilic carbene ligands appear to have several advantages over commonly utilized phosphines: (i) metal complex stabilizing effect, (ii) improved thermal stability, (iii) metal complex resistance to ligand dissociation. These factors reveal that the use of stoichiometric amounts of ligand as excess is not required in order to prevent aggregation of the catalyst, which yields bulk metal.[13c] As a consequence of these attractive features, the number of catalytic reactions making use of nucleophilic carbenes as catalyst modifiers is increasing. Specific examples are the use of metal−carbene complexes in hydrosilylation,[16] Ru-catalyzed furan synthesis,[17] and olefin metathesis.[15a,18] A most successful application of carbenes as supporting ligands is their role in various C−C couplings involving aryl halides. We have successfully employed these ligands in Stille,[19] Suzuki−Miyaura,[20] Kumada,[21] and Hiyama[22] couplings. Reports by Fu, Hartwig, and Buchwald on the use of metal centers modified by donating, sterically demanding phosphine ligands directed us to test bulky electron-donating carbenes as ligands and catalyst modifiers in the amination reaction. An account of early catalytic amination results has appeared.[23] We now present a broader study into the use and applications of the nucleophilic carbene ligands as ancillary ligands in the amination reaction.

Scheme 1. Imidazolium Chloride Ligands



Results and Discussion

From solution calorimetry experiments we now have a clearer picture of the reasons behind the stabilizing effects of nucleophilic N-heterocyclic carbenes on organometallic systems. We have most recently focused our efforts on palladium-mediated processes that appear to benefit from the use of sterically demanding, electron-donating ligands. These electron-rich systems permit the use of aryl chlorides as partners in cross-coupling reactions. The use of aryl chlorides in coupling chemistry has proven difficult but would economically benefit a number of industrial processes.[24] We now present a study on palladium-mediated aryl amination dealing with ligand effects and functional group tolerance.

Effect of the Ligand on the Amination of 4-Chlorotoluene with *N*-Methylaniline. Considering the major effect of the use of bulky carbene ligands in the related C−C bond formation processes discussed above, we wondered if catalytic amination could be performed with the help of a judiciously selected bulky imidazolium salt. On the basis of our recent success with IMes·HCl[25] (**2**, IMes 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and IPr·HCl[21] (**1**, IPr 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as ancillary ligand precursors in cross couplings involving aryl chlorides, a similar protocol was used to perform the amination of aryl chlorides. In an effort to select the most effective imidazolium salt, a number of 1,3-aryl-substituted imidazolium chlorides (Scheme 1, **1**−**4**) were used in a model reaction (Table 1).

The bulky (vide infra) IPr·HCl (**1**) was found to be the most effective imidazolium salt examined, leading to isolation of the coupled product in a 98% isolated yield (Table 1, entry 5). All other imidazolium salts (**2**−**4**) that were investigated required longer reaction times to

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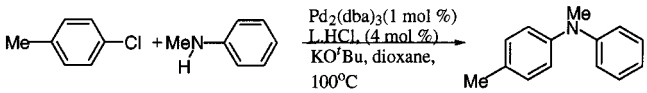
Table 1. Amination of 4-Chlorotoluene Using Different Imidazolium Chlorides



entry	L	time (h)	yield[a] (%)
1	none	3	NR
2	ITol (**7**)	3	<5
3	IXy (**6**)	3	11
4	IMes (**2**)	3	22
5	IPr (**3**)	3	98

[a] Isolated yields are the average of two runs.

achieve complete consumption of the aryl chloride and afforded lower yields.[26]

Susbstitution Patterns in Reactions of Aryl Chlorides with Various Amines. A survey of catalytic cross-coupling of aryl halides with primary and secondary cyclic or acyclic amines using IPr·HCl (**1**) as the supporting ligand is provided in Table 2. The role of the added base KO^{t}Bu is 2-fold: it initially deprotonates the imidazolium chloride to form the free carbene ligand in situ, which can then coordinate to Pd(0). It also serves as a strong base to neutralize the HX formed in the course of the coupling reaction. This catalytic system proved to be general and efficient as shown by results presented in Table 2.

The less reactive unactivated aryl chlorides reacted with various amines including primary (Table 2, entries 6, 7, and 9) and secondary cyclic (Table 2, entries 1−3 and 12) or acyclic (Table 2, entries 5 and 13) amines in high yields. The reaction of 4-chlorotoluene with highly hindered amines (Table 2, entries 8 and 9) led to lower yields.

Room-Temperature Amination of Aryl Bromides and Aryl Iodides. Generally, aminations involving aryl bromides and iodides proceed under conditions milder than those involving aryl chlorides. To examine the halide substituent effect, the efficiency and selectivity of the present catalytic system for amination of aryl bromides and iodides was investigated. Both aryl bromides and iodides (Table 3) reacted with amines smoothly at room temperature. Most interesting in these studies involving an aryl bearing both chloro and iodo (or bromo) substituents is the observation that bromo and iodo functionalities can be converted at room temperature (Table 3, entries 3 and 4) and the remaining chloro functionality can subsequently be converted at more elevated temperatures. This could prove to be a significant advantage in process chemistry.

Effect of the Palladium(0)/Imidazolium Salt Ratio on Amination Reactions. During our optimization efforts and in order to understand the reaction mechanism, the influence of palladium/ligand ratio was investigated. We have found that a 1:1 palladium−ligand ratio affords optimum reaction rates (Table 4).

This optimum stoichiometry was suspected on the basis of previous work on Suzuki−Miyaura couplings mediated by an imidazolium salt/palladium system. Others have also observed this optimum ligand/metal ratio in phosphine/palladium catalytic systems.[27] A general catalytic cycle[1c] for the cross-coupling reaction of nitrogen containing reagents with aryl halides is said to involve an oxidative addition of the aryl halide, followed by transamination and reductive elimination, as outlined in Figure 1.[28] The optimization experiments enable us to gain mechanistic insights into this catalytic system. The electron-rich carbene ligands, usually better donors than tertiary phosphines,[15a,29,30] favor the oxidative addition step.[31] Theoretical studies[32,33a] have suggested that a Pd/L ratio of 1:2 (mutually cis ligands) favor the oxidative addition step, and, as a consequence, the reductive elimination step is thermodynamically disfavored. This is in agreement with the slower reaction rate given by a palladium/imidazolium salt ratio of 1:2 observed for IPr·HCl (**1**). It should be stated here that complexes with two carbene ligands are quite stable as examplified by platinum-based systems recently synthesized in our laboratories.[34] The steric effects provided by ortho substituents on the carbene aryl groups may also influence the efficiency of the catalytic transformation in a dramatic fashion. Our thermochemistry studies[15b,18d] on ruthenium systems involving these carbenes show that ITol is the best electron donor (ITol > IMes = IXy > IPr) while IPr is the most bulky ligand (IPr > IMes > IXy > ITol). As a consequence, three major factors appear to influence the activity of the palladium/imidazolium salt system: electronic properties of the carbene ligands affect the oxidative addition capability of palladium, while their bulk and number around palladium accelerate the reductive elimination step.[30−35] On the basis of these observations, a reactive intermediate can be envisioned as a reactive three-coordinate or most likely a solvent-stabilized or halide-bridging four-coordinate species. The formulation of similar reactive intermediates has been proposed by Hartwig for aryl amination[36] and by Buchwald[37] for Suzuki−Miyaura coupling.

Extended Scope and Applications of Amination Reaction. Amination of Heteroaromatic Halides. The amination technology based on Pd(dba)$_2$/IPr·HCl system is also applicable to heteroaryl halides, as illustrated in Table 5. Using 2-chloropyridine and morpholine as substrates leads to a 99% isolated yield (Table

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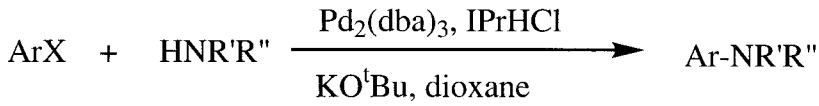
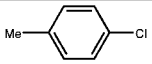
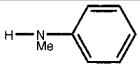
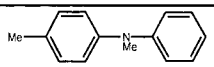
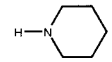
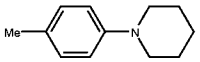
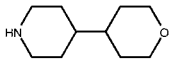
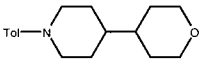
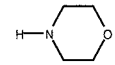
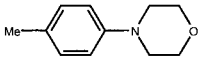
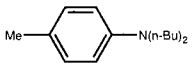
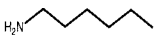
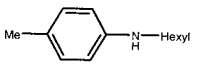
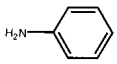
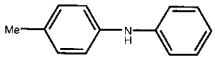
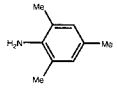
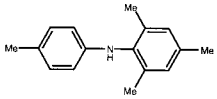
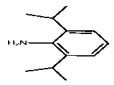
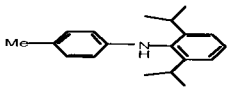
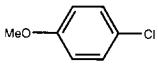
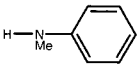
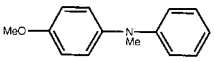
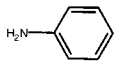
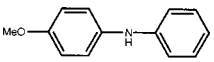
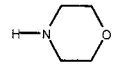
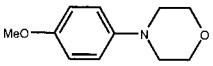
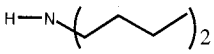
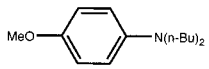
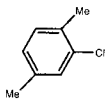
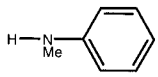
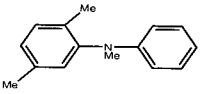
Table 2. Amination of Aryl Chlorides with Various Amines[a]



entry	Ar-X	HNR'R"	Ar-NR'R"	yield (%)[b]
1				99
2				96
3				86
4				82
5				95
6				86
7				96
8				59
9				85
10				91
11				91
12				80
13				98
14				94

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of amine, 1.5 mmol of KO^{t}Bu, 1.0 mol % $Pd_2(dba)_3$, 4.0% IPr·HCl (2 L/Pd), 3 mL of dioxane, 100 °C. Reactions were complete in 3−24 h, and reaction times were not minimized. [b] Isolated yields.

5, entry 1). In general, the coupling of chloropyridines and 2-bromopyridine resulted in high to moderate yields.

It is well-known that nitrogen-cotaining molecules can act as ligands and as a result displace weakly binding ligands with consequences on the activity of catalytic systems. One example is Pd(0)/P(o-tol)$_3$ system, which is not capable of the amination of heteroaryl halides.[38] However, results from Table 5 suggest that the Pd(dba)$_2$/IPr·HCl system is not negatively affected by nitrogen-containing substrates.

Amination of Aryl Halides with an Ammonia Equivalent. The extension of amination reaction to the synthesis of benzophenone imine adducts using benzophenone imine as an ammonia surrogate represents an efficient alternative route to the synthesis of N-unsubstituted anilines.[39] Synthetic routes to N-unsubstituted anilines often involve nitration, reduction, or substitution, and are usually incompatible with many functional groups and often involve protection and deprotection steps.[40]

Given the efficiency IPr·HCl as ancillary ligand for the amination reaction, the same protocol was used to perform the amination of aryl halides with benzophenone imine. This catalytic system proved efficient for catalytic amination of various aryl chlorides with benzophenone imine as shown in Table 6.

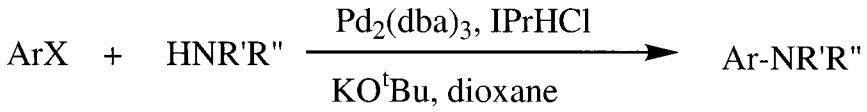
Benzophenone imine reacts with less reactive unactivated aryl chlorides in high yields (Table 6, entries 1, 2, and 5). Ortho-substituted aryl chlorides reacted with benzophenone imine without difficulty (Table 6, entries

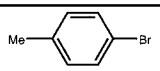
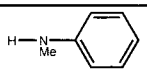
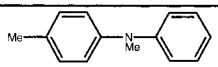
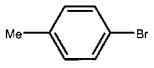
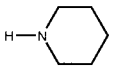
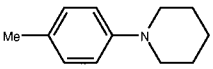
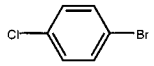
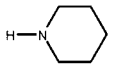
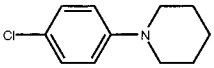
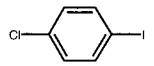
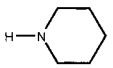
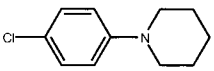
(38) Paul, F.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039.

(39) (a) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron. Lett.* **1997**, *38*, 6367−6370. (b) Mann, G.; Hatwig, J. F.; Driver, M. S.; Fernandez-Rivan, C. *J. Am. Chem. Soc.* **1998**, *120*, 827−828. (c) Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612−2614.

(40) (a)Marchini, P.; Liso, G.; Reho, A. *J. Org. Chem.* **1975**, *40*, 3453−3456. (b) Lane, C. F. *Synth.* **1975**, 135−146.

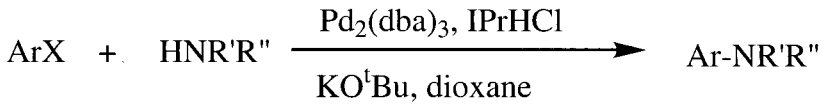
Table 3. Amination Involving Aryl Bromides and Idodides with Various Amines[a]

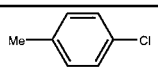
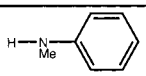
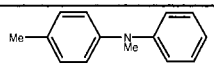
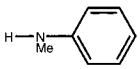
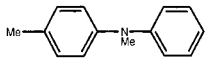
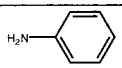
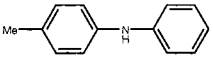
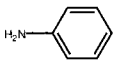
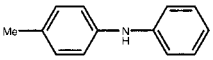
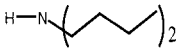
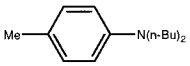
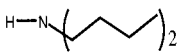
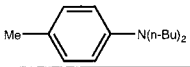
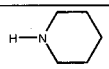
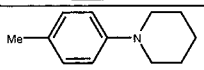
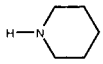
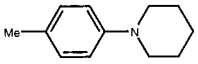


entry	Ar-X	HNR'R"	Ar-NR'R"	yield (%)[b]
1				89
2				83
3				94
4				97

[a] Reaction conditions: 1.0 mmol of aryl halides, 1.2 mmol of amine, 1.5 mmol of KO^{t}Bu, 1.0 mol % $Pd_2(dba)_3$, 4.0% IPr·HCl (2 L/Pd), 3 mL of dioxane, room temperature. Reactions were complete in 3−30 h, and reaction times were not minimized. [b] Isolated yields.

Table 4. Influence of Palladium(0)/Imidazolium Salt Ratio on Amination Reactions[a]



entry	Ar-X	HNR'R"	Ar-NR'R"	Pd(0):L	time (h)	yield (%)[b]
1				1:2	>3	99
2				1:1	1.5	96
3				1:2	>3	96
4				1:1	1.5	92
5				1:2	>3	95
6				1:1	1.5	90
7				1:2	>3	96
8				1:1	1.5	95

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of amine, 1.5 mmol of KO^{t}Bu. 1.0 mol % $Pd_2(dba)_3$, 4.0% IPr·HCl (2 L/Pd) or 2.0% IPr·HCl (1L/Pd), 3 mL of dioxane, 100 °C. [b] Isolated yields.

3 and 4). 4-Chlorotoluene and 4-chloroanisole required longer reaction times at 80° C, and the isolated products were contaminated with benzophenone imine. The reactions are significantly faster and the isolated products are pure when reactions are conducted at 100 °C. The amination reaction of aryl bromides proceed generally in high yields (Table 7) at 100 °C. Performing the reaction at 80 °C resulted in longer reaction times and lower yields. A possible explanation is that, while the oxidative addition of the aryl bromide substrate occurs rapidly, the Pd−N bond formation is slower for the LPd(Ar)Br complex.[33b]

Our attempts to use activated aryl halides and KO^{t}Bu as a base were not successful, due to the base-promoted cleavage of the substrate. Only 3,6-bis(trifluoromethyl)bromobenzene (Table 7, entry 3) and 4-chloropyridine hydrochloride (Table 6, entry 6) afforded a maximum 60% isolated yield. The use of weaker bases such as Cs_2CO_3, K_2CO_3, or K_3PO_4 gave only poor conversions.

The use of benzophenone imine as a coupling partner with various aryl halides lead to excellent results due to its relative low steric hindrance and sp^2 hybridized nitrogen. We believe the reductive-elimination step is facilitated[39a] by these electronic and steric factors. The acidic cleavage[39a] of some benzophenone imine adducts leads to various primary anilines in good to high yields (Table 8).

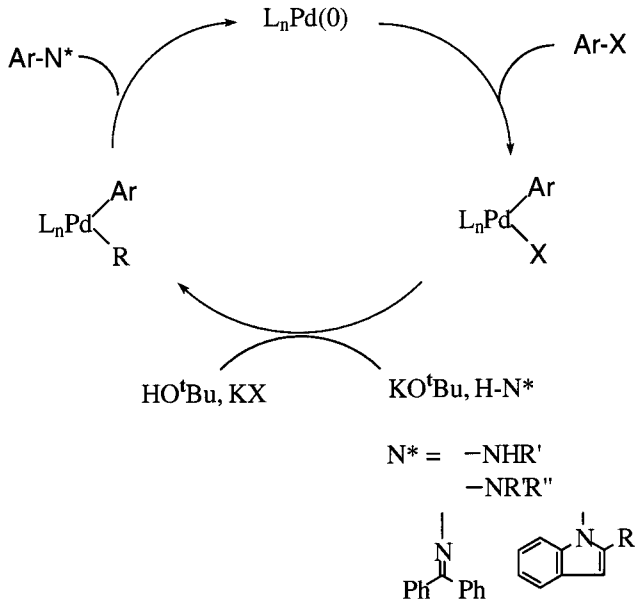
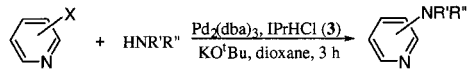
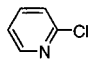
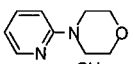
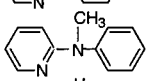
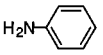
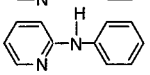
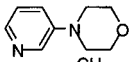
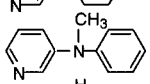
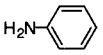
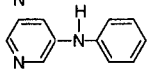
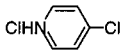
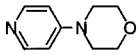
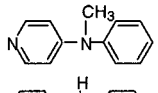
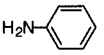
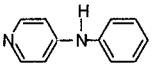
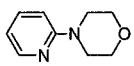
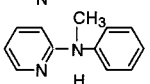
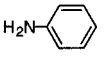
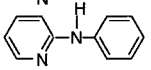


Figure 1. General catalytic cycle for amination reaction.

Table 5. Amination of Chlopyridines and Bromopyridines with Various Amines[a]

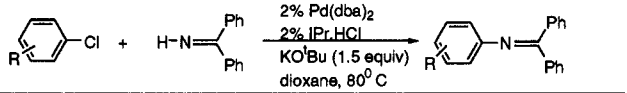


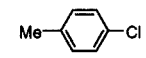
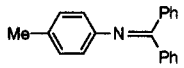
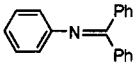
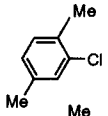
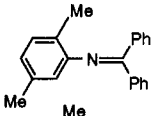
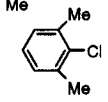
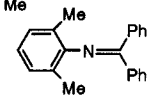
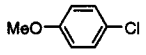
entry	aryl halide	amine	product	yield(%) [b, c]
1				99
2				97
3				88
4				97
5				91
6				98
7				80
8				70
9				83
10				95
11				99
12				96

[a] Reaction conditions: 1.0 mmol of chloro or bromopyridine, 1.1 mmol of amine, 1.5 mmol of KO^{t}Bu, 1.0 mol % $Pd_2(dba)_3$, 2.0 mol % IPr·HCl (L/Pd = 1), 3 mL of dioxane, 100 °C. [b] Isolated yields. [c] All reactions were monitored by GC.

N-Arylation of Aryl Indoles. *N*-Aryl indoles have attracted much attention since they can be biologically active[41] or useful intermediates in the synthesis of biologically active agents.[42] However, catalytic N-arylation of indoles is somehow limited to aryl iodides and bromides due to the involvement in the reaction of aromatic

Table 6. Amination of Aryl Chlorides with Benzophenone Imine[a]



Entry	Aryl Chloride	Product	Time (h)	Yield (%)[b,e]
1			4	99[c]
2			24	96
3			5	99
4			5	98
5			6	99[c]
6			48	60[c,d]

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.05 mmol of benzophenone imine, 1.5 mmol of KO^{t}Bu, 2.0 mol % $Pd(dba)_2$, 2.0 mol % IPr·HCl, 3 mL of dioxane, 80° C. [b] Isolated yields. [c] The reaction was performed at 100 °C. [d] 2.5 mmol of KO^{t}Bu were used. [e] All reactions were monitored by GC.

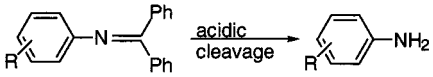
Table 7. Amination of Aryl Bromides with Benzophenone Imine[a]

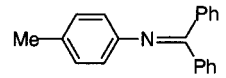
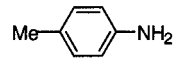
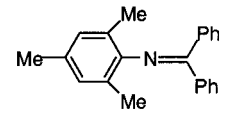
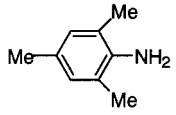
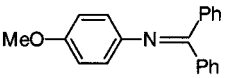
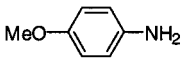
Entry	Aryl Bromide	Product	Time (h)	Yield (%)[b,d]
1			3	98
2			10	99
3			48	60
4			10	99[c]
5			5	99
6			5	98

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.05 mmol of benzophenone imine, 1.5 mmol of KO^{t}Bu, 2.0 mol % $Pd(dba)_2$, 2.0 mol % IPr·HCl, 3 mL of dioxane, 100 °C. [b] Isolated yields. [c] The reaction was performed at 80 °C. [d] All reactions were monitored by GC.

(41) Perregaard, J.; Arut, J.; Bogrso, K. P.; Hyttel, J.; Sánchez, C. *J. Med. Chem.* **1992**, *35*, 1090−1101.

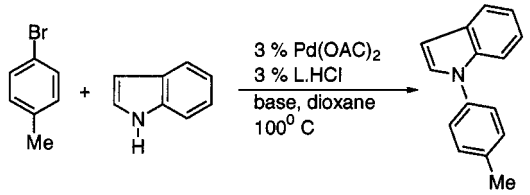
Table 8. Convertion of Benzophenone Imine Adducts to N-Unsubstituted Anilines



entry	benzophenone imine adduct	product	yield (%)[a]
1			94
2			87
3			88

[a] Isolated yields.

Table 9. Effect of the Imidazolium Chlorides and Bases on *N*-Aryl Substitution of Indole with Bromobenzene



entry	L	base	time (h)	yield[a] (%)
1	IPr	NaOH	24	NR
2	ICy	NaOH	3	30
3	SIMes	NaOH	3	66
4	SIPr	NaOH	3	88
5	SIPr	KO^{t}Bu	3	<5
6	SIPr	K_3PO_4	3	<5

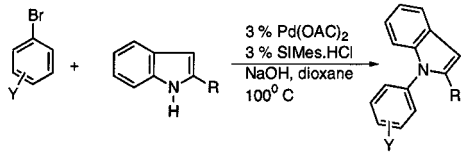
[a] Isolated yields.

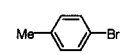
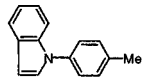
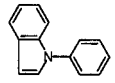
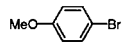
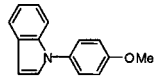
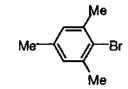
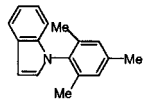
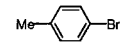
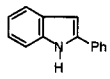
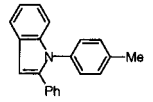
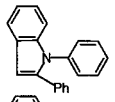
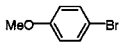
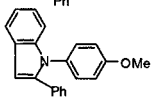
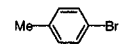
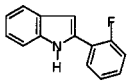
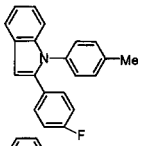
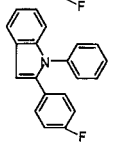
nitrogen.[43] Hartwig and co-workers have reported one example of an aryl chloride as partner in this coupling.[44]

Given the success of Pd(0)/IPr·HCl/KO^{t}Bu system for the amination reaction of aryl and heteroaryl halides as well as for the synthesis of benzophenone imine adducts, we were interested to extend the scope and generality of this system to the synthesis of N-aryl indoles. Nonetheless, we have found that the standard amination conditions did not affect the arylation of indoles. Hence, we sought different carbene ligands and bases in order to functionalize indoles. The $Pd(OAc)_2$/SIPr·HCl (**5**)/NaOH[45] system led to an 88% conversion of 4-bromotoluene in 3 h in the presence of indole (Table 9, entry 3). Investigation of other saturated imidazolium salts and bases led to lower yields. It appears that NaOH is needed to generate the free carbene, the dihydroimidazolium carbene being more donating than IPr.[46]

This catalytic system was found to be effective for a variety of aryl bromides and indole derivatives (Table 10). 4-Bromotoluene and bromobenzene are highly reactive with respect to various substituted indoles, while electron-rich and ortho-substituted substrates lead to low or moderate yields and slower reaction rates.[47]

Table 10. Amination of Aryl Bromides with Various Indoles[a]



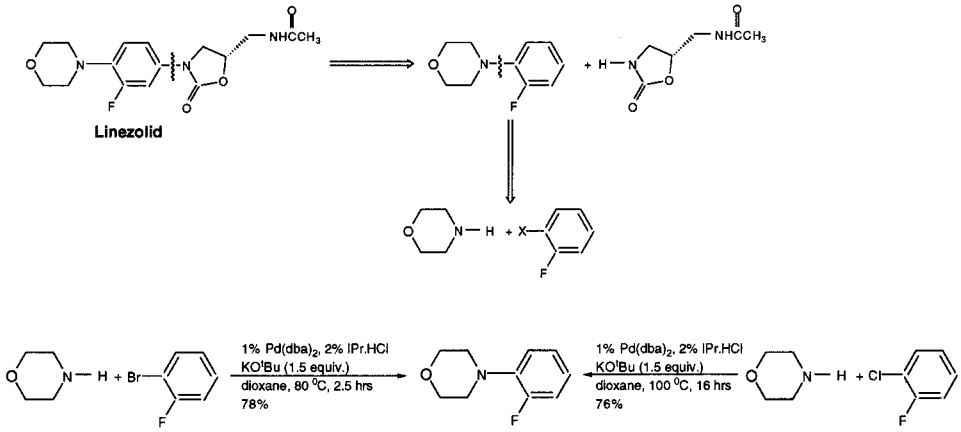
entry	aryl bromide	indole	product	time (h)	yield (%)[b,d]
1				3.5	97
2				1	100
3				3.5	88
4				16	68
5				3	100[c]
6				18	100[c]
7				10	61[c]
8				3	97[c]
9				10	83[c]

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.1 mmol of indole, 2 mmol of KO^{t}Bu, 2.0 mol % $Pd(OAc)_2$, 2.0 mol % SIPr·HCl, 3 mL of dioxane, 100 °C. [b] Isolated yields. [c] The reaction was performed in toluene. [d] All reactions were monitored by GC.

Since the palladium/imidazolium salt systems display high reactivity with aryl chlorides in the arylation of diverse amines, we tested their use in the synthesis of a pharmaceutical target. Linezolid is member of a new class of antibiotics.[48] One of the important features of the oxazolidinones is an aryl N-substituted amine moiety (Scheme 2) that could potentially be assembled via a palladium-mediated C−N bond formation. The synthesis of the strategic intermediate to the oxazolidinones, *N*-(2-fluorophenyl)morpholine, was isolated in good yields under unoptimized conditions (Scheme 2).

(42) Sarges, R.; Howard H. R.; Koe, B. K.; Weissman, A. *J. Med. Chem.* **1989**, *32*, 437−444.
(43) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827−829.
(44) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.
(45) $Pd(dba)_2$ or $PdCl_2$/SIPr·HCl/NaOH systems did not affect the arylation of indole.
(46) (a) Lee, H. M.; Jiang, T.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 1255−1258. (b) Scholl, M.; Sheng, D.; Lee. C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(47) This system has not been found effective for the reaction of aryl chlorides with indoles.
(48) *Chem. Eng. News* **2000**, March 6, 43.

Scheme 2. Synthesis of Linezolid Intermediate



Conclusion

In summary, palladium/imidazolium salt systems were found to be very efficient in the amination reaction involving aryl chlorides and aryl bromides. The Pd(0)/IPr·HCl/KO^{t}Bu system was found to be highly effective for the amination of electron−neutral, electron-poor aryl chlorides, as well as sterically hindered substrates with a variety of primary and secondary cyclic and acyclic amines. This catalytic system proved its effectiveness in the amination of various heteroaryl halides. The use of benzophenone imine as an ammonia equivalent for catalytic amination of a variety of aryl chlorides as well as aryl bromides proceeds in high yields. Acidic cleavage of the imine adducts leads to the formation of primary anilines. The scope of the palladium-nucleophilic carbene aryl amination reaction was extended to the synthesis of substituted aryl indoles. The more donating saturated carbene SIPr in combination with an inexpensive strong base (NaOH) mediates this process. Ongoing catalytic investigations are aimed at expanding the role of nucleophilic carbenes as supporting ligation in homogeneous catalysis.

Experimental Section

General Considerations. All aryl halides (Aldrich), amines and indoles were purchased from Aldrich and purified prior to use. 1,4-Dioxane and toluene (anhydrous, Aldrich) were distilled under argon from sodium benzophenone ketyl. Potassium *tert*-butoxide, potassium phosphate, and sodium hydroxyde (Aldrich) were stored under argon in a MBraun glovebox or in desiccators over anhydrous calcium carbonate. (Tris(dibenzylideneacetone)dipalladium(0), bis-(dibenzylideneacetone)palladium(0), and palladium acetate were purchased from Strem Chemical Co. Flash chromatography was performed on silica gel 60 (230−400 mesh) (Natland International Corp.) using hexanes or hexanes/ethyl acetate = 15:1. The imidazolium salts IPr·HCl (**1**, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride), IMes·HCl (**2**, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride), IXy·HCl (**3**, 1,3-bis(2,6-dimethylphenyl)imidazolium chloride), and ITol·HCl (**4**, 1,3-bis-(tolyl)imidazolium chloride) were prepared according to reported procedures.[49] ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories, Inc.). Elemental analyses were performed by Desert Analysis, Tucson, AZ. All reactions were carried out under an atmosphere of argon in oven-dried-glassware or in screw cap vials with magnetic stirring, unless otherwise indicated. All reported yields are isolated yields, unless otherwise stated, and are the average of two runs.

Synthesis of Dihydroimidazolium Chlorides. Anilines (mesitylamine 0.4 mol 5.4 g) (Aldrich) were reacted in methanol (20 mL) with glyoxal (0.2 mol, 40% aqueous solution, Aldrich) at room temperature in the presence of a few drops of formic acid. After the mixture was stirred for 3 h, the yellow precipitate, the diazabutadiene, was filtered, washed with methanol, and dried in vacuum (yield 92%). Hydrogenation of the diazabutadiene (0.01 mol 3.92 g) was performed in a MeOH/THF (40/60) mixture in the presence of $NaBH_4$ (0.1 mol, 3.78 g). After 1.5 h, the solution turned white, indicating reaction completion. A saturated aqueous solution of NH_4Cl (20 mL) was used to quench the reaction. The diamine was extracted three times with ether (20 mL) and washed with deionized water (10 mL). Ether extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford the substituted diamine (97%, 3.6 g). One equivalent of diamine, 1.1 equiv of NH_4Cl ,and 2.5 equiv of triethyl orthoformate were stirred together at 110 °C under an argon flow. After 1.5 h, the reaction mixture turned to a solid. The solid was dissolved in a minimum amount of $CHCl_3$ and reprecipitated with ether. The ^{1}H NMR of the product was comparable with previously reported spectroscopic data for the desired product.[50] The desired product was obtained in 85% yield in this manner. A similar experimental procedure was used in the synthesis of SIPr·HCl.

General Protocol Used for Amination Reaction. Under an atmosphere of argon 1,4,-dioxane (3 mL), KO^{t}Bu (168 mg, 1.5 mmol), aryl halide (1.0 mmol), and amine (1.2 mmol) were added in turn to a Schlenk tube charged with $Pd_2(dba)_3$ (10 mg, 0.01 mmol), **1** (17 mg, 0.04 mmol or 8 mg, 0.02 mmol), and a magnetic stirring bar. The Schlenk tube was placed in a 100 °C oil bath and stirred for 3−30 h. The mixture was then allowed to cool to room temperature. The mixture was diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated saline solution, and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash chromatography (hexane or hexane/ethyl acetate (10:1)).

Workup Method B. The reaction mixture was allowed to cool to room temperature and absorbed directly on chromatography column.

General Protocol for Amination of Aryl Halides with Benzophenone Imine. Under an atmosphere of argon 1,4,-dioxane (3 mL), KO^{t}Bu (168 mg, 1.5 mmol), aryl halide (1.0 mmol), and benzophenone imine (1.05 mmol) were added in turn to a screw-capped vial equipped with a Teflon septum and magnetic stirring bar charged with $Pd(dba)_2$ (10.9 mg, 0.02 mmol) and (8 mg, 0.02 mmol). The vial was placed in an oil bath at the indicated temperature and stirred for the indicated

(49) (a) Arduengo, A. J., III. US patent 5 077 414, **1991**; (b) Arduengo, A. J., III, Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

(50) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, A.; Hugh, A.; Goerlich, J. R.; William, J. *Tetrahedron* **1999**, *55*, 14523−14534.

time. The reaction was monitored by GC. In some cases, the yields were determined by GC using biphenyl as internal standard. The mixture was then allowed to cool to room temperature. The mixture was directly absorbed onto a chromatography column and eluted with hexane or hexane/ethyl acetate (15:1). Benzophenone imine adducts were converted to the corresponding N-unsubstituted anilines according to the reported procedure.[36a]

General Protocol Used for N-Arylation of Indoles with Aryl Bromides. Under an atmosphere of argon, 1,4 dioxane (3 mL), NaOH (80 mg, 2 mmol), arylhalide (1.0 mmol), and indole (1.1 mmol) were added in turn to a screw-capped vial equipped with a Teflon septum and magnetic stirring bar charged with $Pd(dba)_2$ (10.9 mg, 0.0 mmol), and **5** (8 mg, 0.02 mmol). The vial was placed in an oil bath at the indicated temperature and stirred for the indicated time. The reaction was monitored by GC. In some cases, the yields were determined by GC using biphenyl as internal standard. The mixture was then allowed to cool to room temperature. The mixture was directly absorbed onto chromatography column and eluted with hexane or hexane/ethyl acetate (15:1).

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Supporting Information Available: Experimental procedures, characterization of new compounds and references to known compounds are provided. This material is free of charge via the Internet at http://pubs.acs.org.

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