

Palladium/Nucleophilic Carbene Catalysts for Cross-Coupling Reactions

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Palladium complexes bearing N-heterocyclic nucleophilic carbenes can function as efficient and convenient mediators of C–C and C–N cross-coupling reactions. These phosphine-free systems are highly effective in coupling reactions of aryl bromides and aryl chlorides with a variety of coupling partners. Some applications of these palladium complexes in a range of coupling reactions are described here and catalysts, conditions and results are presented.

Palladium and nickel based catalysts have provided a plethora of new methodologies for synthetic organic chemistry. Palladium-catalysed cross-coupling of aryl halides (or halide analogues) with nucleophiles is firmly established as one of the most important methods available for C–C and C–N bond formation (1–4). These cross-coupling reactions employ a range of transmetallating agents, examples of which are shown in Figure 1.

Palladium and nickel complexes containing phosphine ligands are among the most successful and widely used catalyst precursors for coupling of sp^2 carbons, and bulky electron-rich tertiary alkyl phosphines are particularly effective (5–7). Significant advances have been made in using aryl chlorides as cross-coupling partners, with a

number of processes mediated by palladium-bulky phosphine systems (8, 9). Their success is explained by reference to the catalytic cycle depicted in Figure 2. The increased electron-richness imparted to the metal centre by the electron-donating phosphine assists in the cleavage of an Ar–X bond in the first, oxidative addition, step, while the steric bulk of the ligand promotes the reductive elimination of the Ar–Ar' coupling product following transmetalation with $[M]-Ar'$. While Heck and amination (and CuI-free Sonogashira) reactions do not, strictly speaking, involve a transmetalation step, they are generally included in discussions of cross-coupling chemistry since their catalytic cycles possess essentially the same features.

Recently, alternatives to phosphines have been sought owing to certain of their 'user-unfriendly' properties, namely air- and moisture-sensitivity and thermal instability, which means that excess ligand is often required to stabilise low-valent metal centres during the catalytic cycle.

Highly promising and versatile alternatives to phosphines have been found in the *N*-heterocyclic nucleophilic carbene (NHC) class of ligand (10) (see Figure 3), often referred to as Arduengo carbenes, following their isolation by Arduengo in 1991 (11). These carbenes are neutral two electron σ -donors (12), generally bearing bulky and/or electron-donating *N*-substituents. Arduengo carbenes exhibit greater thermal stability than phosphines and can bind more strongly to a metal centre (10a), eliminating the need for excess ligand

Reaction	Reagent, [M]-Ar'
Suzuki-Miyaura	Ar'-B(OH) ₂
Kumada	Ar'-MgX
Negishi	Ar'-ZnX
Stille	Ar'-SnR'' ₃
Hiyama	Ar'-Si(OR'') ₃
Heck	=C(R'')
Sonogashira	$\text{Y-C}\equiv\text{C-R''}$
Hartwig-Buchwald Amination	HNR''R'''

Fig. 1 Coupling partners for cross-coupling with aryl halides

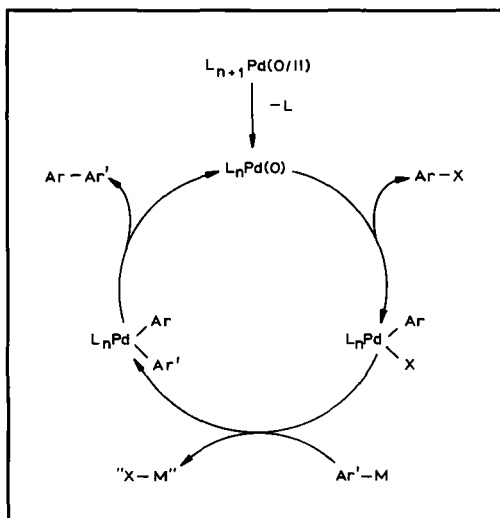


Fig. 2 Catalytic cycle for palladium complex-mediated cross-coupling reactions; where $Ar'-M$ is organoboronic acid, organostannane, organomagnesium, organosilicon, amine, etc.

during catalytic processes. They have proven to be extremely effective ancillary ligands in a broad range of metal complex-catalysed processes (13), with reactivity often surpassing that observed with phosphine ligation (another notable example being in ruthenium-catalysed olefin metathesis (14)). Some of our recent work, in the area of cross-coupling chemistry employing palladium complexes with *N*-heterocyclic nucleophilic carbenes as catalyst precursors, is reviewed here.

Cross-Coupling via Transmetalation

Suzuki-Miyaura Cross-Coupling of Aryl Halides or Pseudo-Halides with Arylboronic Acids (15)

The coupling reaction of aryl and heteroarylboronic acids with aryl and heterocyclic halides or triflates is a powerful method for preparing various biaryl systems and is widely used in synthesising natural products (16). The importance of the palladium-catalysed Suzuki-Miyaura cross-coupling reaction cannot be overstated in view of its general use in a variety of C–C bond formations and is underscored by the large volume of research published in the last year, including extension to aqueous and supercritical CO_2 media and polymer-supported catalysts (17). Indeed, on a

commercial scale the Suzuki-Miyaura reaction is usually preferred to other C–C bond-forming processes since organoboronic acids are conveniently synthesised reagents (18), and are generally thermally stable and inert to water and oxygen. NHC ligands have been employed with great success in this process (19).

Our initial research in this area focused on the use of catalytic quantities of zerovalent $Pd_2(dba)_3$ as the precursor in conjunction with the carbene IMes and Cs_2CO_3 as base (19e). This combination afforded a yield of 59% in the coupling of 4-chlorotoluene with phenylboronic acid. The catalytic protocol could be simplified and improved by the use of air-stable IMes-HCl as ligand precursor and deprotonating *in situ* with Cs_2CO_3 . Other combinations of NHC and base were less effective in this reaction.

Subsequently a simpler catalytic system was achieved by using air-stable Pd(II) precursors, eliminating the need for a drybox to load the catalytic components (20). The catalytic system was activated by heating at 80°C for 30 minutes under an argon atmosphere, during which time the base reacts with the Pd(II) salt and IMes-HCl to generate the NHC and the active Pd(0) catalyst, prior to adding substrate. The catalytic activity of the

R 2,4,6-trimethylphenyl 2,6-di- <i>iso</i> -propylphenyl 4-methylphenyl 2,6-dimethylphenyl cyclohexyl adamantyl	L IMes IPr ITol IXy ICy IAd
R 2,4,6-trimethylphenyl 2,6-di- <i>iso</i> -propylphenyl cyclohexyl	L SIMes SIPr SICy

Fig. 3 *N*-Heterocyclic nucleophilic carbenes (NHCs)

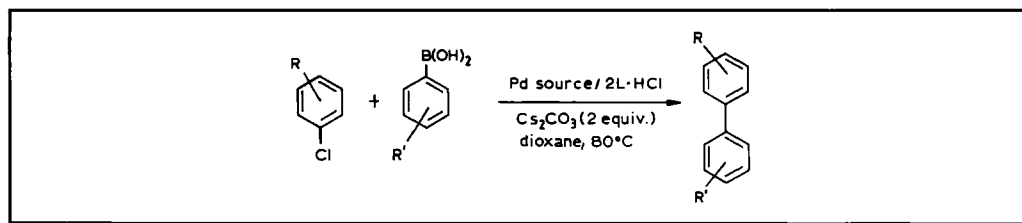


Table I
Functional Group Tolerance of Suzuki-Miyaura Cross-Coupling Using Pd/Imidazolium Salt Catalysts^a

Pd source	R	R'	Time, h	Yield, % ^b	
				IMes·HCl ^c	IPr·HCl ^d
Pd ₂ (dba) ₃	4-CH ₃	H	1.5	90	95
Pd ₂ (dba) ₃	4-CH ₃	4-OCH ₃	1.5	99	99
Pd ₂ (dba) ₃	4-CH ₃	2-CH ₃	1.5	88	97
Pd ₂ (dba) ₃	4-CH ₃	3-OCH ₃	1.5	91	95
Pd ₂ (dba) ₃	4-OCH ₃	H	1.5	93	99
Pd ₂ (dba) ₃	2,5-(CH ₃) ₂	H	1.5	95	95
Pd ₂ (dba) ₃	H	4-OCH ₃	1.5	99	79 ^e
Pd ₂ (dba) ₃	4-C(O)OCH ₃	H	1.5	99	98
Pd ₂ (dba) ₃	4-C(O)CH ₃	H	1.5	81 ^e	99 ^f
Pd ₂ (dba) ₃	4-CN	H	1.5	80 ^e	100 ^f
Pd(OAc) ₂	4-CH ₃	H	2	99	–
Pd(OAc) ₂	4-CH ₃	4-OCH ₃	2	80	–
Pd(OAc) ₂	4-CH ₃	2-CH ₃	2	50	–
Pd(OAc) ₂	4-CH ₃	3-OCH ₃	19	93	–
Pd(OAc) ₂	4-C(O)OCH ₃	H	2	99	–
Pd(OAc) ₂	4-CH ₃	H	8	85	–
Pd(OAc) ₂	3-N(CH ₃) ₂	H	2	98 ^g	–
Pd(OAc) ₂	2,5-(CH ₃) ₂	H	2	94	–
Pd(OAc) ₂	2,5-(CH ₃) ₂	H	2	98 ^h	–
Pd(OAc) ₂	2,5-(CH ₃) ₂	H	2	69 ^g	–

^a Reaction conditions: 1.0 mmol aryl chloride, 1.5 mmol arylboronic acid, 2.0 mmol Cs₂CO₃, 2 L/Pd, 80°C;

^b Isolated yields;

^c Pd₂(dba)₃/IMes·HCl = (1.5 mol%)/(3.0 mol%), Pd(OAc)₂/IMes·HCl = (2.5 mol%)/(2.5 mol%);

^d Pd₂(dba)₃/IPr·HCl = (1.0 mol%)/(2.0 mol%);

^e 16 hours; ^f 3 hours; ^g 5 mol% of IMes·HCl; ^h Pd(OAc)₂/IMes·HCl = (5.0 mol%)/(5.0 mol%)

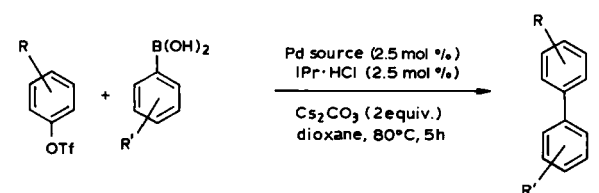
system was also investigated as a function of the imidazolium salt (NHC precursor). NHC *N*-substituents comprising bulky *ortho*-substituted aryl groups (IMes·HCl, IPr·HCl, IXy·HCl) displayed the highest activities, indicating that steric factors dictate the catalytic system effectiveness.

Both Pd(0) (Pd₂(dba)₃/IMes·HCl; Pd₂(dba)₃/IPr·HCl) and Pd(II) (Pd(OAc)₂/IMes·HCl) systems were found to be exceptionally tolerant to functional groups on the aryl chloride and boronic acid. Excellent yields were obtained with some diverse electron-donating and electron-withdraw-

ing substituents, with slightly lower yields observed for sterically-hindered *ortho*-substituted reagents, see Table I. This protocol could also be applied to the cross-coupling of aryl triflates with phenylboronic acids, as shown in Table II.

Kumada-Tamao-Corriu Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents

Arylboronic acids and other organometallic reagents employed in C–C coupling reactions are often prepared from the corresponding Grignard or organolithium reagents (15a). Three years after

			
<p>Table II Functional Group Tolerance of Pd Source/IPr·HCl-Catalysed Suzuki Cross-Coupling of Aryl Triflates with Phenylboronic Acid Derivatives^a</p>			
Pd source	R	R'	Yield, % ^b
Pd(OAc) ₂	4-OCH ₃	H	86
Pd(OAc) ₂	4-OCH ₃	4-OCH ₃	81
Pd ₂ (dba) ₃	4-OCH ₃	H	97
Pd ₂ (dba) ₃	4-OCH ₃	4-CH ₃	98
Pd(OAc) ₂	H	4-OCH ₃	85
Pd ₂ (dba) ₃	H	4-CH ₃	99
Pd(OAc) ₂	4-C(O)CH ₃	H	76
Pd(OAc) ₂	4-C(O)CH ₃	4-OCH ₃	77
Pd ₂ (dba) ₃	4-C(O)CH ₃	4-CH ₃	97

^a Reaction conditions: 1.0 mmol of aryl triflate, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs₂CO₃, 2.5 mol% Pd source, 2.5 mol% IPr·HCl, 80°C; ^b Isolated yields

the first reports, in 1972, of the Ni(II)-catalysed reaction of Grignards with alkenyl or aryl halides (21, 22), the Pd-catalysed reaction was described (23). Several reports have appeared since, detailing phosphine-modified Pd- or Ni-mediated coupling of Grignards with aryl halides (5a, 5b, 5n–5v). We recently reported the first example of successful coupling involving unactivated aryl chlorides and an aryl Grignard reagent (24).

The reaction between 4-chlorotoluene and phenylmagnesium bromide was selected for the initial screening of the Pd source and ligand. The system Pd₂(dba)₃/IPr·HCl in a 1,4-dioxane/THF solvent mixture at 80°C was found to be most effective (quantitative conversion in 3 h), although replacing 1 mol% Pd₂(dba)₃ with 2 mol% Pd(OAc)₂ afforded similar conversions. No additional base was necessary as a small excess of PhMgBr was utilised. The catalytic system was tested with a range of substituted aryl halide substrates and Grignard reagents (Table III) and found to be extremely tolerant of electronic variation in the substituents; even 4-chloroanisole

(which is particularly inactive) afforded quantitative conversion in three hours. Although *ortho*-substituents on the aryl Grignard reagents were tolerated well, *ortho*-substituted aryl chlorides required a larger excess of Grignard (1.8 equivalents) to achieve good yields. Steric congestion around both reactive centres (as encountered in the reactions of 2-chloro-*m*-xylene or 2-bromo-mesitylene with mesityl magnesium bromide) resulted in no conversion.

Stille Cross-Coupling of Aryl Halides with Hypervalent Organostannanes

The use of readily available, air- and moisture-stable organotin reagents, SnR''₃R, as cross-coupling partners represents one of the most versatile of coupling methods in organic chemistry. One important advantage of tin reagents is their compatibility with a large variety of functional groups. However, there are significant disadvantages to their use, most notably the difficulty of removing tin from the product and there are concerns regarding the toxicity of tin. A further

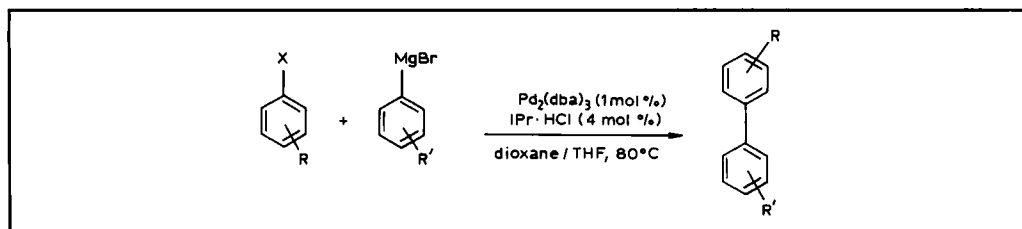


Table III
Palladium/Imidazolium Salt-Catalysed Cross-Coupling of Aryl Halides with Aryl Grignard Reagents^a

X	R	R'	Time, h	Yield, % ^b
Cl	4-CH ₃	H	3	99
Cl	4-CH ₃	H	3	99 ^c
Br	4-CH ₃	H	1	99
Cl	4-OCH ₃	H	3	97
Cl	2,5-(CH ₃) ₂	H	3	85
Cl	2,6-(CH ₃) ₂	H	5	87 ^d
Br	4-CO ₂ CH ₃	H	5	69
I	4-OH	H	3	96 ^e
Cl	4-OH	H	5	95 ^e
Cl	4-OCH ₃	4-CH ₃	3	99
Cl	4-OCH ₃	3-CH ₃	3	83
Cl	4-OCH ₃	2-F	3	99
Cl	4-OCH ₃	2,4,6-(CH ₃) ₃	3	95
Cl	2,6-(CH ₃) ₂	2,4,6-(CH ₃) ₃	24	0
Br	2,4,6-(CH ₃) ₃	2,4,6-(CH ₃) ₃	24	0

^a The reactions were carried out according to the conditions indicated by the above equation, 1.2 equivalents 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 Pd₂(dba)₃; ^d 1.8 equivalents of phenylmagnesium bromide were used; ^e 2.5 equivalents of phenylmagnesium bromide were used

limitation is their high stability which results in a slow transmetalation step in the catalytic cycle. To avoid these limitations we investigated the use of hypervalent stannate species. Fluorophilic organostannanes (25) react with fluoride anion to give hypervalent five-coordinate intermediates which are more labile than the parent organostannanes and thus expected to transmetallate more effectively (26).

We identified a hypervalent fluorostannate anion by ¹⁹F NMR spectroscopy after treating SnMe₃Ph with 2 equivalents of tetrabutylammonium fluoride (TBAF). In the presence of catalytic amounts of Pd(OAc)₂ and IPr·HCl this intermediate coupled with 4-chlorotoluene to afford the desired biaryl cross-coupling product (27). Other bases that were screened for activity (CsF, KOBu', Cs₂CO₃, NaOH) were essentially ineffective. The

TBAF appears to play a dual role in the catalytic system, acting both as the base/nucleophile to deprotonate the NHC precursor imidazolium salt and as the fluorinating agent, accelerating the transmetalation step via formation of the more reactive hypervalent organostannate. An additional advantage of using TBAF is that it serves as a fluorous medium for tin extraction, aiding the removal of tin by simple water extraction. Both the Pd(II)/IPr·HCl and Pd(II)/IAd·HCl systems were effective in the cross-coupling of electron-neutral and electron-deficient aryl bromides with SnMe₃Ph or Sn(Buⁿ)₃Ph (see Table IV). Electron-rich 4-bromoanisole proved less facile and only coupled rapidly with the more reactive SnMe₃Ph employing IPr·HCl as ligand precursor. *Ortho*-substituted aryl bromides required longer reaction times with SnMe₃Ph. Unactivated aryl chlorides

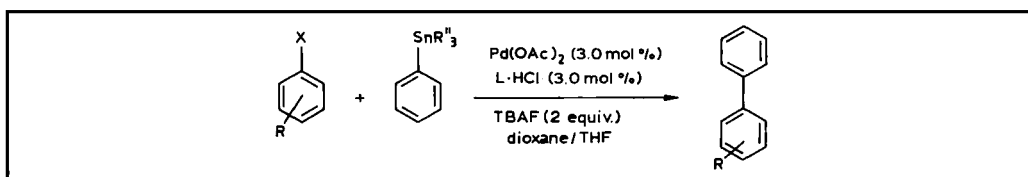


Table IV
Pd(OAc)₂/L·HCl-Catalysed Stille Coupling^a

X	R	Tin reagent	L	Time, h	Yield, % ^b
Br	4-CH ₃	SnMe ₃ Ph	IPr·HCl	1.5	90
Br	4-CH ₃	Sn(Bu ⁿ) ₃ Ph	IAd·HCl	3	91
Br	4-C(O)CH ₃	SnMe ₃ Ph	IPr·HCl	0.5	92
Br	4-C(O)CH ₃	SnMe ₃ Ph	IAd·HCl	1	86
Br	2,4,6-(CH ₃) ₃	SnMe ₃ Ph	IPr·HCl	48	86
Br	4-OCH ₃	SnMe ₃ Ph	IPr·HCl	2	92
Br	2-CN	SnMe ₃ Ph	IPr·HCl	48	80
Cl	4-CH ₃	SnMe ₃ Ph	IPr·HCl	24	54
Cl	4-CH ₃	Sn(Bu ⁿ) ₃ Ph	IAd·HCl	12	45
Cl	4-C(O)CH ₃	SnMe ₃ Ph	IPr·HCl	1	91
Cl	4-OCH ₃	SnMe ₃ Ph	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

were unsuitable coupling partners for this catalytic system, although good yields were obtained with 4-chloroacetophenone.

The same catalytic method also effected the

coupling of aryl bromides with vinylstannanes in good to moderate yields, (Table V) although for the aryl chlorides, moderate conversion was observed only with the electron-deficient

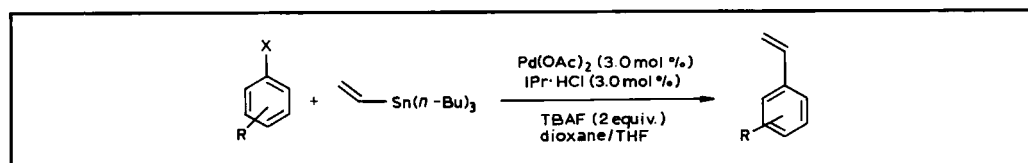


Table V
Pd(OAc)₂/IPr·HCl-Catalysed Cross-Coupling of Aryl Halides with Vinylstannane^a

X	R	Time, h	Yield, % ^b
Br	4-C(O)CH ₃	3	92
Br	4-OCH ₃	48	69
Br	2,4,6-(CH ₃) ₃	48	25
Br	4-CH ₃	48	98
Cl	4-C(O)CH ₃	3	83
Cl	4-OCH ₃	24	15
Cl	4-CH ₃	12	41

^a Reaction conditions: 1.0 mmol aryl halide, 1.1 mmol 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

4-chloroacetophenone. The results suggest that coupling of aryl chlorides is facilitated by electron-withdrawing substituents, consistent with a rate determining oxidative addition step.

Organosilanes as Coupling Partners

Silicon-derived compounds are viable alternatives to other transmetallating agents owing to their low cost, easy availability, low-toxicity byproducts and stability to different reaction conditions (28). However, for electron-rich or -neutral aryl chlorides high yields are only obtained with high catalyst and phosphine loadings.

The reaction of one equivalent of aryl halide with two of phenyltrimethoxysilane in the presence of 3 mol% each of Pd(OAc)₂ and IPr-HCl and two equivalents (per Pd) TBAF in 1,4-dioxane at 80°C afforded both the desired coupling products and the homocoupling product (29, 30). As in Stille coupling, rapid, quantitative conversion was achieved with aryl bromides and electron-deficient aryl chlorides (4-chloroacetophenone, 4-chlorobenzonitrile) but poor activity was observed with unactivated chlorides (4-chlorotoluene, 4-chloroanisole) despite prolonged reaction times. This protocol was also applicable to heteroaryl halides,

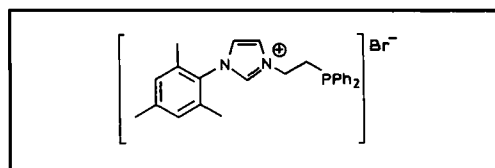


Fig. 4 Chelating carbene-phosphine (imidazolium salt depicted)

affording moderate yields with longer reaction times. A further analogy with the tin chemistry is suggested by a preliminary study which indicated that substituted styrenes are obtained in quantitative yield (after prolonged reaction times) from the reaction of aryl halides with vinyltrimethoxysilane.

Cross-Coupling with Alkenes: Heck Reaction

The Heck reaction involves initial oxidative addition of an aryl halide to generate ArPdX, followed by insertion of an alkene into the Pd-Ar bond and subsequent liberation of the new alkene by β-hydrogen elimination (as HX) with concomitant regeneration of the Pd(0) catalyst. Thus a base is required to promote the removal of HX and provide additional driving force for the reaction. Heck coupling of an aryl moiety to an alkene is widely employed in organic synthesis in the prepa-

Table VI			
Pd/Chelating Carbene-Phosphine-Catalysed Heck Reaction of Aryl Halides with <i>n</i> -Butyl Acrylate ^a			
X	R	Time, h	Yield, % ^b
Br	4-C(O)H	0.25	100
Br	H	1	100
Br	4-CH ₃	1.5	100
Br	2-CH ₃	1	35
Br	3,5-CH ₃	1	99
Br	4-OCH ₃	3	99
Br	3-OCH ₃	2	99
Cl	H	2	13

^a Reaction conditions: 1 mmol aryl halide; 1.4 mmol *n*-butyl acrylate;

^b GC yield (diethyleneglycol di-*n*-butyl ether as GC standard; average of two runs)

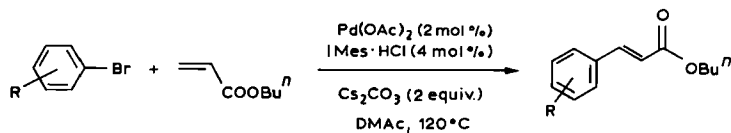


Table VII

Pd(OAc)₂/IMes·HCl-Catalysed Heck Coupling of Aryl Bromides with *n*-Butyl Acrylate^a

R	Time, h	Yield, % ^b
4-C(O)H	0.25	100
4-CN	0.5	100
H	1	97
4-CH ₃	1	94
4-CH ₃	1	99 ^c
2-CH ₃	0.5	16
2-CH ₃	1	97 ^c
3,5-(CH ₃) ₂	1	94
4-OCH ₃	1	65 ^d
4-OCH ₃	1	91
4-OCH ₃	1	99 ^c
4-OCH ₃	1	88 ^e
4-OCH ₃	1	66 ^f
4-OCH ₃	1	99

^a Reaction conditions: 1.0 mmol aryl bromide, 1.6 mmol *n*-butyl acrylate, 2 ml of DMAc;^b GC yield (diethyleneglycol di-*n*-butyl ether as GC standard); an average of two runs; ^c with addition of [Buⁿ,N]Br (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

ration of substituted olefins, dienes and precursors to conjugated polymers (50, 31). While monodentate phosphines have provided efficient catalyst modifiers, in reactions with less reactive aryl bromides and chlorides bulky electron-donating phosphines, such as PBu₃, are necessary (50). At the elevated temperatures required for Heck chemistry, both phosphines and their Pd complexes are prone to decomposition, so higher catalyst loadings are needed. Increased stability can be imparted by using chelating phosphines but only limited success has then been achieved in catalysis.

However, a high degree of efficiency has been observed in Heck reactions mediated by palladium carbene complexes (32). Following a recent theoretical study which suggested that mixed carbene-phosphine chelates were suitable for the Pd-catalysed Heck reaction (33), we prepared the carbene-phosphine chelating ligand shown in Figure 4 and investigated its efficacy in the cross-coupling of aryl bromides with *n*-butyl acrylate (34).

Optimal conditions were found using Pd(*dba*)₂ with one equivalent of L·HBr, (L = the ligand in Figure 4), two equivalents of Cs₂CO₃, and the polar solvent *N,N*-dimethylacetamide (DMAc) at 120°C. Excellent yields were obtained with a range of activated and unactivated aryl bromides (Table VI). The protocol was, however, intolerant of sterically hindered *ortho*-substituted substrates and ineffective for unactivated aryl chlorides, with prolonged reaction times resulting in side reactions in both cases.

These results were compared with those obtained employing non-chelating NHC ligands (35). Both Pd(0) and Pd(II) precursors were effective with IMes·HCl and the system using 2 mol% Pd(OAc)₂/4 mol% IMes·HCl was selected for study owing to its greater ease of execution. When the same protocol was used as that for the chelating NHC-phosphine system, high yields of *trans* coupling products were obtained with a range of aryl bromides (Table VII). With 4-bromoanisole,

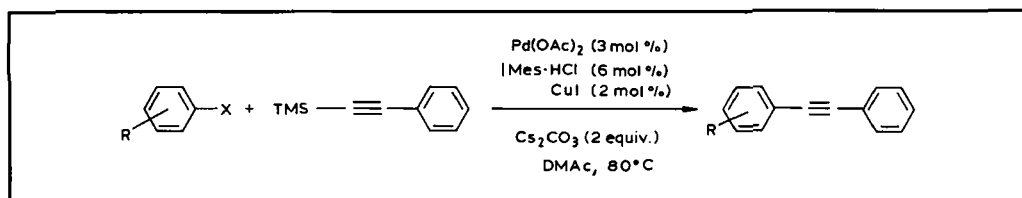


Table VIII

Pd(OAc)₂/IMes-HCl-Catalysed Sonogashira Reaction of Aryl Halides with 1-Phenyl-2-(trimethylsilyl)-acetylene^a

X	R	Time, h	Yield, % ^b
Br	4-C(O)H	0.25	100 (92) ^c
Br	H	0.5	100 (91) ^c
Br	4-CH ₃	0.5	96 (86) ^c
Br	4-CH ₃	0.5	99
Br	2-CH ₃	0.5	100 (93) ^c
Br	4-OCH ₃	0.5	82 ^c
Br	4-OCH ₃	3	94 ^d
Br	4-OCH ₃	0.5	96 (88)
Br	4-OCH ₃	1	43 ^{c, e}
Br	2-OCH ₃	0.5	100 (93)
Br	2-OCH ₃	0.5	95 ^f
Br	2,4,6-(CH ₃) ₂	1	90 (82)
Cl	H	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

4-bromotoluene and 2-bromotoluene, the conversion was improved when 20 mol% [Bu₄N]Br was added to the reaction. Aryl chlorides proved unsuitable for this system.

Cross-Coupling with Terminal Alkynes: Sonogashira Reaction

Palladium complexes are active for the coupling of terminal alkynes with aryl or alkenyl halides to give arylalkynes or conjugated enynes. These are important in assembling bioactive natural molecules and for new materials (36, 37). The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides provides a straightforward and powerful method for their synthesis (37, 38). The Pd(0)-catalysed Sonogashira coupling is most efficient when CuI is added as cocatalyst. CuI activates the alkyne by forming copper acetylide, which transmetalates with an arylpalladium halide to form the alkynyl-aryl-palladium species.

Reductive elimination affords the arylalkyne coupling product and regenerates the Pd(0) catalyst and CuI.

A recent report described the unusually high activity of a palladium system modified by PBu₃ in the Sonogashira coupling of aryl bromides (39). To our knowledge only a handful of Pd/NHC-mediated Sonogashira reactions have been reported, and these deal only with activated aryl bromides (40, 41). After different ligands and bases were screened, a similar set of conditions to that used for Heck coupling was adopted, namely the combination: Pd(OAc)₂/IMes-HCl/Cs₂CO₃ in DMAc at 80°C. Nitrogen bases are commonly used in the Sonogashira reaction but in this case produced inactive systems. Undesired dimerisation products were obtained when phenylacetylene was employed as the alkyne source. This side reaction was suppressed by using 1-phenyl-2-(trimethylsilyl)-acetylene as coupling partner with

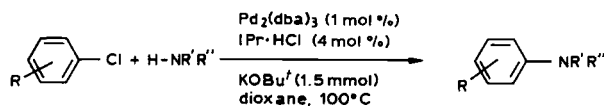


Table IX

Pd₂(dba)₃/IPr·HCl-Catalysed Amination of Aryl Chlorides^a

R	Amine, HNR'R''	Yield, % ^b
4-CH ₃	<i>N</i> -methylaniline	99
4-CH ₃	piperidine	96
4-CH ₃	piperidine, 4-(tetrahydro-2 <i>H</i> -pyran-4-yl)	86
4-CH ₃	morpholine	82
4-CH ₃	HN(Bu ⁿ) ₂	95
4-CH ₃	H ₂ N(Bu ⁿ)	86
4-CH ₃	aniline	96
4-CH ₃	mesitylaniline	59
4-CH ₃	2,6-(Pr ⁱ) ₂ -aniline	85
4-OCH ₃	<i>N</i> -methylaniline	91
4-OCH ₃	aniline	91
4-OCH ₃	morpholine	80
4-OCH ₃	HN(Bu ⁿ) ₂	98
2,5-(CH ₃) ₂	<i>N</i> -methylaniline	94

^a Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of amine, 1.5 mmol of KOBu^t, 1.0 mol% Pd₂(dba)₃, 4.0 mol% IPr·HCl (2 L/Pd), 3 ml of dioxane, 100°C. Reactions were complete in 3–24 hours and reaction times were not minimised.
^b Isolated yields

aryl bromides (35). Under optimised conditions excellent product yields were obtained; however, it is noteworthy that these high yields were achieved under CuI-free conditions. Adding CuI increased reaction rates, most notably with deactivated or sterically encumbered aryl bromides. The catalytic system was even effective for chlorobenzene, although the yield was moderate.

C–N Bond-Forming Reactions

Hartwig-Buchwald Amination

Only recently has metal-catalysed displacement of aryl halides with primary and secondary alkyl- and arylamines been developed as a useful synthetic method (42). Pd- and Ni-mediated aminations have attracted significant interest owing to the importance of this reaction in organic synthesis and materials science. The careful selection of ligands dictates the efficiency of a catalytic system, with bulky monodentate and chelating phosphines giving the best results (43), although a recently reported two-coordinate palladium-carbene system

has proved very effective for amination of aryl chlorides (44). After the success of the Pd/NHC system in mediating C–C bond formation we turned our attention to C–N coupling processes. The use of the bulky NHC precursor IPr·HCl with KOBu^t as base and 1,4-dioxane as solvent permitted the catalytic C–N coupling of aryl iodides and bromides at room temperature and the catalytic coupling of aryl chlorides at elevated temperature. High conversions were achieved with primary and secondary, cyclic and acyclic amines with various aryl halides. 4-Chlorotoluene and *ortho*-substituted aryl halides were aminated in good to excellent yields.

The effective coupling of 4-chloroanisole with sterically unhindered amines makes this the most effective catalytic system to date (45, 46). Data for the coupling of aryl chlorides with a variety of amines are presented in Table IX.

The scope of the Hartwig-Buchwald reaction was extended to the amination of heteroaromatic halides. No problems were encountered with

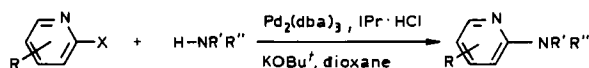


Table X

Pd₂(dba)₃/IPr·HCl-Catalysed Amination of Chloropyridines and Bromopyridines^a

Aryl halide	Amine, HNR'R''	Yield, % ^b
2-chloropyridine	morpholine	99
2-chloropyridine	<i>N</i> -methylaniline	97
2-chloropyridine	aniline	88
3-chloropyridine	morpholine	97
3-chloropyridine	<i>N</i> -methylaniline	91
3-chloropyridine	aniline	98
4-chloropyridine·HCl	morpholine	80
4-chloropyridine·HCl	<i>N</i> -methylaniline	70
4-chloropyridine·HCl	aniline	83
2-bromopyridine	morpholine	95
2-bromopyridine	<i>N</i> -methylaniline	99
2-bromopyridine	aniline	96

^a Reaction conditions: 1.0 mmol chloro- or bromopyridine, 1.1 mmol amine, 1.5 mmol KOBu', 1 L/Pd, 3 ml dioxane, 3 h, 100°C;^b Isolated yields

coordination of *N*-containing substrates to the metal, and moderate to high conversions were achieved with 2-chloro- and 2-bromopyridine (Table X).

Amination of Aryl Halides with an Ammonia Analogue

Benzophenone imine adducts have been prepared using benzophenone imine as an ammonia surrogate. This represents an efficient alternative route to the synthesis of *N*-unsubstituted anilines owing to its low cost, availability of reagent and stability to varied reaction conditions (42e, 47). Under the conditions established for catalytic amination, benzophenone imine reacted readily with unactivated and *ortho*-substituted aryl chlorides in high yield at 80°C. The reactions with 4-chlorotoluene and 4-chloroanisole were faster and cleaner at 100°C, as were reactions with aryl bromides. However, activated aryl halides were incompatible with the strong base KOBu' in this process, resulting in base-promoted cleavage of the substrate. Primary anilines were obtained in good yields by acidic cleavage of the benzophenone imine adducts, see Table XI.

N-Arylation of Aryl Indoles

N-Aryl indoles themselves can be biologically active (48), or can be useful intermediates in the synthesis of biologically active agents (49). As such they are attractive synthetic targets. The involvement of aromatic nitrogen in the reaction limits the use of the *N*-arylation of indoles to more reactive aryl iodides and bromides. While our general amination procedure was ineffectual for the arylation of indoles, good results were obtained when coupling a number of aryl bromides and indole derivatives using a Pd(OAc)₂/SIPr·HCl/NaOH catalytic system. This protocol additionally overcame a common problem in indole synthesis, namely the formation of *C*-arylation side products. Results are presented in Table XII.

Conclusions

NHCs have been shown to be highly effective as supporting ligands in a range of catalytic processes. Their superior thermal stability, together with electronic and steric tunability imparted by facile variation of the *N*-substituents, and the ease of manipulation (and *in situ* deprotonation) of the

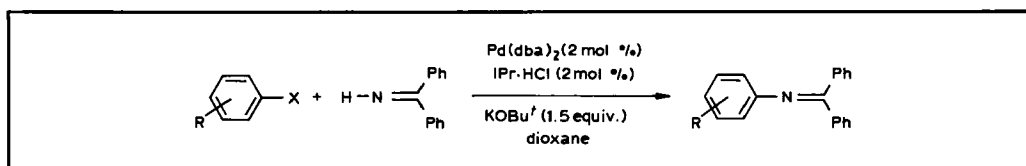


Table XI
Amination of Aryl Chlorides and Bromides with Benzophenone Imine^a

X	R	Time, h	Yield, % ^b
Cl	4-CH ₃	4	99 ^c
Cl	H	24	96
Cl	2,5-(CH ₃) ₂	5	99
Cl	2,6-(CH ₃) ₂	5	98
Cl	4-OCH ₃	6	99 ^c
Br	4-CH ₃	3	98 ^c
Br	3,5-(CH ₃) ₂	10	99 ^c
Br	3,5-(CF ₃) ₂	48	60 ^c
Br	2,4,6-(CH ₃) ₃	10	99
Br	4-OCH ₃	5	99

^a Reaction conditions: 1.0 mmol aryl halide, 1.05 mmol benzophenone imine, 1.5 mmol KOBu', 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

NHC-precursor imidazolium salts, makes NHCs the ancillary ligands of choice in many palladium-catalysed cross-coupling processes. Indeed, unprecedented catalytic activity has been observed in some cases, particularly with 'difficult' aryl chloride substrates.

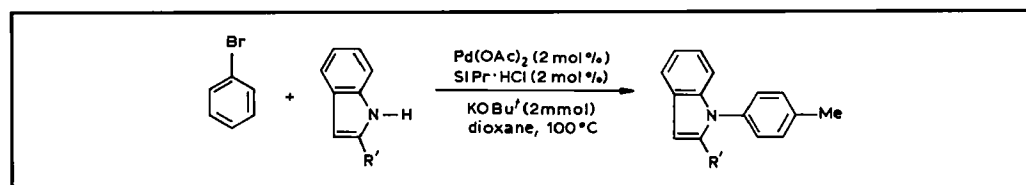


Table XII
Amination of Aryl Bromides with Indoles^a

R	R'	Time, h	Yield, % ^b
4-CH ₃	H	3.5	97
H	H	1	100
4-OCH ₃	H	3.5	88
2,4,6-(CH ₃) ₃	H	16	68
4-CH ₃	Ph	3	100 ^c
H	Ph	18	100 ^c
4-OCH ₃	Ph	10	61 ^c
4-CH ₃	2-F-C ₆ H ₄	3	97 ^c
H	2-F-C ₆ H ₄	10	83 ^c

^a Reaction conditions: 1.0 mmol aryl bromide, 1.1 mmol indole, 2 mmol KOBu', 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

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Automotive Fuel Cells: A U.K. Perspective

The Institution of Mechanical Engineers held a one-day conference in London on 28th February on Fuel Cells for Automotive Applications. The main topics discussed were technical issues, implementation of the technology and potential markets.

Melanie Sadler (QinetiQ) addressed challenges and developments across the entire spectrum of fuel cell vehicles, paying attention to fuel storage and cost reduction. Achieving lower costs has been examined for many components, including the noble metal content in electrodes. Careful use of chemistry and engineering ought to optimise the platinum and ruthenium content in a fuel cell.

Work with alkaline fuel cells was described by A. Willett (Fuel Cell Systems). These were the first fuel cells to be seriously demonstrated (by Francis Bacon in 1959). NASA have used alkaline fuel cells with platinum group metal electrodes since the Apollo programme. The low operating temperature provides some benefits for vehicles, but carbon dioxide has to be removed from the air intake. This technology has 'trickle-charged' an electric taxi.

Chris Dudfield (Intelligent Energy) gave details on more conventional platinum-based proton exchange membrane technology for sole power in a car. He listed many prototypes using this technology.

A project underway to put a fuel cell into use in the town of Woking, U.K., was described by J. Kenna (Energy for Sustainable Development). He showed the logistical and regulatory challenges

which lie even beyond the immediate technical hurdles.

Finally, the motion: 'This house believes that the fuel cell electric vehicle will comprise 10% of a new car market in 2010', was defeated, despite strong support from Gary Acres (Consultant) and many positive comments. Professor James Randle (University of Birmingham) won the day. Nonetheless, the impression was given of a market almost on the verge of expansion. D. M. JOLLIE

David Jollie is Manager of the online resource Fuel Cell Today (fuelcelltoday.com), sponsored by Johnson Matthey, Hatton Garden, London. David's main interests are the industrial development and utilisation of fuel cells.

Fuel Cells: Science and Technology 2002

The next Grove-organised fuel cell conference 'Scientific Advances in Fuel Cell Systems' takes place in Amsterdam on 25th and 26th September. Topics covered will include materials (and membranes), stack and cell engineering, electrochemistry and catalysis, fuel processing, hydrogen storage and distribution and balance of plant. For further information please contact Ms C. Norris, Fax: +44 (0)118 377 4696; E-mail: claire@eventive.org.uk.

Catalysis for Low Temperature Fuel Cells

Unfortunately publication of the second part of this paper has had to be postponed until a later issue. We apologise to readers who were hoping to read this item in this issue of *Platinum Metals Review*.