Synthesis and catalytic applications of palladium N-heterocyclic carbene complexes as efficient pre-catalysts for Suzuki-Miyaura and Sonogashira coupling reactions

Lamia Boubakri, S. Yasar, V. Dorcet, T. Roisnel, Christian Bruneau, N. Hamdi, I. Ozdemir

Synthesis and catalytic applications of palladium *N*-heterocyclic carbene complexes: As efficient pre-catalyst for Suzuki Miyaura and Sonogashira coupling reactions

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A new palladium complex series with *N*-heterocyclic carbene (NHC), pyridine and phosphine ligands, ($PdCl_2$(L)NHC (**2a-c**)(L=NHC), ($PdCl_2$(L^1)NHC(**3a-c**)(L^1=pyridine), ($PdCl_2$(L^2)NHC(**4a-c**)(L^2=triphenylphosphine), were synthesised and fully characterized. The catalytic activities of these complexes were screened for the Sonogashira and Suzuki-Miyaura reactions between arylhalides and phenylacetylene, and phenylboronic acid, respectively. The results pointed out that carbene/phosphine complexes, **4a-c** exhibited excellent catalytic activities as compared to **2a-c**, **3a-c**, and the well-known systems for palladium-catalysed Sonogashira reaction. The reactivity of **4a-c** in these preliminary Sonogashira coupling tests seems higher than that of previously reported catalytic systems based on Pd(NHC) moities. These new palladium NHC complexes are among the first reported palladium catalysts that are efficient to catalyse the Sonogashira reaction from arylchloride substrates.

Introduction

N-heterocyclic carbenes (NHCs) and phosphines have been among the most remarkable ligands for homogeneous catalysis with transition metals towards medical applications and industry.[1] The use of different metal complexes have led to important innovation in homogeneous catalysis.[2] With these developments, numerous metal-NHC derivatives including Ag,[3] Co,[4] Fe,[5] Cu,[6] Ni,[7] Ru,[8] Ir,[9] Rh,[10] and Pd[11] complexes have been prepared. Although there are numerous metal-carbene complexes, the prominence of Pd-NHC complexes is likely due to their catalytic efficiency and robustness against air, moisture and high temperature. The basis of this interest lies in the facile modulation of electronic and steric parameters reflected by a strong σ-donor and weak π-acceptor ability and the ease of adjusting the steric effects of NHCs by variation of nitrogen atom substituent. Complex bearing sterically bulky and electron-rich ligands exhibit enhanced catalytic activity in oxidative addition, and reductive elimination reactions that are key elemental steps of many catalytic reactions.[12-17] These unique features have contributed to make them indispensable ligands for transition metals in homogeneous and heterogeneous catalysis.[18-30]

The cross-coupling reactions were successfully performed under homogeneous and heterogeneous catalyse conditions.[30] This two catalyse system has unique advantages and disadvantages. Homogeneous catalyze system is suffer from high cost, low efficiency in separation of product and low recycling of catalyst. However, heterogeneous catalyze offer efficiently recycle and easy product separation in the reaction mixture with a decrease reaction rate[30c] or diffuse difficulty of reagents to catalyst.[30d] Homogeneous palladium-NHC complex catalyzed Suzuki-Miyaura cross-coupling reaction is one of the most powerfull and widely used reaction for the C-C bond formation. Nolan,[31] Organ,[32] Song,[33] Mandal,[34] Fu,[35] Ying,[36] Thiel [37] and Lee[38] have achieved significicant improvements in Suzuki-Miyaura reaction. In recent studies, Pd-NHC complexes have revealed good activity in the difficult Suzuki coupling reaction of arylchlorides under mild conditions.[31-42]

The Sonogashira reaction is an another important cross-coupling reaction to produce valuable compounds by coupling terminal alkyne derivatives and arylhalides.[43] Palladium complexes and copper(I) salts still represent the most preferred catalysts combination for Sonogashira reaction. One limitation of the early catalytic combinations based on phosphine-containing catalysts was the sensitivity to air,[44,45] but modified protocols were developed for different applications.[46,47] Efficient, stable palladium catalysts are still needed to achieve the Sonogashira coupling reaction with low catalyst loading under copper-free conditions.[48,49]

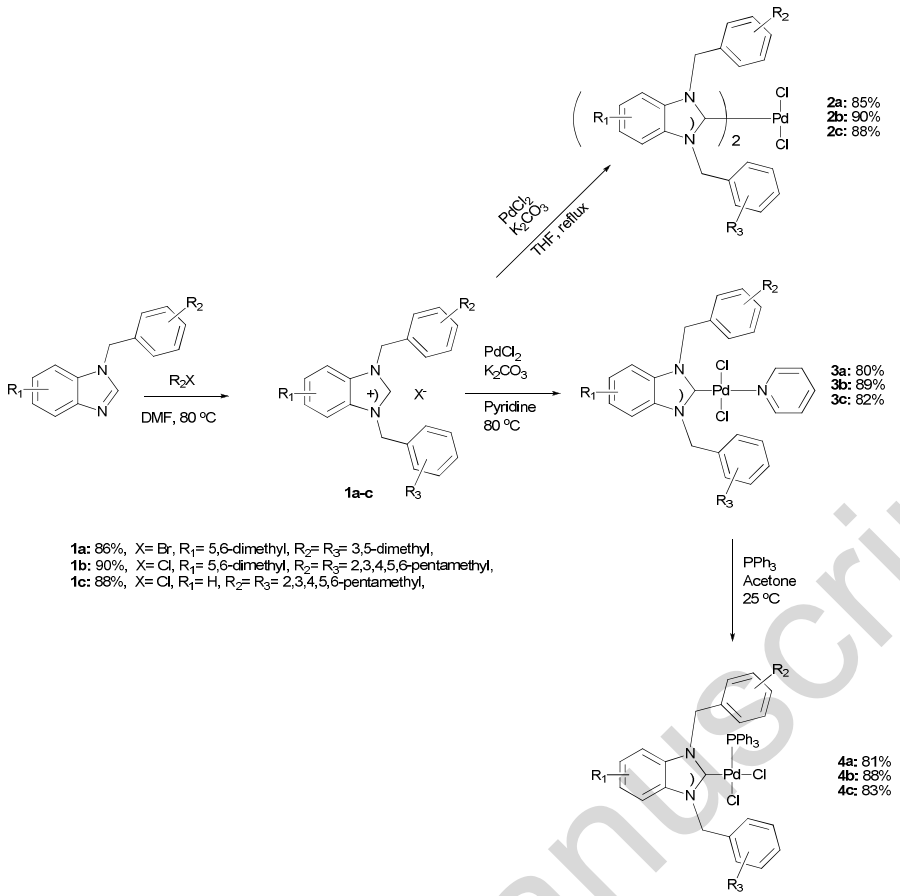
In order to improve catalytic activity, we turned our attention to new Pd(NHC)(L)Cl_2(L=NHC, pyridine, PPh_3) palladium complexes and investigated their catalytic performance as catalysts in Sonogashira and Suzuki-Miyaura coupling reactions at low catalyst loading.

Results and discussion

Materials and methods

Benzimidazole-based NHC palladium complexes $PdCl_2$(L)(NHC)(**2a-c**)(L=NHC) and ($PdCl_2$(L1)(NHC)(**3a-c**)(L1= pyridine) were prepared in very good yields (80-90%) in one step from $PdCl_2$ and benzimidazolium salts in the presence of K_2CO_3 as a base (Scheme 1). Importantly, the benzimidazolium halides **1a-c**, the NHC precursors, were easily obtained in 86-90% yield according to reported methods, and their spectroscopic features were consistent with the literature data.[50-52]

The straight forward reaction of **1a-c** with $PdCl_2$ and K_2CO_3 in THF afforded the bis(NHC)palladium complexes $Pd(NHC)_2Cl_2$ (**2a-c**) in up to 90% yield. PEPPSI complexes **3a-c** (PEPPSI= pyridine-enhanced precatalyst preparation, stabilisation, and initiation) were synthesized according to the method reported by Organ (Scheme 1):[32] the reaction of NHC precursors **1a-c** with $PdCl_2$ in pyridine at



Scheme 1 Synthesis pathway for palladium complexes **2a-4c**

80 °C in the presence of K_2CO_3 afforded the palladium complexes **3a-c** in 80, 89 and 82% yield, respectively. The addition of 1 eq. of PPh_3 to a solution of **3a**-c in acetone afforded the $PdCl_2(PPh_3)$(NHC) complexes **4a-c** in 81-88 % yield in two steps. All these complexes were purified by column chromatography on silica using dichloromethane as eluent, and characterized by ^1H and ^{13}C NMR, and HR-MS spectroscopy, elemental analysis, and X-ray single crystal diffraction for complexes **3b** and **4b**. NC*H*N proton signals of **1a-c** at low field disappeared in the ^1H NMR spectra for **2a-c**, and **3a-c**, which indicated that the formation of the NHC complexes took place. Characteristic pyridine hydrogen signals disappeared in the ^1H NMR spectra of complexes **4a-c** due to substitution of pyridine by triphenylphosphine ligand. Also, in ^{13}C {^1H} NMR, an important down field shift of the NCN carbon from **1a-c** to **2a-c** was observed. Indeed, the ^{13}C {^1H} N-C-N signals of **1a**, **1b** and **1c**, which are respectively equal to 140.5, 137.9 and 141.4 ppm were shifted to 180.9, 181.0 and 181.5 ppm, respectively, in **2a**, **2b** and **2c**. Similarly, the^{13}C {^1H} N-C-N signals of **3a-c** were observed at 161.9, 161.3 and 163.7 ppm, respectively, whereas in the case of **4a-c**, the corresponding signals appeared at 172.5, 171.5, and 173.8 ppm, respectively. Observation of the phosphorus atoms by ^{31}P NMR at 27.1, 27.4 and 26.5 ppm for **4a**, **4b** and **4c**, respectively confirmed the substitutions of the pyridine by the triphenylphosphineligand.

Structural characterization of 3b and 4b

Crystals of **3b** and **4b** suitable for X-ray crystallography were grown in a dichloromethane solution layered with diethyl ether. The molecular structures of **3b** and **4b** were supported by X-ray diffraction analysis. Details of data are given in the supporting information section. The ORTEP ellipsoid plot at 50% probability of the molecular structure of **3b** and **4b** are shown in Figs. 1 and 2.

Suzuki-Miyaura cross-coupling reaction

To study the efficiency of the novel palladium-NHC complexes **2a**, **3a** and **4a** in Suzuki-Miyaura coupling reactions, 4-chloroacetophenone and phenylboronic acid were selected as model substrates. The palladium complexes were associated with different bases and solvents at 80 °C with reaction times limited to 3 h in order to discriminate the most reactive catalysts and find the efficient catalytic systems (Table 1).

The catalytic systems exhibited different reactivity depending not only on the palladium precursor but also on the nature of the base and the solvent. With K_2CO_3 or *t*-BuOK as a base, DMF/water (1:1) mixture was a good solvent for the Suzuki reaction in the presence of the pyridine-containing palladium complex **3a** (Table 1, entries 5, 6), whereas much better activities were obtained in toluene with complexes **2a** and **4a** using *t*-BuOK as a base (Table 1). The low catalyst concentration causes to decrease the activity and the amount of product increases with the extended reaction time(table 1, entries 10-15). With the complex **4a**, low yield were obtained in the DMF/water mixture, which might be attributed to the low solubility of **4a** due to containing triphenylphosphine ligand.

These results reveal that the base/solvent combination selection for this catalytic system was a key parameter and should be made according to the structural diversity of the complexes. However, in toluene, it was possible to reach high solubility and high conversion whatever the catalyst precursor.

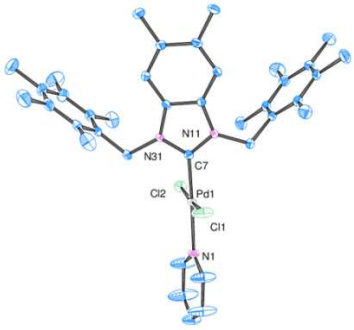


Fig. 1 The molecular structure of **3b** showing the atom numbering scheme. Selected bond lengths [Å]: Pd1-C7 = 1.9590(19), Pd1- N1 =2.1546(16), Pd1-Cl1 = 2.3005(5), Pd1-Cl2 = 2.3099(5), C7-N11 = 1.346(2), C7-N31 = 1.352(2). Selected bond angles [°]: C7- Pd1- N1 = 177.34(7), C7-Pd1-Cl1 = 85.76(6), N1-Pd1-Cl1 = 92.77(5), N11-C7-N31 = 108.09(16), N11-C7-Pd1 = 127.26(14),N31-C7-Pd1 = 124.56(14).

With the optimized reaction conditions, the reaction scope was investigated with electron-rich and electron-deficient aryl chloride and bromide substrates. As shown in Table 2, a very wide range of substituents on the chloride and bromide substrates were tolerated by the catalytic system. With all palladium precursors, bromides substrates were efficiently coupled with phenylboronic acid with high yields (Table 2, entry 2,4,6,8). As expected, the aryl bromides substituted by an electron-withdrawing group (MeCO- or HCO – entries 2 and 4) in *para*-position were more reactive than those substituted by an electron-donating group (MeO- or Me – entries 6 and 8). Starting from aryl chlorides, only the electron-deficient *p*-chloroacetophenone provided excellent yields (77-91%) and formation of the sole coupling product with all palladium catalysts. *p*-Chlorobenzaldehyde was also a good partner using **2a-c** and **3a-c** as catalyst, but no reaction occurred in the presence of **4a-c** (Table 2, entry 3). Starting from the electron-rich *p*-chloroanisole and *p*-chlorotoluene, the reactions proved to be more difficult and longer reactions time (12h) made possible the formation of the coupling products in moderate yield in the presence of catalytic amounts of **2a-c** and **3a-c** (Table 2, entries 5, 7). On the other hand complexes **4a-c** were not active in these Suzuki coupling reactions. This may be due to the structure of the catalyst and the location of the triphenylphosphine ligand in the *-cis* position to the carbene ligand. This can make the oxidative addition of the substrate difficult to active catalyst and led to low yield. The same behaviour was observed starting from chlorobenzene (Table 2, entry 9).

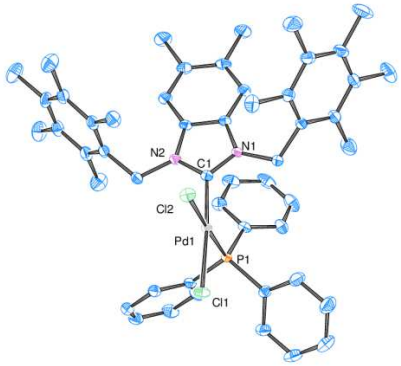
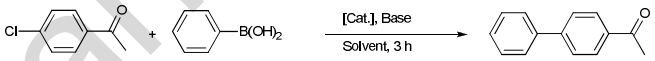


Fig. 2 The molecular structure of **4b** showing the atom numbering scheme. Selected bond lengths [Å]: Pd1-C1 =1.984(2), Pd1-P1 = 2.2572(6), Pd1-Cl1 = 2.3418(6), Pd1-Cl2 = 2.3515(6), N1-C1 = 1.347(3). Selected bond angles [°]: C1-Pd1-P1= 92.95(7), C1-Pd1-Cl1= 175.86(6),P1-Pd1-Cl1= 86.79(2), C1-Pd1-Cl2= 87.93(7), P1-Pd1-Cl2= 177.27(2), Cl1-Pd1-Cl2 =92.52(2),N2-C1-N1=108.17(18), N2-C1-Pd1= 123.85(16), N1-C1-Pd1= 127.96(17)

Table 1. Condition optimization with 4-chloroacetophenone[a]



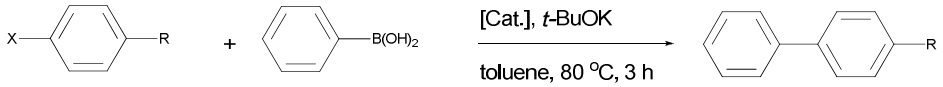
Entry	Complex	Base	Solvent	Yield(%)[b]
1		*t*-BuOK	Toluene	88
2	**2a**	K_2CO_3	DMF/H_2O(1:1)	12
3		*t*-BuOK	DMF/H_2O(1:1)	Trace
4		*t*-BuOK	Toluene	84
5	**3a**	K_2CO_3	DMF/H_2O(1:1)	83
6		*t*-BuOK	DMF/H_2O(1:1)	84
7		*t*-BuOK	Toluene	77
8	**4a**	K_2CO_3	DMF/H_2O(1:1)	Trace
9		*t*-BuOK	DMF/H_2O(1:1)	nr
10[c]	**2a**	*t*-BuOK	Toluene	60
11[c]	**3a**	*t*-BuOK	Toluene	56
12[c]	**4a**	*t*-BuOK	Toluene	45
13[d]	**2a**	*t*-BuOK	Toluene	98
14[d]	**3a**	*t*-BuOK	Toluene	98
15[d]	**4a**	*t*-BuOK	Toluene	93

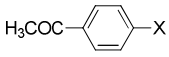
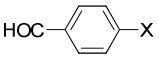
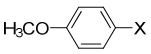
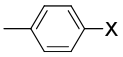
[a] Reaction conditions : Phenylboronic acid (0.75 mmol), aryl halide (0.5 mmol), catalyst (0.25 mol%), base (1 mmol), solvent (6 ml), 80 °C, 3h. [b] GC yield against calibrated internal standart (undecane). [c] catalyst (0.125 mol%) [d] catalyst (0.125 mol%), 80 °C, 8h. nr: No reaction.

Finally, with the different types of palladium complexes featuring at least one NHC, with an additional pyridine or phosphine ligands, we observed that palladium *N*-heterocyclic complexes (**2a-c**) and

PEPPSI complexes (**3a-c**) were more active than the mixed phosphine/*N*-heterocyclic carbene palladium complexes (**4a-c**). Also, these lower catalyst performances of **4a-c** might be attributed to stronger σ-donor and π-acceptor properties of PPh_3 ligand which located at *–cis* position to NHC. Moreover, the catalytic systems were not poisoned by pyridinic substrates when heterocyclic halide substrates were used. Thus, complete yields were obtained starting from 2,6-dibromopyridine in the presence of 0.25 mol% of catalysts **2** and **3** with high diarylated product selectivity (Table 3, entry 1). With catalysts **4a-c**, the efficiency and selectivity towards diarylated products were much lower. Using 2-chloropyridine substrate even with longer reaction time, low yields were performed by all catalysts (Table 3, entry 2).

Table 2. Suzuki coupling reaction with various aryl chlorides and bromides[a]

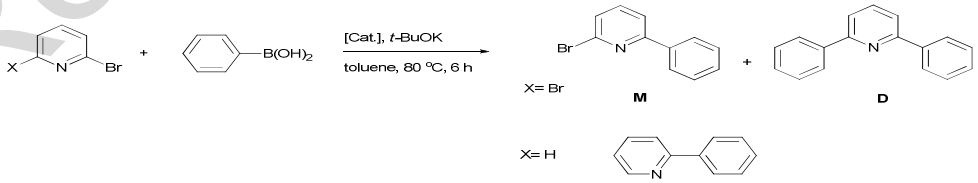


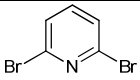
Entry	Substrate	X	[**catalyst**]/ yield (%)[b]								
			2a	**2b**	**2c**	**3a**	**3b**	**3c**	**4a**	**4b**	**4c**
1		Cl	88	95	98	84	86	89	77	90	91
2		Br	94	94	94	93	91	95	91	89	90
3		Cl	89	95	94	80	90	89	nr	nr	nr
4		Br	95	96	96	88	92	95	97	96	97
5		Cl	12[d]	56[d]	68[d]	39[d]	11[d]	14[d]	Trace[d]	Trace[d]	Trace[d]
6		Br	65[c]	72	71	93	85	86	80	72	85
7		Cl	20[d]	31[d]	50[d]	24[d]	39[d]	41[d]	nr[d]	nr[d]	nr[d]
8		Br	70[c]	93	96	92	94	93	57	79	81
9		Cl	59[d]	71[d]	72[d]	61[d]	71[d]	71[d]	nr[d]	nr[d]	nr[d]

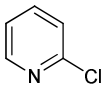
[a]Reaction conditions : Phenylboronic acid (0.75 mmol), aryl halide (0.5 mmol), catalyst (0.25 mol%), t-BuOK (1 mmol), toluene (6 ml), 80°C, 3h. [b] GC yield against calibrated internal standart (undecane). nr: no reaction. [c] 6 h. [d] 12h.

There is a lot of data in the literature for Suzuki coupling reactions catalysed by Pd(NHC)-derived complexes in a variety of different experimental conditions.[39-52] With respect to the related Organ's system ((Pd-PEPPSI:2 mol%, chloroanisole (1 mmol), $PhBF_3K$ (1.0 mmol), 60 °C, 24h, MeOH) in the Suzuki-Miyaura reaction,[32] our results show that complexes **2a-c** and **3a-**c exhibit modorate activity. When the catalytic activities of **2a-c** and **3a-c** were compared among themselves, complex **2a** gave slightly better results in each case with different substrates. This performance can be attributed to the increased electron richness of **2a**, which facilitates the oxidative addition step. Also, in each series, complexes **2b** and **2c** on one hand, and complexes **3b** and **3c** on the other hand are more active than the corresponding complexes **2a** and **3a**. This could be due to the higher steric pressure imposed by two penta methyl-substituted benzylic groups as compared to 3,5-dimethyl substituents on the benzylic groups of **2a** and **3a**, which is known to facilitate the final reductive elimination step.[52-55] When the catalyst concentration is considered, with respect to the related literature in the Suzuki-Miyaura cross-coupling reaction, our catalyse system exhibit better activity than Mandal,[34] Fu,[35] Ying,[36] Lee[38] studies and worst activity than Nolan,[31] Song,[33], Thiel[37] studies.

Table 3. Suzuki coupling reaction with 2,6-dibromopyridine and 2-chloropyridine[a]



Entry	Substrate	[Cat.]/ (M/D) Yield ratio[b]								
		2a	**2b**	**2c**	**3a**	**3b**	**3c**	**4a**	**4b**	**4c**
1		29/54	10/81	13/75	0/90	0/92	0/91	19/10	14/23	15/19

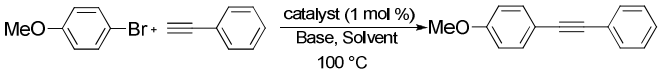
2		8[c]	33[c]	26[c]	47[c]	54[c]	51[c]	Trace	Trace	Trace

[a]Reaction conditions : Phenylboronic acid (0.75 mmol), heteroaryl halide (0.5 mmol), catalyst (0.25 mol%), *t*-BuOK (1 mmol), toluene (6 ml), 80 °C, 6h. [b] GC yield against calibrated internal standart (undecane). [c]12h.

Sonogashira coupling reaction

Several palladium–NHC complexes have been tested as catalysts for Sonogashira coupling reaction,[56] but these complexes have not performed a satisfactory high reactivity except with reactive aryl iodides under copper-free conditions. Copper salts are used as co-catalyst in the Sonogashira reaction, although it makes the Sonogashira process air sensitive and promotes Glaser-Hay coupling of the alkyne product.[57] Despite this disadvantage, copper salts in the presence of a base have been used extensively for the formation of Cu-alkynyl species that transmetallate to palladium in the catalytic cycle. In line with these observations, we tested our new palladium NHC complexes as catalyst in the copper-free Sonogashira coupling of aryl bromides and chlorides with terminal alkynes.[58]

Table 4. Optimization of the solvent and base for the Sonogashira coupling of *p*-bromoanisole with phenylacetylene[a]



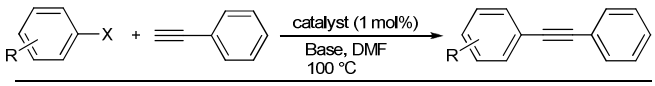
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	**4b**	K_2CO_3	DMF	62
2	**4b**	Cs_2CO_3	DMF	80
3	**4b**	*t*-BuOK	DMF	91
4	**4b**	*t*-BuOK	DMF/H_2O	53
5	**4b**	*t*-BuOK	Toluene	51
6	**4b**	K_2CO_3	EtOH/H_2O	0
7	**4b**	Cs_2CO_3	EtOH/H_2O	20
8	**4b**	NEt_3	DMF	trace
9	**4b**	Pyridine	DMSO	trace
10[c]	**4b**	*t*-BuOK	DMF	59
11[d]	**4b**	*t*-BuOK	DMF	91
12[d]	**4a**	*t*-BuOK	DMF	81
13	**2a**	*t*-BuOK	DMF	0
14	**2c**	*t*-BuOK	DMF	0
15	**3a**	*t*-BuOK	DMF	0

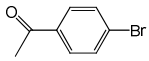
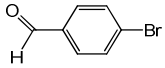
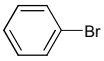
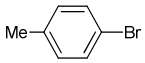
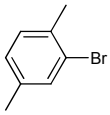
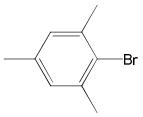
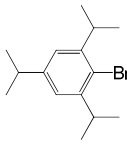
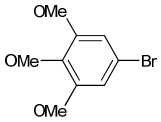
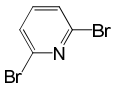
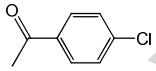
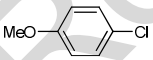
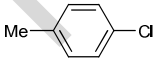
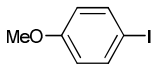
[a]Reaction conditions : *p*-bromoanisole (0.6 mmol), phenylacetylene (1.2 mmol), catalyst (1 mol%), base (1.2 mmol), solvent (10 ml), 100 °C, 3h, under Argon, conversions were determined by GC. [b] GC yield against calibrated internal standart (undecane) [c]CuI (2 mol%) as co-catalyst. [d]1 h.

In order to evaluate and compare the activities of our catalytic systems, Biffis's[59] reaction conditions were initially selected for the Sonogashira reaction. Preliminary results and optimization were conducted starting from *p*-bromoanisole and a twofold excess of phenylacetylene in the presence of a catalytic amount of the phosphine-containing complex **4b** (Table 4). K_2CO_3, Cs_2CO_3, *t*-BuOK with DMF as solvent were suitable bases to achieve the Sonogashira coupling at 100 °C for 3 h with yield higher than 62% (Table 4, entry 1-3). Protic solvents such as water and ethanol or organic bases led to poor conversions. By contrast and unexpectedly, the other palladium NHC complexes **2a**, **2c** and **3a** did not show any activity in the Sonogashira reaction involving *p*-bromoacetopheneone and phenylacetylene (Table 4, entry 13-15). This inactivity of **2a-c** and **3a-c** may be attributing to low stability of this complex in catalytic reaction condition expecially high reaction temperatures. A blank experiment revealed that in the absence of palladium catalyst no reaction took place even in the presence of CuI (2 mol%). We also investigated the effect of CuI as a co-catalyst, and no positive contribution of CuI as co-catalyst was observed in the Sonogashira reaction catalysed by **4b** (Table 4, entry 3, 10). In the presence of catalysts **4a** and **4b**, the reaction times could be reduced to 1 h without deleterious effects on the conversions (Table 4, entries 11, 12).

After optimisation, DMF was selected as solvent and *t*-BuOK as base to evaluate the scope of the reaction with 1 mol% of palladium (NHC) complexes. Under these conditions, mixed phosphine/N-heterocyclic carbene palladium complexes **4a-c** were found to efficiently convert activated and unactivated aryl bromides and phenylacetylene into the corresponding internal alkynes within one hour (Table 5, entries 1-7). These results with catalysts **4a-c** are among the best results reported to date for Sonogashira reaction. With these encouraging results in hands, we explored the catalysts activities with more electron-donating or more sterically demanding aryl bromide substrates. Good to excellent conversions were obtained with the more electron-donating or more sterically hindered methyl and methoxy-substituted aryl bromide substrates under the selected reaction catalyzed by **4b** after 6h (Table 5, entries 8-14). Efficient double coupling was observed from 2,6-dibromopyridine in the presence of **4b** in 6h, indicating that the catalytic system was not poisoned by pyridine substrates. As (pyridine)palladium complexes **3a-c** are not catalysts for the Sonogashira reaction, this result likely shows that the phosphine ligand is not replaced by a pyridine ligand during the catalytic cycle. When we explored the reaction scope with aryl chloride, the situation was less favourable than starting from aryl bromides (table 5, entry 16) but the reaction could be efficiently achieved with the activated 4-chloroacetophenone after prolonged reaction time. In this case, complexes **4b** and **4c** performed convincing activities after 24 h, which represents the best results shared by all (NHC)Pd-based catalysts reported to date for the Sonogashira reaction (Table 5, entries 17-21). As expected, in the presence of catalyst **4b**, the more reactive iodoanisole provided a complete conversion within one hour (Table 5, entry 22).

Table 5. Sonogashira coupling of phenylacetylene with aryl halides catalyzed by palladium complexes[a]



Entry	Ar-X	Catalyst	Time (h)	Yield (%)[b]
1		**4a**	0.25	55
2		**4b**	0.25	74
3		**4b**	1	93
4		**4b**	1	48
5		**4a**	1	92
6		**4a**	1	92
7		**4b**	1	93
8		**4a**	6	69
9		**4b**	6	90
10		**4c**	6	88
11		**4a**	6	86
12		**4b**	6	87
13		**4b**	6	89
14		**4b**	6	91
15[c]		**4b**	6	80
16		**4b**	6	24
17		**4b**	24	66
18		**4b**	24	68
19		**4a**	24	9
20		**4b**	24	55
21		**4b**	24	61
22		**4b**	1	89

[a]Reaction conditions: aryl halide (0.6 mmol), phenylacetylene (1.2 mmol), catalyst(1 mol%), t-BuOK (1.2 mmol), DMF (10 ml). [b] GC yield against calibrated internal standart (undecane) [c] 2,6-dibromopyridine (0.6 mmol), phenylacetylene (2.4 mmol), *t*-BuOK (2.4 mmol), DMF (10 ml).

It is interesting to point out that the catalytic activity observed with **4b-c** appears to be due to facile reductive elimination from the palladium complex, which may be attributed to excellent stability due to balance of strong σ-donation and π-acceptor properties of NHC and PPh_3 ligand, respectively, in complexes **4b-c**. This superiority contributes positively to the activity of these catalysts.

In summary, the reactivity of **4a-c** in these preliminary Sonogashira coupling tests seems higher than that of previously reported catalytic systems based on Pd(NHC) moities.[56-59] Most importantly, these new (NHC) complexes are among the first reported palladium catalysts that are efficient to catalyse the Sonogashira reaction from aryl chloride substrates.[56-59] Further investigations in order to fine-tune the characteristics of the ligands for Sonogashira reaction with aryl chlorides are in progress.

Experimental

General considerations

All commercial chemicals were used as received. Unless stated otherwise, all procedures were carried out under argon atmosphere. All solvents were purified and dried by MBraun SPS 800 solvent purification system. The melting points of the complexes and NHC precursors were determined using Stuart automatic melting point apparatus (SMP-40). ^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d^6 solutions operating on a Bruker Advance II 300 and 400 MHz NMR spectrometer and chemical shifts were reported relative to tetramethylsilane for ^{1}H, ^{13}C NMR spectra as standard. Signals are quoted in parts per million as δ downfield from tetramethyl silane (δ 0.00) as an internal standard. Coupling constants (*J* values) are given in hertz. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet signal. All reactions were monitored on a Shimadzu GC2010 Plus system by GC-FID with a HP-5 column of 30 m length, 0.32 mm diameter and 0.25 µm film thickness. Elemental analyses were performed by ElementarVario EL III Carlo Erba 1108.

1,3-Bis-(3,5-dimethylbenzyl)-5,6-dimethylbenzimidazolium bromide, 1a

m.p: 250.9 °C.Yield: 86%.^{1}H NMR (300.1 MHz, $CDCl_3$,25 °C): δ=11.40 [s, 1H, NC*H*N], 7.25[s, 2H, $C_6H_2(CH_3)_2$-5,6], 6.96 [s, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 6.86[s, 2H, $CH_2C_6H_3(CH_3)_2$-3,5], 5.65 [s, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 2.26 [s, 6H, $C_6H_2(CH_3)_2$-5,6], 2.19 [s, 12H, $CH_2C_6H_3(CH_3)_2$-3,5]. ^{13}C NMR (75 MHz, $CDCl_3$,25 °C): δ=140.5, 138.0, 136.4, 131.7, 129.7, 128.9, 124.6, 112.3, 50.1, 20.2, 19.7.Anal.Calcd.for $C_{27}H_{31}BrN_2$: C,69.97; H, 6.74; N, 6.04. Found: C, 70.12; H, 6.88, N, 6.25.

1,3-Bis-(2,3,4,5,6-pentamethylbenzyl)-5,6-dimethylbenzimidazolium chloride, 1b

m.p: 232.1 °C. Yield: 90%.^{1}H NMR (300.1 MHz, D_2O, 25 °C): δ=not observed due to substitued with doterium [s, 1H, NC*H*N], 7.60[s, 2H, $C_6H_2(CH_3)_2$-5,6], 5.38 [s, 4H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.25 [s, 6H, $C_6H_2(CH_3)_2$-5,6], 1.89 [m, 30H, $CH_2C_6(CH_3)_5$-2,3,4,5,6]. ^{13}C NMR (75 MHz, D_2O,25 °C): δ=137.9, 133.9, 133.4, 130.6, 125.6, 112.7, 45.8, 19.6, 16.3, 15.9, 15.2.Anal.Calcd.for $C_{33}H_{43}ClN_2$: C, 78.77; H, 8.61; N, 5.57. Found: C, 78.89; H, 8.79, N, 5.74.

1,3-Bis-(2,3,4,5,6-pentamethylbenzyl)benzimidazolium chloride, 1c

This known compound was synthesized according to literature procedure and characterized by spectroscopic techniques. Results are consistent with the literature.[50]

Preparation of the NHC-palladium complexes, (2a-c)

A Schlenk was charged with benzimidazole salts, **1a-c,** (1 mmol), $PdCl_2$ (0.5 mmol; 0.09g), K_2CO_3 (0.6 g) and a stir bar under argon. Dry THF (25 ml) was then added as a solvent. The mixture was heated under reflux for 24h. The reaction mixture was cooled at r.t and the solvent was removed under vaccum. The residue was solved in DCM and purified by flash column, eluting with DCM/hexane (8:2) until the product was completely recovered. Solvents were removed under reduce pressure and the further purification was done using recrystallization (DCM-Hexane) or (DCM–ether) to get pure complexes for analysis and catalysis.

Dibromodi-[1,3-bis-(3,5-dimethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]palladium(II), 2a

m.p: 299.6 ^{o}C. Yield: 85%.^{1}H NMR (300.1 MHz, $CDCl_3$, 25 ^{o}C): δ=7.03 [s, 4H, $C_6H_2(CH_3)_2$-5,6], 6.81[s, 8H, $CH_2C_6H_3(CH_3)_2$-3,5], 6.73[s, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 5.76 [s, 8H, $CH_2C_6H_3(CH_3)_2$-3,5], 2.20 [s, 12H, $C_6H_2(CH_3)_2$-5,6], 2.13 [s, 24H, $CH_2C_6H_3(CH_3)_2$-3,5]. ^{13}C NMR (75 MHz, $CDCl_3$,25 ^{o}C): δ=180.9, 137.9, 135.7, 133.4, 131.6, 129.1, 125.5, 125.4, 111.4, 52.2, 30.9, 21.1, 20.2. Anal.Calcd.for $C_{50}H_{52}N_4Cl_2Pd$: C, 67.76; H, 5.91; N, 6.32. Found: C, 67.88; H, 6.05, N, 6.52.

Dichlorodi-[1,3-bis-(2,3,4,5,6-pentamethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]palladium(II), 2b

m.p: 329.5 ^{o}C. Yield: 90%.^{1}H NMR (300.1 MHz, $CDCl_3$,, 25 ^{o}C): δ=6.31 [s, 8H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 6.06[s, 4H, $C_6H_2(CH_3)_2$-5,6], 2.35 [s, 24H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.19 [s, 12H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.14 [s, 24H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 1.83 [s, 12H, $C_6H_2(CH_3)_2$-5,6].^{13}C NMR (75 MHz, $CDCl_3$,25 ^{o}C): δ=181.0, 135.3, 134.4, 133.6, 132.8, 130.5, 128.9, 112.0, 51.1, 20.3, 17.7, 17.1, 16.8.Anal.Calcd.for $C_{66}H_{84}Cl_2N_4Pd$: C,71.48; H, 7.62; N, 5.04. Found: C, 71.48; H, 5.76, N, 5.30.

Dichlorodi-[1,3-bis-(2,3,4,5,6-pentamethylbenzyl))benzimidazole-2-ylidene] palladium(II), 2c

m.p: 320.6 ^{o}C. Yield: 88%. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ^{o}C): δ=6.67 [s, 4H, C_6H_4], 6.39 [s, 8H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 6.34 [s, 4H, C_6H_4], 2.34 [s, 24H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.19 [s, 12H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.15 [s, 24H, $CH_2C_6(CH_3)_5$-2,3,4,5,6]. ^{13}C NMR (100 MHz, $CDCl_3$,25 ^{o}C): δ=181.5, 134.5, 134.0, 133.3, 132.0, 128.0, 127.5, 127.2, 121.0, 110.6, 50.4, 16.7, 16.1, 15.8.Anal.Calcd.for $C_{62}H_{76}Cl_2N_4$ Pd: C,71.26; H, 7.10; N, 5.19. Found: C, 71.34; H, 7.25, N, 5.34.

Preparation of the NHC-palladium-pyridine (PEPPSI) complexes, (3a-c)

In air, a pressure tube was charged with $PdCl_2$ (180 mg, 1mmol), NHC·HCl (1.1mmol), K_2CO_3 (700 mg, 5mmol) and 3 mL of pyridine. The reaction mixture was heated with vigorous stirring for 7 h at 80^{o}Cthen cooled to room temperature and diluted with dichloromethane (DCM). A short silica column was used for filtration. All volatiles were evaporated. Residue yellow solid was washed with hexane (2x10 mL) and diethyl ether (2x10 mL).

Dichloro[1,3-bis-(3,5-dimethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]pyridinepalladium(II), 3a

m.p: 226.8 ^{o}C. Yield: 80%.^{1}H NMR (300.1 MHz, $CDCl_3$, 25 ^{o}C): δ= 8.90 [m, 2H, C_5H_5N], 7.65 [m, 1H,C_5H_5N], 7.18 [m, 6H, $C_6H_2(CH_3)_2$-5,6 and C_5H_5N and $CH_2C_6H_3(CH_3)_2$-3,5], 6.84 [m, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 6.00[m, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 2.23 [s, 12H,$CH_2C_6H_3(CH_3)_2$-3,5], 2.12 [s, 6H, $C_6H_2(CH_3)_2$-5,6]. ^{13}C NMR (75 MHz, $CDCl_3$,25^{o}C): δ=161.9, 152.6, 152.1, 151.3,138.3, 138.0, 137.9, 137.8, 135.3, 135.2, 135.1, 133.5, 133.3, 133.2, 132.3, 132.2, 132.1, 129.6, 125.8, 125.7, 125.6, 125.4, 111.6, 53.2, 52.9, 52.6, 21.3, 20.3. Anal.Calcd.for $C_{30}H_{31}N_3Cl_2Pd$: C, 58.98; H, 5.11; N, 6.88. Found: C, 59.12; H, 5.26, N, 7.05.

Dichloro[1,3-bis-(2,3,4,5,6-pentamethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene] pyridinepalladium(II), 3b

m.p: 262.4 ^{o}C. Yield: 89%.^{1}H NMR (300.1 MHz, $CDCl_3$, 25 ^{o}C): δ=8.87 [d, J=5.1 Hz, 2H, C_5H_5N], 7.77 [t, J=7.5 Hz, 1H,C_5H_5N], 7.34 [t, J=6.6 Hz, 2H,C_5H_5N], 6.23 [s, 4H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 6.15 [m, 2H, $C_6H_2(CH_3)_2$-5,6], 2.34 and 2.25 [s, 30H,$CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.00 [s, 6H, $C_6H_2(CH_3)_2$-5,6]. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ=161.3, 151.1, 137.8, 135.6, 134.7, 133.6, 133.0, 131.2, 128.3, 124.2, 111.5, 50.9, 20.3, 17.5, 17.2, 16.9. Anal.Calcd.for $C_{38}H_{47}Cl_2N_3Pd$: C, 63.12; H, 6.55; N, 5.81. Found: C, 63.24; H, 6.67, N, 5.94.

Dichloro[1,3-bis-(2,3,4,5,6-pentamethylbenzyl)benzimidazole-2-ylidene] pyridinepalladium(II), 3c

m.p: 332.5 ^{o}C. Yield: 82%. ^{1}H NMR (300.1 MHz, $CDCl_3$, 25 ^{o}C): δ=8.84 [d, J=4.8 Hz, 2H, C_5H_5N], 7.70 [t, J=7.5 Hz, 1H,C_5H_5N], 7.26 [t, J=7.5 Hz, 2H,C_5H_5N], 6.72 and 6.36 [dd, J= 3 Hz, 4H, C_6H_4], 6.30 [s, 4H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.25, 2.24 and 2.16 [s, 30H,$CH_2C_6(CH_3)_5$-2,3,4,5,6]. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ=163.7, 151.1, 137.9, 135.8, 135.0, 134.6, 133.0, 127.9, 124.3, 122.4, 111.2, 51.5, 17.5, 17.3, 16.9.Anal.Calcd.for $C_{36}H_{43}Cl_2N_3Pd$: C, 62.21; H, 6.24; N, 6.05. Found: C, 62.34; H, 6.38, N, 6.21.

Preparation of the NHC-palladium-triphenylphosphine complexes, (4a-c)

Under argon atmosphere, a Schlenk tube was charged with **3a** (1mmol), PPh_3(2 mmol) and 30 mL of dry acetone. The reaction mixture was vigorous stirring for 1h at room temperature. All volatiles were evaporated. Residue white solid was washed with hexane (2x10 mL) and diethyl ether (2x10 mL).

Dichloro[1,3-bis-(3,5-dimethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]triphenylphosphinepalladium(II), 4a

m.p: 268.1 ^{o}C. Yield: 81%.^{1}H NMR (300 MHz, DMSO-d^6, 25 ^{o}C): δ= 7.63-7.32 [m, 15H, PPh_3], 7.21 [d, j=7.2 Hz, 4H, $CH_2C_6H_3(CH_3)_2$-3,5], 6.89 [s, 2H, $C_6H_2(CH_3)_2$-5,6], 6.68 [m, 2H, $CH_2C_6H_3(CH_3)_2$-3,5], 6.08 [m, 2H, $CH_2C_6H_3(CH_3)_2$-3,5],5.0 [m, 2H, $CH_2C_6H_3(CH_3)_2$-3,5], 2.19 [s, 12H, $CH_2C_6H_3(CH_3)_2$-3,5], 2.08 [s, 6H, $C_6H_2(CH_3)_2$-5,6]. ^{13}C NMR (75 MHz, DMSO, 25 ^{o}C): δ= 172.5, 137.3, 134.7, 134.4, 133.8, 131.1, 129.3, 128.5, 128.3, 125.8, 111.6, 54.9, 20.8, 19.7.^{31}P NMR (300 MHz, DMSO-d^6, 25 ^{o}C): δ= 25.1 ppm. Anal.Calcd.for $C_{45}H_{45}Cl_2N_2PPd$: C, 65.74; H, 5.52; N, 3.41. Found: C, 65.82; H, 5.62;N, 3.64.

Dichloro[1,3-bis-(2,3,4,5,6-penthamethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]triphenylphosphinepalladium(II), 4b

The synthesis of **4b** was performed following the same procedure employed for the preparation of **4a**, starting from **3b**.

m.p: 295.1 ^{o}C. Yield: 88%.^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ= 7.32 [m, 15H, PPh_3], 6.52 [d, j=14.4 Hz, 2H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 5.40 [s, 2H, $C_6H_2(CH_3)_2$-5,6], 4.91 [d, j=14.4 Hz, 2H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.20 [s, 6H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.11 [s, 12 H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 1.91 [s, 12 H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 1.71 [s, 6 H, $C_6H_2(CH_3)_2$-5,6]. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ= 171.5, 136.1, 134.6, 133.8, 132.9, 131.5, 128.6, 128.5, 127.2, 111.5, 51.3, 20.3, 17.3, 17.2, 16.8.^{31}P NMR (600 MHz, $CDCl_3$, 25 ^{o}C): δ= 27.05 ppm. Anal.Calcd.for $C_{51}H_{57}Cl_2N_2PPd$: C, 67.59; H, 6.34; N, 3.09. Found: C, 67.71; H, 6.46,N, 3.24.

Dichloro[1,3-bis-(2,3,4,5,6-penthamethylbenzyl)benzimidazole-2-ylidene]triphenylphosphinepalladium(II), 4c

The synthesis of 4c was performed following the same procedure employed for the preparation of 4a, starting from 3c.

m.p: 297.5 ^{o}C. Yield: 83%.^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ= 7.98-7.32 [m, 15H, P*Ph*$_3$], 6.55 [m, 4H, C_6H_4 and $CH_2C_6(CH_3)_5$-2,3,4,5,6], 5.78 [dd, j=3.3 Hz, 2H, C_6H_4], 5.01 [d, j=14.4 Hz, 2H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.20 [s, 6H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 2.11 [s, 12 H, $CH_2C_6(CH_3)_5$-2,3,4,5,6], 1.92 [s, 12 H, $CH_2C_6(CH_3)_5$-2,3,4,5,6]. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ= 173.8, 136.3, 135.2, 134.4, 133.1, 128.7, 128.5, 126.9, 122.4, 111.3, 51.6, 17.3, 17.2, 16.9.^{31}P NMR (600 MHz, $CDCl_3$, 25 ^{o}C): δ= 27.00 ppm. Anal.Calcd.for $C_{49}H_{53}Cl_2N_2PPd$: C, 67.01; H, 6.08; N, 3.19. Found: C, 67.15; H, 6.19,N, 3.38.

General procedure for Suzuki-Miyaura Reaction

In air, **2a-e** (1.0 mmol %), aryl chloride (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), and 3 mL of 1:1 mixture of water/DMF were added to a small round bottom flask and the mixture was heated at 80 ^{o}C for 3 h. The reaction mixture was cooled to room temperature and extracted with Et_2O. Extract was filtered through a pad of silica with copious washing of diethyl ether. The purity of the compounds was checked by GC using internal standart undecane). The yields are based on aryl chloride.

General Procedure for Sonogashira Cross-Coupling Reaction

Under argon atmosphere, palladium catalyst (1.0 mmol %), aryl halide (1.0 mmol), phenylacetilene (1.5 mmol), K_2CO_3 (2 mmol), and 10 mL of DMF were added to a small round bottom flask and the mixture was heated at 100 ^{o}C for 3 h. The reaction mixture was cooled to room temperature and extracted with Et_2O. Extract was filtered through a pad of silica with copious washing of diethyl ether. The purity of the compounds was checked by GC using internal standart undecane). The yields are based on aryl halide.

Conclusions

In conclusion, we have synthesized a new series of benzimidazole-based palladium NHC complexes. These palladium(II) complexes have been employed as precatalysts in Suzuki-Miyaura and Sonogashira cross-coupling reactions. Suzuki coupling reaction of electronically poor aryl chlorides and all types of aryl bromides were catalysed by **2a-c** and **3a-c** complexes in moderate to excellent yields. For the Sonogashira coupling reaction, only complexes **4a-c** show productive catalytic activity, and most importantly they display very interesting activities from aryl chlorides.

In these coupling reactions, we believe that the bulky and electron-donor NHC ligands associated with pyridine in complexes **3** and triphenylphosphine in complexes **4** provide the synergetic steric and electronic effects to confer the metal center the appropriate properties to make the elemental steps of the catalytic cycles optimum.

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