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Journal of Organometallic Chemistry 653 (2002) 69–82

Journal of Organometallic Chemistry

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Mini review

# Catalytic cross-coupling reactions mediated by palladium/nucleophilic carbene systems

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Received 30 July 2001; received in revised form 4 December 2001; accepted 5 December 2001

**Abstract**

In this mini-review, we present a summary of our recent work in the field of palladium-catalyzed cross-coupling reactions, with emphasis on the use of nucleophilic N-heterocyclic carbenes (NHC) as ancillary ligand. The palladium-mediated coupling reactions investigated include the Suzuki–Miyaura, Kumada–Tamao–Corriu, Heck, Sonogashira, Stille, Hiyama and aryl amination reactions. 

*Keywords:* Cross-coupling reactions; N-heterocyclic carbenes; Palladium

## 1. Introduction

Cross-coupling reactions represent an extremely versatile tool in organic synthesis [1]. Indeed, C–C bond formation is the key step in a wide range of preparative organic processes, from the synthesis of natural products [2] to supramolecular chemistry and material science [3]. Palladium- and nickel-catalyzed cross-coupling reactions of aryl halides or halide equivalents with various nucleophiles have been shown to be highly effective and practical methods for the formation of C–C bonds [4]. These coupling reactions make use of a variety of transmetalating agents such as organoboron [5], organomagnesium [6], organosilicon [7], organostannane [8] and organozinc [9] reagents. In a closely related area, the palladium- and nickel-mediated coupling of aryl halides with amines has attracted substantial interest owing to its importance in organic synthesis and material science [10].

The importance of careful selection of ancillary ligand can be explained by reference to the generally accepted postulated mechanism for nickel- and palladium-mediated cross-coupling reactions (Scheme 1). A zerovalent palladium species, stabilized by an electron-donating and/or bulky ligand(s), undergoes oxidative addition with an aryl halide to afford a Pd(II)(Ar)(X) complex. Ar′–M then effects transmetalation with this species, removing the halide as 'MX' to afford a divalent Pd(Ar)(Ar′) intermediate, which undergoes a reductive elimination to couple the two aryl moieties and regenerate the palladium(0) species. Thus, a proper choice of supporting ligands can affect both the oxidative addition and the reductive elimination steps, via preferential stabilization of the metal center at different stages of the catalytic cycle.

Monodentate, bulky, electron-donating tertiary phosphines are generally employed as ancillary ligands in coupling systems [11]. Specific applications benefit from, or require the use of, sterically demanding phosphine ligation to stabilize reactive intermediates [12]. Although tertiary phosphine ligands are useful in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis [11], they usually require air-free handling to prevent ligand oxidation. More importantly, they are subject to P–C bond degradation at elevated temperatures. In certain catalytic processes this results in deactivation of the catalyst and as a consequence, higher phosphine concentrations are required [1b].

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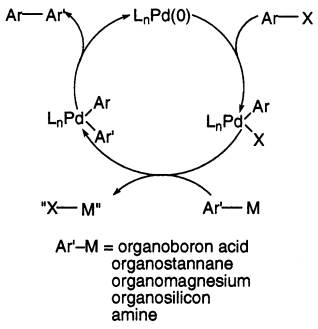
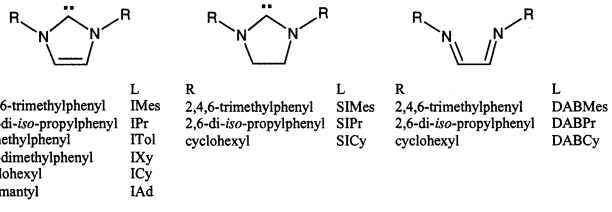



Scheme 1. Postulated catalytic cycle for palladium-mediated cross-coupling reactions.

Nucleophilic N-heterocyclic carbenes (NHC), the imidazol-2-ylidenes (Scheme 2) are considered as neutral, two electron donor ligands with negligible π-back-bonding tendency [13]. As such they have attracted considerable attention as alternatives to phosphines [14]. Thermochemical and structural studies have shown that in the Cp*Ru(L)Cl system (Cp* = η-$C_5Me_5$; L = nucleophilic carbene, tertiary phosphine) the carbenes studied are (with the exception of the adamantyl-substituted carbene) more effective donors than bulky tertiary phosphines [14d]. Thus, the carbenes appear to confer a greater degree of thermal stability with regard to dissociation of the ligand from the metal center. As a consequence 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 [15], Ru-catalyzed furan synthesis [16] and olefin metathesis [17]. Most notably, nucleophilic NHC have found highly successful applications as supporting ligands in cross-coupling reactions of various aryl halides with amines, organomagnesium (Kumada–Tamao–Corriu reaction), organosilicon, organotin (Stille reaction) and organoboron (Suzuki–Miyaura reaction) reagents. In this contribution, we summarize our recent work employing palladium–imidazol-2-ylidene and –diazabutadiene complexes as mediators of cross-coupling reactions.




Scheme 2. Nucleophilic carbenes, related diazabutadienes and nomenclature.

## 2. Suzuki–Miyaura cross-coupling of aryl halides with aryl boronic acids

The Suzuki–Miyaura reaction [18] is very versatile and has found extensive use in natural product synthesis [19]. An organoboron reagent, typically $ArB(OH)_2$ (Ar = phenyl or substituted aromatic group), is employed as coupling partner with aryl halides or pseudo-halides.

A cross-coupling methodology employing organoboron reagents is attractive since a wide variety of air- and thermally stable organoboron reagents are available, either commercially or via straightforward syntheses [20]. Nucleophilic NHC have recently been used as ancillary ligands for this process with great success [21].

### *2.1. Pd(0)- and Pd(II)-imidazolium chloride catalytic systems [22,23]*

The reaction of 4-chlorotoluene with phenylboronic acid in the presence of catalytic amounts of $Pd_2(dba)_3$, the carbene IMes and $Cs_2CO_3$ as base resulted in a modest yield (59%) of the diaryl coupling product [22]. Subsequently, we turned our attention to developing a simplified protocol employing the air-stable imidazolium salt rather than the free carbene. Initial investigations using IMes·HCl with different bases revealed that $Cs_2CO_3$ was the base of choice, with other inorganic bases requiring longer reaction times for complete consumption of aryl chloride. When the organic base triethylamine was tested the reaction ceased within minutes and precipitation of palladium black was observed. Screening of different imidazolium chlorides showed that IMes·HCl performed best.

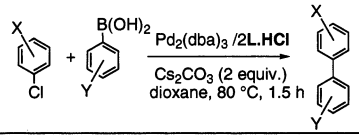
We then sought a further simplification and extended the reaction to air-stable Pd(II) catalyst precursors [23], eliminating the need for a drybox to handle the Pd(0) complex. Initial studies focused on the protocol established for the Pd(0) system, employing $Pd(OAc)_2$–IMes·HCl with $Cs_2CO_3$ as base. The catalytic components and substrates were weighed in air, loaded in the reaction vessel under counterflow of argon on a Schlenk line and heated for 2 h. Only low yields of the desired coupled products were obtained, however. An alternative approach, loading only $Pd(OAc)_2$, IMes·HCl and $Cs_2CO_3$, adding 1,4-dioxane and heating to 80 °C for 30 min, followed by cooling, addition of substrates, then heating for a further 2 h, afforded complete conversion for 4-chlorotoluene and phenylboronic acid. Thus, it appears that an activation period is essential, during which the base reacts with the Pd(II) salt and IMes·HCl to generate the carbene ligand and the active Pd(0) species. This protocol represents a significant improvement over the initial procedure employing air-sensitive Pd(0) and IMes, in terms of both isolated yield and ease of execution.

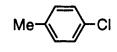
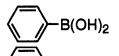
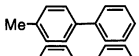
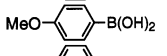
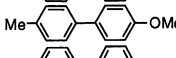
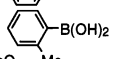
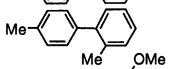
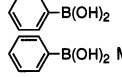
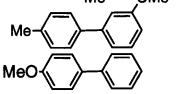
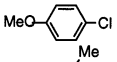
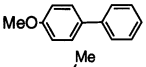
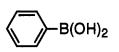
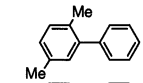
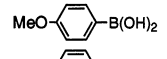
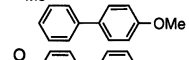
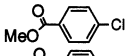
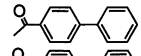
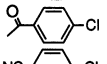
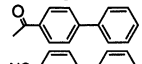
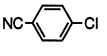
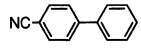
An investigation of the activity of the catalytic system as a function of the imidazolium salt revealed that, as for the Pd(0) system, IMes·HCl displayed the best catalytic behavior. All other imidazolium salts investigated required longer reaction times to achieve complete consumption of the aryl chloride and afforded moderate to low yields. In these systems, steric factors appear to dictate catalytic reactivity, with bulkier carbenes possessing N-aryl *ortho*-substituents (IMes·HCl, IPr·HCl, IXy·HCl) displaying the best activity. On the other hand, the better electron donor, but less bulky, ICy·HCl gave only poor yields.

As illustrated in Table 1, both Pd(0)($Pd_2(dba)_3$–IMes·HCl or $Pd_2(dba)_3$–IPr·HCl) systems were found to be exceptionally tolerant towards different functional groups on the aryl choride and boronic acid. Excellent yields of coupling products were achieved with a variety of electron-withdrawing and -donating substituents. Marginally lower yields were obtained with sterically hindered *ortho*-substituted reagents.

Aryl triflates are valuable partners in cross-coupling since they are easily synthesized from phenols [24]. It was found that the initial conditions could be applied successfully to aryl triflates, with fairly high tolerance to steric and electronic modulation in the different triflates and arylboronic acids (Table 2).

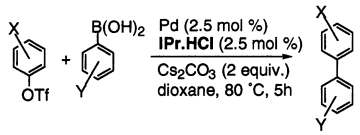
Table 1
Functional group tolerance of $Pd_2(dba)_3$–L·HCl Catalyzed Suzuki cross-coupling reactions of aryl chlorides with phenylboronic acid derivatives [a]

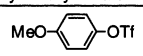
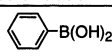
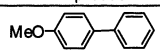
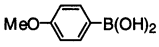
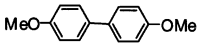
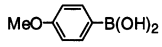
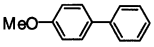
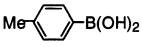
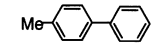
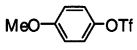
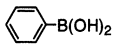
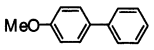
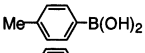



| entry | aryl halide | boronic acid | product | yield(%)[b,g] IMes.HCl[c] | IPr.HCl[d] |
|---|---|---|---|---|---|
| 1 |  |  |  | 90 | 95 |
| 2 |  | |  | 99 | 99 |
| 3 | |  |  | 88 | 97 |
| 4 | |  |  | 91 | 95 |
| 5 |  |  |  | 93 | 99 |
| 6 |  |  |  | 95 | 95 |
| 7 |  |  |  | 99 | 79[e] |
| 8 |  | |  | 99 | 98 |
| 9 |  | |  | 81[e] | 99[f] |
| 10 |  | |  | 80[e] | 100[f] |

[a]Reaction conditions: 1.0 mmol of aryl chloride, 1.5 mmol of arylboronic acid, 2.0 mmol $Cs_2CO_3$, 2L/Pd, 80 °C. [b]Isolated yields. [c]1.5 mol% $Pd_2(dba)_3$ was used. [d]1 mol% $Pd_2(dba)_3$ was used. [e]The reaction time was 16 h. [f]The reaction time was 3 h. [g]All reactions were monitored by TLC.

Table 2
Functional group tolerance of $Pd(OAc)_2(Pd(dba)_2)$–IPr·HCl catalyzed Suzuki cross-coupling reactions of aryl triflates with phenylboronic acid derivatives [a]




| entry | aryl triflate | boronic acid | product | yield(%)[b,e] |
|---|---|---|---|---|
| 1 |  |  |  | 86[c] |
| 2 | |  |  | 81[c] |
| 3 |  |  |  | 85[c] |
| 4 | |  |  | 99[d] |
| 5 |  |  |  | 97[d] |
| 6 | |  |  | 98[d] |
| 7 |  |  |  | 76[c] |
| 8 | |  |  | 77[c] |
| 9 | |  |  | 97[d] |

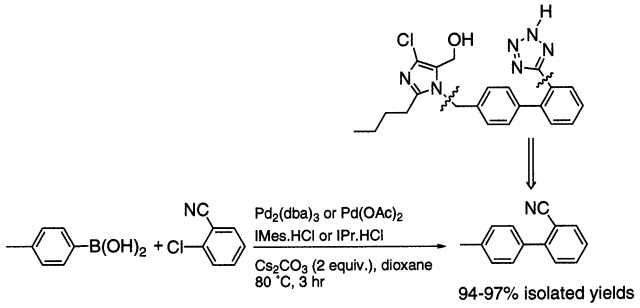
[a]Reaction conditions: 1.0 mmol of aryl triflate, 1.5 mmol of arylboronic acid, 2.0 mmol $Cs_2CO_3$, 2.5 mol% $Pd(OAc)_2$, or 2.5 mol% $Pd(dba)_2$, 2.5 mol% IPr·HCl (**3**) (1L/Pd), 80 °C. [b]Isolated yields. [c]2.5 mol% $Pd(OAc)_2$ was used. [d]2.5 mol% $Pd(dba)_2$ was used. [e]All reactions were monitored by TLC.

This procedure has been successfully applied to the synthesis of two pharmaceutical targets. Fenbufen [25] (γ-oxo-{1,1′-biphenyl}-4-butanoic acid) belongs to a class of non-steroidal *anti*-inflammatory drugs possessing analgesic properties, which acts by inhibition of prostaglandin synthesis. The $Pd(OAc)_2$–IMes·HCl–$Cs_2CO_3$-catalyzed cross-coupling of commercially available 3-(4-chlorobenzoil)propionic acid and phenylboronic acid afforded high isolated yields (Scheme 3). Losartan [26] is a non-peptide angiotensin II receptor antagonist with a critical role in blood pressure regulation [26,27]. An important structural feature of this AII antagonists is a biphenyl moiety, therefore aryl–aryl coupling is potentially a key step in their synthesis. Our protocol has permitted the synthesis of the strategic intermediate 2-cyano-4′-methylbiphenyl in high yields (Scheme 4).

Further investigations with the Pd(0)–IMes·HCl system have permitted some mechanistic insight. Varying the ligand–Pd ratio has demonstrated that a ratio of 1/1 is optimal, with a 2/1 ratio affording slower rates.




Scheme 3. Synthesis of Fenbufen via Suzuki–Miyaura coupling.




Scheme 4. Synthesis of Losartan intermediate via Suzuki–Miyaura coupling.

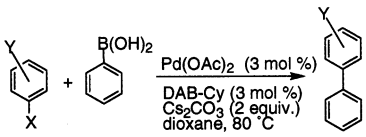
Three factors are believed to influence the activity of the Pd–imidazolium salt systems. The electronic properties of the carbene affect its ability to stabilize the Pd(0) catalyst precursor and the oxidative addition capabilities of Pd. Then, the bulk and number of ligands around the metal center accelerate the reductive elimination step. Here, as a 1/1 ratio is optimal, we envisage a reactive three-coordinate or (more probably) a solvent-stabilized or halide-bridged four-coordinate intermediate species. Similar intermediates have been proposed by Buchwald [28] and Hartwig [29].

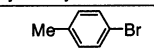
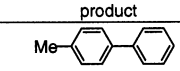
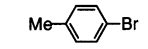
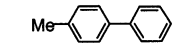
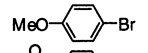
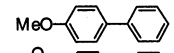
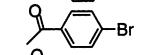
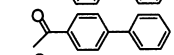
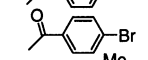
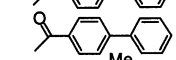
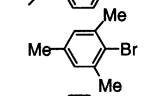
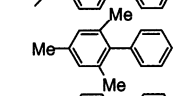
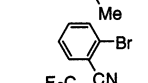
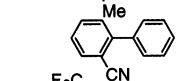
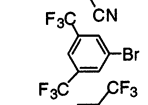
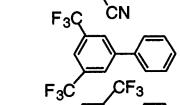
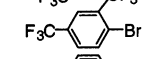
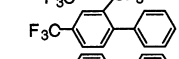
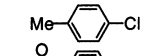
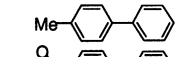
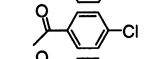
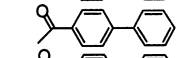
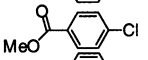
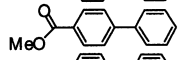
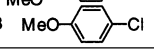
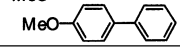
### 2.2. Pd(II)–diazabutadiene catalytic systems [30]

On the basis of a report of a Pd(II) cyclometalated imine catalyst that mediated both Suzuki [31] and Heck [32] reactions, we decided to test the chelating diazabutadiene (DAB-R, Scheme 2) ligands in Suzuki–Miyaura couplings. An initial survey of different DAB-R ligands in the reaction of 4-bromotoluene with phenylboronic acid indicated that in general alkyl *R*-substituents were more effective, presumably owing to their stronger electron-donating ability which makes them more electron-rich ligands than the aryl-substituted DAB ligands. DAB-Cy was found to be the best of the ligands tested, with quantitative conversion in 3 h. This reaction could also be conducted in air, reaching 90% conversion after 5 h. The commercially available nitrogen chelates 2,2′-bipyridine and 1,10-phenanthroline afforded only very poor results. An investigation of the influence of base suggested that $Cs_2CO_3$ was the reagent of choice. $K_2CO_3$, which was effective for Milstein's cyclopalladated imine catalyst, was less effective here. KF and CsF afforded moderate results, whereas other inorganic bases investigated ($Na_2CO_3$, $Ca(OH)_2$, NaOMe, KO$^t$Bu, KOMe, $Ba(OH)_2 \cdot xH_2O$) were all ineffective. The $Pd(OAc)_2$–DAB-Cy–$Cs_2CO_3$ system was very active towards the coupling of aryl bromides with phenylboronic acid and displayed excellent tolerance towards both 'deactivating' electron-donating and sterically encumbering *ortho*-substituents on the aryl bromide, albeit with slightly longer reaction times (Table 3). The activated aryl chloride 4-chloroacetophenone gave moderate yields, employing a higher reaction temperature, but coupling of electron-neutral 4-chlorotoluene or electron-rich 4-chloroanisole was unsuccessful. Attempted coupling of aryl triflates and tosylates with phenylboronic acid was similarly unsatisfactory, with long reaction times ( > 20 h) necessary to obtain reasonable yields [33]. An investigation of different arylboronic acids with 4-bromotoluene resulted in excellent yields with *para*-substituted aryl groups, good yields with *ortho*-substituents (with longer reaction times) and low yields with *meta*-substituents.

The use of DAB-R as supporting ligands for the Suzuki–Miyaura cross-coupling reaction represents a general, efficient methodology and provides an interesting alternative to existing catalytic systems based on the use of tertiary phosphine ligands. The high activity observed is unprecedented for a bis(nitrogen) system.

Table 3
$Pd(OAc)_2$–DAB-Cy catalyzed cross-coupling of aryl halides with phenylboronic acid [a]




| entry | aryl halide | product | time (h) | yield(%)[b,g] |
|---|---|---|---|---|
| 1 |  |  | 3 | 99 |
| 2 |  |  | 5 | 90[c] |
| 3 |  |  | 5 | 95 |
| 4 |  |  | 1 | 98 |
| 5 |  |  | 20 | 99[d] |
| 6 |  |  | 4 | 97 |
| 7 |  |  | 1 | 98 |
| 8 |  |  | 2 | 95 |
| 9 |  |  | 21 | 98 |
| 10 |  |  | 4.5 | 20[e,f] |
| 11 |  |  | 4 | 98[e] |
| 12 |  |  | 5 | 85[e] |
| 13 |  |  | 24 | 35[e,f] |

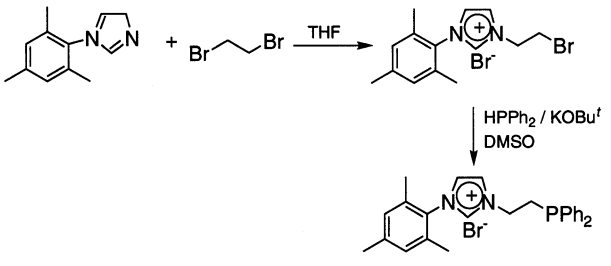
[a]Reaction conditions: 1.0 mmol of aryl halide, 1.5 mmol of phenylboronic acid, 2 mmol $Cs_2CO_3$, 3.0 mol% $Pd(OAc)_2$, 3.0 mol% DAB-Cy, 3 ml dioxane, 80 °C. [b]Isolated yields. [c]The reaction was performed in the air. [d]The reaction was performed using $Pd(OAc)_2$ only. [e]The reaction was performed at 100 °C. [f]GC yield. [g]All reactions were monitored by GC. Yields are average of two runs.

## 3. Heck reaction

The Heck reaction is widely employed in organic synthesis in the preparation of variously substituted olefins, dienes and precursors to conjugated polymers [34]. The use of monodentate phosphines in the palladium catalyzed Heck reaction has afforded efficient catalytic systems for the synthesis of substituted olefins. Reactions involving the less reactive aryl bromides and chlorides require bulky electron-donating phosphines such as $P(^tBu)_3$, [35]. Under Heck conditions both the phosphines and their palladium complexes are prone to decomposition and excess phosphine is required, reducing reaction rate, necessitating higher Pd loading and increasing the cost of large-scale processes. Bidentate chelating phosphines improve stability but have thus far achieved limited success in catalytic systems. Several palladium carbene complexes have proved highly efficient in Heck reactions [36]. A recent theoretical treatment of mixed carbene–phosphine chelates suggested their suitability for the Pd-catalyzed Heck reaction [37]. We therefore prepared a mixed carbene–phosphine chelating ligand (Scheme 5) and examined its utility in the cross-coupling of aryl bromides with butyl acrylate [38].

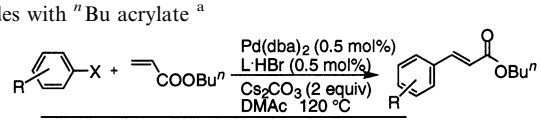
The reaction between 4-bromotoluene and butyl acrylate in the presence of $Pd(dba)_2$ and L·HBr was employed in optimization studies examining the effects of base and solvent. The optimal conditions were found with the polar solvent *N*,*N*-dimethylacetamide (DMAc) and two equiv of $Cs_2CO_3$ as base. Substitution of $Pd(dba)_2$ by $Pd(OAc)_2$ resulted in a significant decrease in activity. The optimized conditions led to excellent yields of coupled products with an array of activated and unactivated aryl bromides (Table 4). The protocol proved intolerant of sterically hindered substrates such as 2-bromotoluene, and ineffective with electron neutral chlorobenzene. Prolonged reaction times resulted in undesired side reactions.

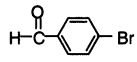
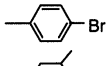
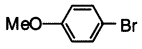
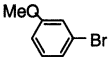
For comparison, the Heck reaction employing non-chelating carbene ligands was investigated [39]. Initial screening for the reaction of 4-bromotoluene with $^n$Bu acrylate, employing Pd(0) and Pd(II) precursors with different imidazolium chlorides, demonstrated that IMes·HCl was the most effective ligand for both, with ICy·HCl and SIPr·HCl also effective in combination with Pd(II). Activity was subsequently examined for the $Pd(OAc)_2$–IMes·HCl system owing to the greater ease of manipulation. The protocol employed for the carbene system (2 mol% Pd(II), 4 mol% IMes·HCl, two equivalents $Cs_2CO_3$, DMAc, 120 °C) was found to be effective for a large number of aryl bromides (Table 5). In the case of 4-bromoanisole, 4- and 2-bromotoluene, the reaction yield was improved by the addition of 20 mol% $[^nBu_4N]Br$. In all cases, the *trans* products were selectively obtained. No activity was observed with aryl chloride substrates.




Scheme 5. Synthesis of L·HBr (L = (1-ethylenediphenylphosphino-3-(mesityl))imidazol-2-ylidene).

Table 4
Pd–chelating carbene–phosphine catalyzed heck reaction of aryl halides with $^n$Bu acrylate [a]



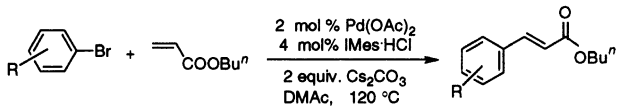

| entry | substrate | time (h) | yield (%) |
|---|---|---|---|
| 1 |  | 0.25 | 100 |
| 2 |  | 1 | 100 |
| 3 |  | 1.5 | 100 |
| 4 |  | 1 | 35 |
| 5 |  | 1 | 99 |
| 6 |  | 3 | 99 |
| 7 |  | 2 | 99 |
| 8 |  | 2 | 13 |

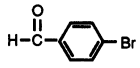
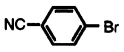
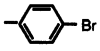
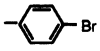
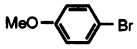
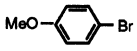
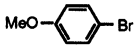
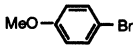
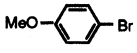
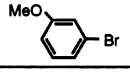
[a]Reaction conditions: 1 mmol aryl halide, 1.4 mmol $^n$Bu acrylate. [b]GC yield (ditethyleneglycol di-*n*-butyl ether as GC standard; an average of two runs).

## 4. Sonogashira reaction

Arylalkynes and conjugated enynes play an important role in the assembly of bioactive natural molecules and new materials [40]. The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides provides a most straightforward and powerful method for their synthesis [40,41]. Usually, the Sonogashira reaction is mediated by a palladium–phosphine complex and copper(I) iodide as a co-catalyst. Recently, a palladium system modified by a bulky, electron-rich phosphine ligand, $P^tBu_3$, has been reported to display unusually high activity in Sonogashira coupling of aryl bromides [42]. The use of nucleophilic carbenes in Sonogashira coupling has so far resulted in limited success [43]. To the

Table 5
$Pd(OAc)_2$–L·HCl catalyzed Heck reaction of aryl bromide with $^n$Bu acrylate [a]




| entry | aryl bromide | time (h) | yield (%) [b] |
|---|---|---|---|
| 1 |  | 0.25 | 100 |
| 2 |  | 0.5 | 100 |
| 3 |  | 1 | 97 |
| 4 |  | 1 | 94 |
| 5 |  | 1 | 99 [c] |
| 6 |  | 0.5 | 16 |
| 7 |  | 1 | 97[C] |
| 8 |  | 1 | 94 |
| 9 |  | 1 | 65[d] |
| 10 |  | 1 | 91 |
| 11 |  | 1 | 99[c] |
| 12 |  | 1 | 88[e] |
| 13 |  | 1 | 66[f] |
| 14 |  | 1 | 99 |

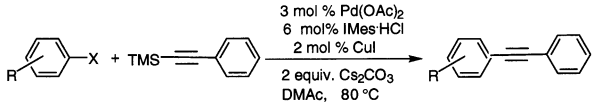
[a]Reaction condition: 1.0 mmol aryl bromide, 1.6 mmol $^n$Bu acrylate, 2 ml of DMAc. [b]GC yield (diethylenegly-col di-*n*-butyl ether as GC standard); an average of two runs.[c]With addition of $^n Bu_4NBr$ (20 mol%). [d]2 mol% $Pd(dba)_2$ as Pd source. [e]4 mol% ICy·HCl as ligand. [f]4 mol% SIPr·HCl as ligand.

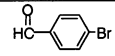
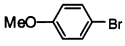
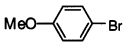
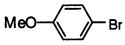
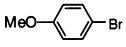
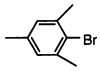
best of our knowledge, only four Sonogashira reactions mediated by palladium NHC complex have been reported. Furthermore, the protocol used only dealt with activated arylbromides (4-bromoacetophenone and 4-bromofluorobenzene) as substrates [44].

Our optimization studies employing 4-bromoanisole as a test substrate resulted in our selecting the combination $Pd(OAc)_2$–IMes·HCl–$Cs_2CO_3$, with DMAc as reaction medium [45]. The base typically used in Sonogashira reaction, triethylamine, led to inactive systems, as did other inorganic or organic bases. Employing phenylacetylene as alkyne source resulted in formation of significant quantities of side product via dimerization of phenylacetylene. This could be suppressed using 1-phenyl-2-(trimethylsilyl)acetylene as coupling partner with arylbromides [46].

Under optimized conditions (3 mol% $Pd(OAc)_2$, 6 mol% IMes·HCl, with or without 2 mol% CuI, two equivalents of $Cs_2CO_3$, DMAc, 80 °C) excellent product yields could be obtained from a wide array of arylbromides with 1-phenyl-2-(trimethylsilyl)acetylene in a very short time (Table 6). This catalytic system was equally efficient for electron-rich arylbromides. It is noteworthy that the above-mentioned high activities were achieved under copper-free conditions. The addition of 2 mol% CuI as co-catalyst can increase reaction rates, notably with deactivated arylbromides. A nearly complete conversion was observed for 4-bromoanisole using this protocol. The catalytic system was also highly efficient for sterically encumbered substrates. Remarkably, the catalytic system was effective for chlorobenzene in moderate yield.

Table 6
$Pd(OAc)_2$–L·HCl catalyzed Sonogashira reaction of aryl halide with 1-phenyl-2-(trimethylsilyl)-acetylene [a]




| entry | aryl halide | time (h) | yield (%) [b] |
|---|---|---|---|
| 1 |  | 0.25 | 100 (92) [c] |
| 2 |  | 0.5 | 100 (91)[c] |
| 3 |  | 0.5 | 96 (86) [c] |
| 4 |  | 0.5 | 99 |
| 5 |  | 0.5 | 100 (93) |
| 6 |  | 0.5 | 82[c] |
| 7 |  | 3 | 94[d] |
| 8 |  | 0.5 | 96 (88) |
| 9 |  | 1 | 43[c], [e] |
| 10 |  | 0.5 | 100 (93) |
| 11 |  | 0.5 | 95[f] |
| 12 |  | 1 | 90 (82) |
| 13 |  | 1 | 51 |

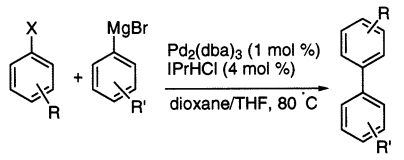
[a]Reaction conditions: 1.0 mmol aryl halide, 1.4 mmol 1-phenyl-2-(trimethylsilyl)-acetylene, 2 ml of DMAc. [b]GC yields based on aryl halide; number in parenthesis is isolated yield (average of two runs). [c]Without CuI. [d]Reaction temperature 60 °C. [e]3 mol% $Pd(dba)_2$ as Pd source. [f]6 mol% IPr·HCl as ligand.

## 5. Kumada–Tamao–Corriu reaction

Arylboronic acids and other organometallic reagents used in C–C coupling reactions are often synthesized from the corresponding Grignard or organolithium reagents [18a]. A general method employing these reagents directly in cross-coupling would prove valuable. In 1972, Kumada and co workers [47] and Corriu [48] reported independently that the reaction of Grignards with alkenyl or aryl halides (the Kumada–Corriu reaction) was catalyzed by Ni(II) complexes. The Pd-catalyzed Kumada–Corriu reaction was first reported by Murahashi in 1975 [49]. In recent years several reports have appeared dealing with phosphine-modified Pd- or Ni-mediated coupling involving inexpensive aryl halides as substrates [50]. Our report [51] was the first example of successful coupling involving unactivated aryl chlorides and an aryl Grignard reagent.

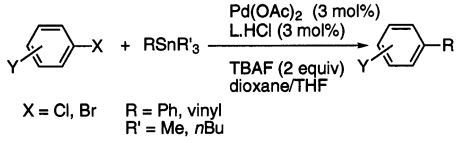
In order to test our Pd–carbene system, we selected the reaction between 4-chlorotoluene and phenylmagnesium bromide. Initial tests demonstrated that the system $Pd_2(dba)_3$–IPr·HCl in a 1,4-dioxane–THF solvent mixture at 80 °C was most effective, giving quantitative conversion in 3 h [52]. A small excess of PhMgBr (1.2 equivalents) was utilized to deprotonate the imidazolium salt, rather than adding a base. The efficacy of this catalytic system was tested with a number of aryl chloride, bromide and iodide substrates (Table 7). As expected, the reactions were faster with the aryl bromides and iodides. Significantly, the unactivated aryl chloride 4-chloroanisole gave essentially quantitative conversion in 3 h. A further major challenge in coupling reactions is the tolerance of the catalytic system to functional groups on the substrate. The Pd(0)–IPr·HCl system displayed formidable tolerance to a variety of aryl halide and aryl Grignard substituents. Halides bearing methoxy or even hydroxy groups reacted with unsubstituted aryl Grignards to give excellent yields of the corresponding biaryls. Similarly, *ortho*-substituents, in the aryl Grignard reagents 2-fluoro- and 2,4,6-trimethylphenyl magnesium bromide, posed no problem, coupling with 4-chloroanisole with no difficulty. Where the aryl chloride possessed *ortho*-substituents, good yields were obtained by using a slightly larger excess of the Grignard (1.8 equivalents). Steric congestion around both reactive centers, however, as encountered in the reactions of 2-chloro-*m*-xylene or 2-bromomesitylene with mesityl magnesium bromide, resulted in no conversion in 24 h.

Table 7
Palladium–imidazolium salt-catalyzed cross-coupling aryl halides with aryl Grignard reagents [a]




| Entry | Ar–X | Ar′ | Time (h) | Yield (%) [b] |
|---|---|---|---|---|
| 1 | 4-$MeC_6H_4$–Cl | $C_6H_5$ | 3 | 99 |
| 2 | 4-$MeC_6H_4$–Cl | $C_6H_5$ | 3 | 96 [c] |
| 3 | 4-$MeC_6H_4$–Br | $C_6H_5$ | 1 | 99 |
| 4 | 4-$MeOC_6H_4$–Cl | $C_6H_5$ | 3 | 97 |
| 5 | 2,5-$(Me)_2C_6H_3$–Cl | $C_6H_5$ | 3 | 85 |
| 6 | 2,6-$(Me)_2C_6H_3$–Cl | $C_6H_5$ | 5 | 87 [d] |
| 7 | 4-$MeO_2CC_6H_4$–Br | $C_6H_5$ | 5 | 69 |
| 8 | 4-$HOC_6H_4$–I | $C_6H_5$ | 3 | 96 [e] |
| 9 | 4-$HOC_6H_4$–Cl | $C_6H_5$ | 5 | 95 [e] |
| 10 | 6-MeO–Np-2-Br | $C_6H_5$ | 1 | 98 |
| 11 | 4-$MeOC_6H_4$–Cl | 4-$MeC_6H_4$ | 3 | 99 |
| 12 | 4-$MeOC_6H_4$–Cl | 3-$MeC_6H_4$ | 3 | 83 |
| 13 | 4-$MeOC_6H_4$–Cl | 2-$FC_6H_4$ | 3 | 99 |
| 14 | 4-$MeOC_6H_4$–Cl | 2,4,6-$(Me)_3C_6H_2$ | 3 | 95 |
| 15 | 2,6-$(Me)_2C_6H_3$–Cl | 2,4,6-$(Me)_3C_6H_2$ | 24 | 0 |
| 16 | 2,4,6-$(Me)_3C_6H_2$–Br | 2,4,6-$(Me)_3C_6H_2$ | 24 | 0 |

[a] The reactions were carried out according to the conditions indicated by the above equation, 1.2 equivalent of PhMgBr (1.0 M solution in THF) used unless otherwise stated.
[b] Isolated yields (average of two runs) after flash chromatography.
[c] 2.0 mol% of $Pd(OAc)_2$ used instead of 1.0 mol% of $Pd_2(dba)_3$.
[d] 1.8 equivalent of phenylmagnesium bromide was used.
[e] 2.5 equivalents of phenylmagnesium bromide.




Scheme 6. Stille coupling reaction.

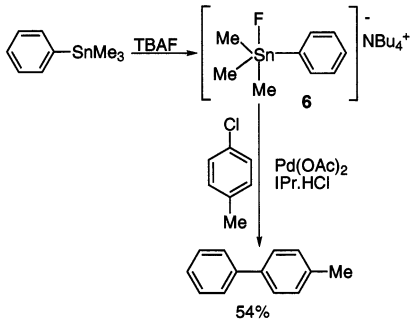
## 6. Stille reaction

The Stille reaction (Scheme 6) employs a tin reagent as coupling partner with aryl, vinyl or allyl halides (or pseudo-halides). The use of organostannanes in coupling chemistry has attracted much attention, largely owing to their ready availability, air- and moisture-stability and compatibility with a variety of functional groups. However, difficulties in removing tin from the product and tin toxicity represent major limitations/concerns associated with the Stille reaction.

Kosugi and co workers reported that a $Pd(dba)_2$–$PPh_3$–TBAF system (TBAF = tetra($^n$Bu)ammonium fluoride, [$^n Bu_4N$]F) did not catalyze the Stille coupling of aryl chlorides [53]. To overcome the limitations of the Stille reaction (slow transmetalation step and removal of tin byproducts), we investigated the use of hypervalent stannate species. Tin is fluorophilic [54] and organostannanes react with fluoride anion to afford hypervalent

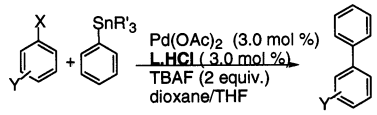
five-coordinate intermediates. These species are more labile than the organostannanes ($SnR_3R'$) themselves and are more effective in the transmetalation step [55]. Treatment of 1.1 equivalents of $Me_3PhSn$ with two equivalents of TBAF resulted in formation of a hypervalent fluorostannate anion, identified by $^{19}F$-NMR spectroscopy. This coupled with 4-chlorotoluene in the presence of $Pd(OAc)_2$–IPr·HCl (1:1 ratio of Pd–IPr·HCl) to afford the desired coupling product (Scheme 7) [56]. CsF was less effective as fluorinating agent/base when a 1:1 ratio of metal to ligand was employed, but a 1:2 M:L ratio afforded considerably better yields. The use of CsF as base with other aryl halides was, however, ineffective, as were other bases tested ($KO^tBu$, $Cs_2CO_3$, NaOH). Thus the TBAF additive appears to play a double role in the catalytic system as follows. The strong nucleophile $F^-$ initially deprotonates the imidazolium chloride to form the free carbene in situ, which coordinates to palladium. It also accelerates the transmetalation step via formation of the more reactive hypervalent species. An additional advantage of TBAF is that it serves as fluorous medium for tin extraction, facilitating removal of tin by simple water extraction. Investigation of other imidazolium salts as ligand precursors demonstrated that the bulkier and less electron-donating IAd·HCl was also an effective ligand for the cross-coupling of 4-chlorotoluene and $Me_3PhSn$. In contrast to its performance in Suzuki–Miyaura, IMes·HCl was found to be ineffective in the Stille reaction. Both Pd(II)–IPr·HCl and Pd(II)–IAd·HCl were effective in the cross-coupling of electron-neutral and -deficient aryl bromides with either $Me_3PhSn$ or ($^nBu)_3PhSn$ (Table 8). The electron-rich 4-bromoanisole coupled rapidly only with the more reactive $Me_3PhSn$ using IPr·HCl as ligand, leading to a 92% yield. *Ortho*-substituted aryl bromides required longer reaction times with $Me_3PhSn$. These catalyst–ligand systems were unsuitable for couplings involving electron-neutral and -rich aryl chlorides, although good yields were obtained with 4-chloroacetophenone.

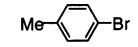
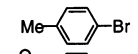
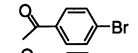
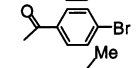
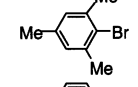
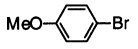
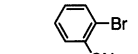
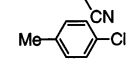
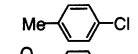
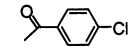
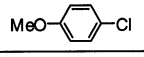
Similar catalytic behavior was observed for the coupling of aryl halides with vinylstannanes (Table 9).




Scheme 7. Formation of hypervalent organostannate followed by Stille coupling reaction.

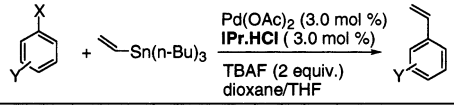
Table 8
$Pd(OAc)_2$–L·HCl-catalyzed cross-coupling of aryl halides with arylstannanes [a]

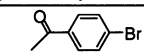
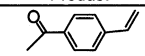
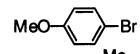
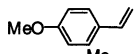
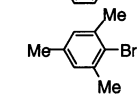
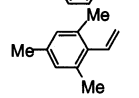
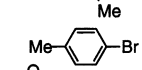
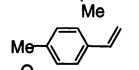
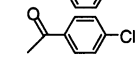
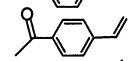
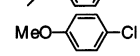
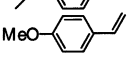
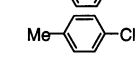
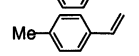



| Entry | Aryl Halide | Tin Reagent | L | Time (h) | Yield(%)[b,c] |
|---|---|---|---|---|---|
| 1 |  | $Me_3PhSn$ | IPr.HCl | 1.5 | 90 |
| 2 |  | $Ph(n\text{-}Bu)_3Sn$ | IAd.HCl | 3 | 91 |
| 3 |  | $Me_3PhSn$ | IPr.HCl | 0.5 | 92 |
| 4 |  | $Me_3PhSn$ | IAd.HCl | 1 | 86 |
| 5 |  | $Me_3PhSn$ | IPr.HCl | 48 | 86 |
| 6 |  | $Me_3PhSn$ | IPr.HCl | 2 | 92 |
| 7 |  | $Me_3PhSn$ | IPr.HCl | 48 | 80 |
| 8 |  | $Me_3PhSn$ | IPr.HCl | 24 | 54 |
| 9 |  | $Ph(n\text{-}Bu)_3Sn$ | IAd.HCl | 12 | 45 |
| 10 |  | $Me_3PhSn$ | IPr.HCl | 1 | 91 |
| 11 |  | $Me_3PhSn$ | IPr.HCl | 48 | 35 |

[a]Reaction conditions: 1.0 mmol of aryl halide, 1.1 mmol of arylstannane, 2 mmol TBAF, 3.0 mol% $Pd(OAc)_2$, 3.0 mol% L·HCl, 1 ml dioxane, 80 °C for aryl bromides (100 °C for aryl chlorides). [b]Isolated yields. [c]All reactions were monitored by GC.

Table 9
$Pd(OAc)_2$–IPr·HCl-catalyzed cross-coupling of aryl halides with vinylstannane [a]




| Entry | Aryl Halide | Product | Time (h) | Yield(%)[b,c] |
|---|---|---|---|---|
| 1 |  |  | 3 | 92 |
| 2 |  |  | 48 | 69 |
| 3 |  |  | 48 | 25 |
| 4 |  |  | 48 | 98 |
| 5 |  |  | 3 | 83 |
| 6 |  |  | 24 | 15 |
| 7 |  |  | 12 | 41 |

[a]Reaction conditions: 1.0 mmol of aryl halide, 1.1 mmol of vinylstannane, 2 mmol TBAF, 3.0 mol% $Pd(OAc)_2$, 3.0 mol% IPr·HCl, 1 ml dioxane, 80 °C for aryl bromides (100 °C for aryl chlorides). [b]GC yields. [c]All reactions were monitored by GC.

Unlike aryl bromides that reacted easily with tributylvinylstannane, only moderate conversion was observed with the electron-deficient 4-chloroacetophenone. These results suggest that the coupling of aryl chlorides requires more vigorous conditions and is facilitated by electron-withdrawing substituents, consistent with the rate-determining step of the reaction being oxidative addition of the aryl halide to the metal.

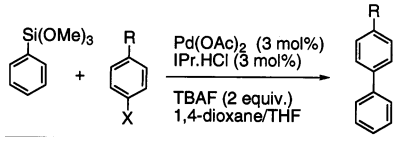
## 7. Cross-coupling with phenyl- or vinyltrimethoxysilane

The use of silicon-derived compounds as transmetalation reagents presents a viable option to other coupling processes owing to its low cost, easy availability, nontoxic byproducts and stability to different reaction conditions [57]. However, high catalyst and phosphine loading are usually required to obtain high yields for unactivated aryl chlorides with this methodology.

The reaction of one equivalent aryl halide with two equivalents phenyltrimethoxysilane in the presence of 3 mol% $Pd(OAc)_2$ and 3 mol% IPr·HCl in 1,4-dioxane–THF at 80 °C gave both the desired coupling products and the homocoupling product [58,59]. The best catalytic activity was observed with aryl bromides and activated aryl chlorides (Table 10). Only poor activity was achieved with 4-chlorotoluene and 4-chloroanisole, even with prolonged reaction times. The reaction was applicable to heteroaryl halides (Scheme 8), affording moderate yields after longer reaction times.

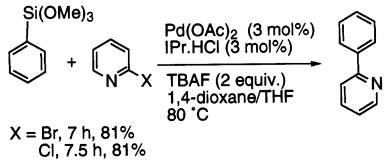
A preliminary study demonstrated that the $Pd(OAc)_2$–IPr·HCl catalytic system also mediates the coupling of aryl halides with vinyltrimethoxysilane to form substituted styrenes (Scheme 9). The reactions are quantitative but require longer reaction times.

Table 10
Pd–IPr catalyzed cross-coupling of aryl halides with phenyltrimethoxysilane

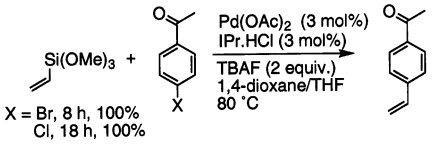



| Entry | X | R | Time (h) | Yield (%) [a] |
|---|---|---|---|---|
| 1 | Br | H | 3 | 100 |
| 2 | Br | Me | 6 | 93 [b] |
| 3 | Br | COMe | 1 | 100 |
| 4 | Cl | OMe | 17 | 19 [c] |
| 5 | Cl | Me | 4 | 29 |
| 6 | Cl | COMe | 3 | 100 |
| 7 | Cl | CN | 2 | 100 |

[a] GC yields.
[b] 60 °C; three equivalents of $PhSi(OMe)_3$.
[c] Isolated yield.




Scheme 8. Pd–IPr catalyzed cross coupling of 2-chloro- and 2-bromopyridine with phenyltrimethoxysilane.



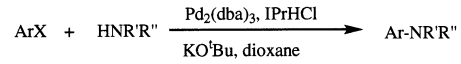

Scheme 9. Pd–IPr catalyzed coupling of 4-bromo-acetophenone with vinyltrimethoxysilane.

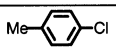
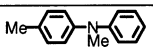
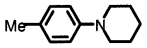
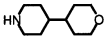
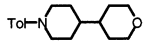
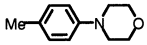
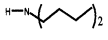
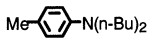
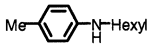
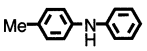
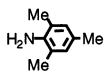
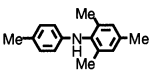
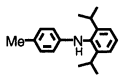
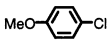
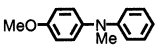
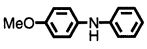
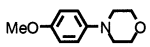
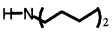
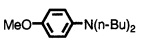
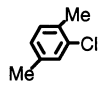
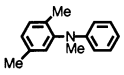
## 8. Amination

Pd- and Ni-mediated coupling of aryl halides with amines has attracted significant interest owing to the use of this methodology in organic synthesis and materials science [10]. The pioneering studies of Hartwig and Buchwald on catalytic amination demonstrated that the supporting ligands on the metal center play a crucial role in dictating the efficiency of a catalytic system [60]. Hartwig showed recently that bulky monodentate tertiary phosphines can be used as ancillaries in aryl amination [61]. The success of the Pd–imidazolium salt system as a mediator of C–C bond-forming reactions prompted us to turn our attention to C–N coupling processes [62,63]. We found that the protocol previously employed in Suzuki–Miyaura and Kumada–Corriu couplings, using the bulky nucleophilic carbene precursor IPr·HCl as supporting ligation, permitted the catalytic C–N coupling of aryl iodides and bromides at room temperature and the less reactive aryl chlorides (at elevated temperature). The use of $KO^tBu$ as added base and 1,4-dioxane as solvent led to high yields of coupling products from primary and secondary, cyclic and acyclic amines with various aryl halides (Table 11). The role of added $KO^tBu$ is twofold. It effects deprotonation of the imidazolium salt to liberate free carbene ligand, and it acts as a strong base to neutralize the HX formed in the course of the coupling reaction. 4-Chlorotoluene and *ortho*-substituted aryl halides could be aminated in good to excellent yields with a range of amines. Even 4-chloroanisole coupled with sterically unhindered amines in good to excellent yields. Initial studies employed a Pd–IPr·HCl ratio of 1:2 [62]. Subsequent investigation, however, revealed that optimal conditions were achieved with a 1:1 M:L ratio [63].

The scope of the reaction was expanded to the amination of heteroaromatic halides. N-Containing molecules can have an adverse effect on the activity of catalytic processes, via undesired coordination to the

Table 11
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 |

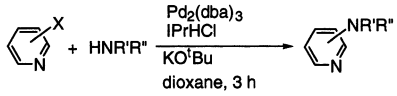
[a]Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of amine, 1.5 mmol of KO$^t$Bu, 1.0 mol% $Pd_2(dba)_3$, 4.0% IPr·HCl (2L/Pd), 3 ml of dioxane, 100 °C. Reaction was complete in 3–24 h and reaction times were not minimized. [b]Isolated yields.

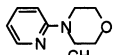
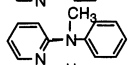
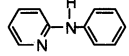
metal. In this case, no problems were encountered and both 2-chloro- and 2-bromopyridine were aminated in good to excellent yields (Table 12).

### 8.1. Amination of aryl halides with an ammonia analogue

Synthetic routes to N-unsubstituted anilines often involve nitration, reduction or substitution and are usually incompatible with functional groups, necessitating protection and deprotection steps [64]. The extension of the amination reaction to the synthesis of benzophenone imine adducts using benzophenone imine as an ammonia surrogate represents an efficient alternative route owing to its low cost, easy availability and stability

Table 12
Amination of chloropyridines 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 |

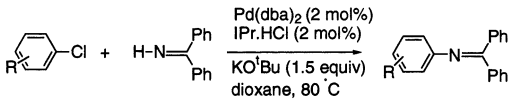
[a]Reaction conditions: 1.0 mmol of chloro or bromopyridine, 1.1 mmol of amine, 1.5 mmol KO$^t$Bu, 1L/Pd, 3 ml dioxane, 3 h 100 °C. [b]Isolated yields. [c]All reactions were monitored by GC.

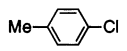
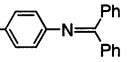
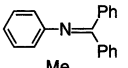
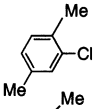
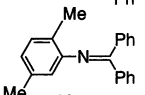
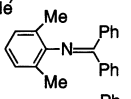
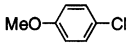
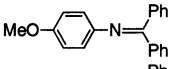
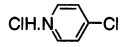
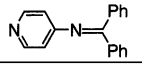
to many reaction conditions [10c,10e,65]. Employing the established amination catalytic conditions, benzophenone imine reacted readily with unactivated and *ortho*-substituted aryl chlorides in high yield at 80 °C (Table 13). The reactions with 4-chlorotoluene and 4-chloroanisole were faster and cleaner at 100 °C. Aryl bromides (Table 14) similarly required higher temperatures (100 °C), possibly because although oxidative addition of the aryl bromide occurs rapidly, Pd–N bond formation is slower for the LPd(Ar)Br complex [66]. Attempts using activated aryl halides and KO$^t$Bu as base were unsuccessful, owing to base promoted cleavage of the substrate. Weaker bases such as $Cs_2CO_3$, $K_2CO_3$ or $K_3PO_4$ gave only poor conversion. Finally, acidic cleavage of the benzophenone imine adducts afforded primary anilines in good to high yields.

### 8.2. N-Arylation of aryl indoles

N-Aryl indoles are attractive synthetic targets since they can be biologically active [67] or useful intermediates in the synthesis of biologically active agents [68]. Catalytic N-arylation of indoles is generally restricted to

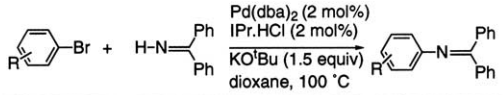
Table 13
Amination of aryl chlorides with benzophenone imine [a]

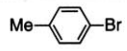
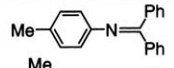
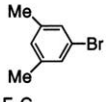
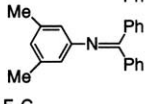
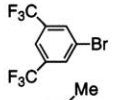
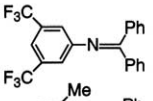
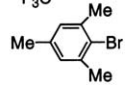
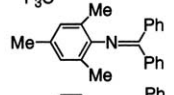
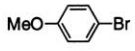
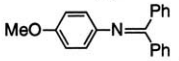
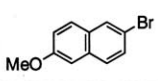
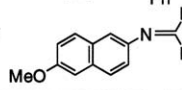



| Entry | Aryl Chloride | Product | Time (h) | Yield (%)[b,e] |
|---|---|---|---|---|
| 1 |  |  | 4 | 99[c] |
| 2 |  |  | 24 | 96 |
| 3 |  |  | 5 | 99 |
| 4 |  |  | 5 | 98 |
| 5 |  |  | 6 | 99[c] |
| 6 |  |  | 48 | 60[c,d] |

[a]Reaction conditions: 1.0 mmol of aryl chloride, 1.05 mmol of benzophenone imine, 1.5 mmol KO$^t$Bu, 2.0 mol% $Pd(dba)_2$, 2.0 mol% IPr·HCl, 3 ml 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 14
Amination of aryl bromides with benzophenone imine [a]



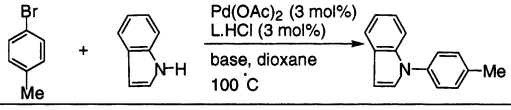

| Entry | Aryl Bromide | Product | Time (h) | Yield (%)[b,d] |
|---|---|---|---|---|
| 1 |  |  | 3 | 98 |
| 2 |  |  | 10 | 99 |
| 3 |  |  | 48 | 60 |
| 4 |  |  | 10 | 99[c] |
| 5 |  |  | 5 | 99 |
| 6 |  |  | 5 | 98 |

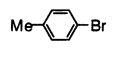
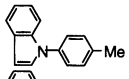
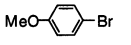
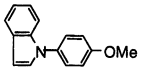
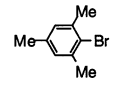
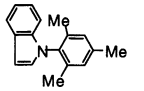
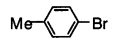
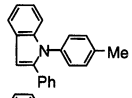
[a]Reaction conditions: 1.0 mmol of aryl bromide, 1.05 mmol of benzophenone imine, 1.5 mmol KO$^t$Bu, 2.0 mol% $Pd(dba)_2$, 2.0 mol% IPr·HCl, 3 ml dioxane, 100 °C. [b]Isolated yields. [c]The reaction was performed at 80 °C. [d]All reactions were monitored by GC.

aryl iodides and bromides owing to involvement of aromatic nitrogen in the reaction [69]. A handful of examples involving arylchlorides and indole derivatives have been reported [70]. Our general amination procedure did not effect the arylation of indoles. Screening other ligands and bases in search of a suitable combination to activate the strong *N*(aromatic)–H bond, we obtained the best results with a $Pd(OAc)_2$–SIPr·HCl–NaOH system. This protocol was effective for a variety of aryl bromides and indole derivatives (Table 15) and in addition overcomes a widely encountered problem in N-substituted aryl indole synthesis associated with C-arylation side products.

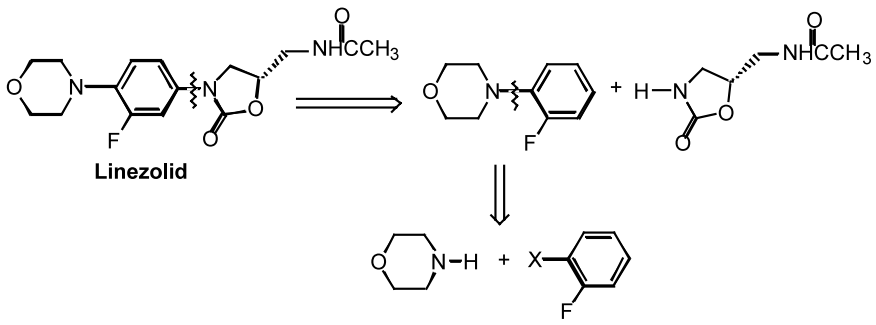
We tested the palladium–imidazolium salt systems in the synthesis of a pharmaceutical target. Linezolid is a member of a new class of oxazolidinone-derived antibiotics [71]. One of the important features of the oxazolidinones is an aryl N-substituted amine moiety (Scheme 10), which could potentially be assembled via a palladium-mediated C–N bond formation. The strategic intermediate to the oxazolidinones, *N*-(2-fluorophenyl)morpholine, was isolated in good yields under unoptimized conditions (Scheme 11).

Table 15
Amination of aryl bromides with various indoles [a]

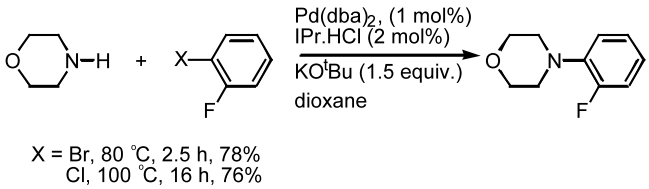



| entry | aryl bromide | indole | product | time (h) | yield (%)[b,d] |
|---|---|---|---|---|---|
| 1 |  |  |  | 3.5 | 97 |
| 2 |  | |  | 1 | 100 |
| 3 |  | |  | 3.5 | 88 |
| 4 |  | |  | 16 | 68 |
| 5 |  |  |  | 3 | 100[c] |
| 6 |  | |  | 18 | 100[c] |
| 7 |  | |  | 10 | 61[c] |
| 8 |  |  |  | 3 | 97[c]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

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




Scheme 10. Synthesis of linezolid intermediate.




Scheme 11.

## 9. Conclusions

N-Heterocyclic nucleophilic carbenes have been shown to be excellent substitutes for phosphines in a wide range of catalytic processes. Their application to palladium-mediated cross-coupling reactions has resulted in some unprecedented catalytic activity, particularly with the 'difficult' aryl chlorides as substrates. Their superior qualities as supporting ligands can be attributed to their thermal stability and to their tunable steric and electronic parameters that stabilize the zerovalent palladium intermediate prior to oxidative-addition of the substrate. In conclusion, nucleophilic carbenes are an attractive ancillary ligand set, and their use in metal-catalyzed processes is very promising.

## Acknowledgements

The National Science Foundation, the Louisiana Board of Regents, the Petroleum Research Fund administered by the American Chemical Society are gratefully acknowledged for support of this research.

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