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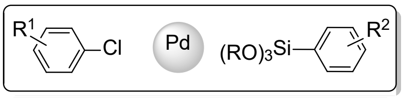
A General Palladium-Catalyzed Hiyama Cross-Coupling Reaction of Aryl and Heteroaryl Chlorides

On Ying Yuen[a,b], Chau Ming So*[a,b], Ho Wing Man[a] and Fuk Yee Kwong*[a,b]

Abstract: A general palladium-catalyzed Hiyama cross-coupling reaction of aryl and heteroaryl chlorides with aryl and heteroaryl trialkoxysilanes by a $Pd(OAc)_2$/**L2** catalytic system is presented. A newly developed water addition protocol can dramatically improve the product yields. The conjugation of the Pd/**L2** system and the water addition protocol can efficiently catalyze a broad range of electron-rich, -neutral, -deficient, sterically hindered aryl chlorides and heteroaryl chlorides with excellent yields within 3 h and the catalyst loading can be down to 0.05 mol% Pd for the first time. Hiyama coupling of heteroaryl chlorides with heteroaryl silanes is also reported for the first time. The reaction can be easily scaled up 200 times (100 mmol) without any degasification and purification of reactants; this facilitates the practical application in routine synthesis.

Palladium-catalyzed cross-coupling reactions have become versatile protocols in organic synthesis for construction of carbon-carbon or carbon-heteroatom bonds.[1] Suzuki,[2] Negishi,[3] Kumada,[4] and Stille[5] reactions are common methods for the preparation of biaryls which have numerous applications in pharmaceutical, material, and agricultural chemistry.[6] Hiyama[7] cross-coupling reaction is one of the most attractive methods to produce biaryl compounds because organosilicon reagents are of low cost, low toxicity, commercially available, easy to prepare and handle and highly stable to a variety of reaction conditions. However, organosilicons are less reactive electrophiles owing to their less polarized carbon and silicon bonds.

Aryl(alkoxy)silane is one of the most extensively studied organosilicons[8] in Hiyama coupling since the first report by Shibata and coworkers.[9] Reactive aryl iodides and bromides have been predominantly used as electrophiles in the Hiyama coupling reactions instead of the relatively cheaper and commercially more available aryl chlorides.[10] Since the first attempt to use 10 mol% Pd_2dba_3/John-phos system for the Hiyama coupling of $PhSi(OMe)_3$ with 4-chloroacetophenone that gave a product yield of 47%[11], the effectiveness of the Hiyama coupling of aryl chlorides has not been significantly improved compared with other cross-coupling methods. Palladium catalytic systems such as Pd/(o-tol)$_3$P[12], Pd/i-Pr-DPE phos[13], Pd/(4-FC_6H_4)$_3$P[14], Pd/phosphite[15], Pd/phosphonate[16], Pd/carbene ligand[17], Pd/diamine ligand[18], Pd/diimine ligand[19], Pd/thiourea ligand[20], Pd/MIDA ligand[21], ligand free Pd/C systems[22] and SBA-15-supported Pd nanoparticles[23] for the Hiyama coupling of aryl(alkoxy)silanes with aryl chlorides have been reported. However, these reports in general have several limitations. 1) narrow substrate scope (unreactive/poor results for the electron rich aryl chlorides and/or functionalized aryl chlorides); 2) limited examples (only a few aryl chlorides are demonstrated in some reports); 3) high catalyst loading (3-5 mol% Pd catalysts are commonly used) and 4) long reaction time (10-24 h for conventional heating techniques). Moreover, in some cases, increasing the reaction temperature is not an effective means to improve the yields.[16, 18]



General limitations of previous works:
- Medium to high catalyst loading (0.5-10 mol%Pd)
- Narrow substrate scope
- Long reaction time (10-24 h)
- Lack of the use of heteroaryl silanes

This work:
- Lowest catalyst loading (0.05-0.2 mol%Pd)
- Broad substrate scope (42 examples)
- First example of heteroaryl-heteroaryl synthesis
- Solvent free for most of aryl chlorides (32 examples)
- Short reaction time (3 h)
- Solvent-less large scaled synthesis (100 mmol scale)
- Acetic acid or water protocol to minimize side products

Figure 1. General limitations of Hiyama-coupling of aryl chlorides by conventional heating techniques.

Recent breakthroughs such as lowering the catalyst loading to 0.5 mol% Pd, shorter reaction time, wider substrate scope (steric hindered aryl chlorides) have been achieved by Verkade and coworkers' Pd/ $^t\mathrm{Bu_2P\text{-}N{=}P}(^i\mathrm{BuNCH_2CH_2})_3\mathrm{N}$ catalyst[24], Jin and coworkers' β-diketiminatophosphane Pd complex[19b] and Wang and coworkers' dinuclear NHC/Pd complex[17c]. Yet, catalyst loading remains high and the heteroaryl–heteroaryl Hiyama coupling had not been reported. Microwave irradiation is found to be an alternative to improve the catalytic activity of the Hiyama coupling of aryl chlorides.[25,26] Despite of the high cost, the availability of the microwave instrument and technical concerns such as solvent and heat control especially for large scale synthesis[27], aryl bromides are still predominantly used in current microwave irradiated Hiyama coupling reaction. Therefore, development of highly effective catalyst for the Hiyama coupling reactions is highly desired.

We envision that combining a highly active catalyst that can facilitate the activation of aryl chlorides and an efficient reaction protocol that can minimize the disadvantages of the inferior reactivity of organosilicons may provide the key of success to tackle the existing limitations and achieve the breakthroughs in multiple aspects such as lowering the catalyst loading[28], expanding the substrate scope, and applying the catalysis to pilot scale (50-200 mmol[28]) for the palladium-catalyzed Hiyama coupling of aryl chlorides.

In order to investigate the feasibility of palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides, sterically

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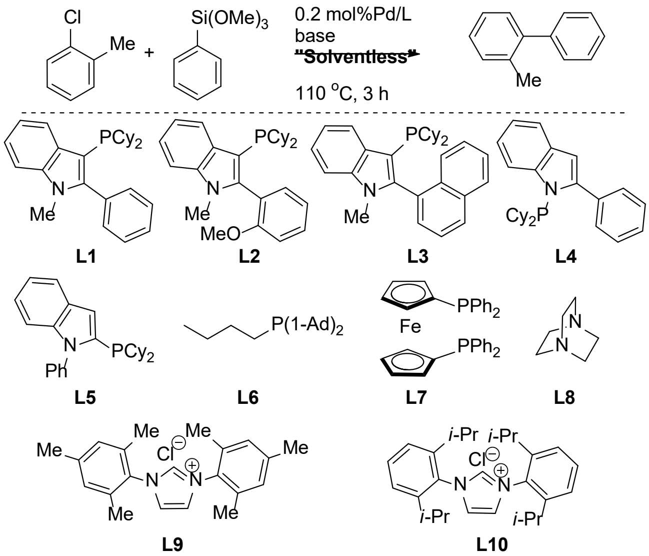
hindered 2-chlorotoluene and phenyltrimethoxysilane were chosen as the benchmark substrates. Indole-scaffolded phosphine ligands, which have been developed by our group, showed excellent activities towards a broad range of palladium-catalyzed coupling reactions.[29] Among them, the CPCy Phendole-phos **L1** which is an effective ligand in various coupling reactions with aryl chlorides was first attempted in this reaction.[30]

Table 1. Initial screenings of palladium-catalyzed Hiyama cross-coupling reaction of 2-chlorotoluene with phenyltrimethoxysilane.[a]

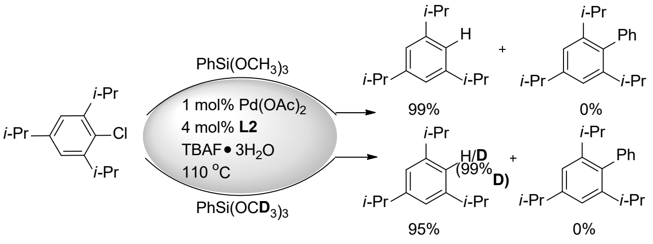


entry	Pd source	promotor/base	ligand	% yield[b]
1	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L1	69
2	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L2	87
3	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L3	77
4	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L4	0
5	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L5	33
6	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L6	4
7	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L7	0[c]
8	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L8	0
9	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L9	0
10	$Pd(OAc)_2$	$TBAF\bullet 3H_2O$	L10	0
11	$Pd(OAc)_2$	KF	L1	0
12	$Pd(OAc)_2$	CsF	L1	trace
13	$Pd_2(dba)_3$	$TBAF\bullet 3H_2O$	L1	61
14	$PdCl_2(CH_3CN)_2$	$TBAF\bullet 3H_2O$	L1	82

[a] Reaction condition: 2-Chlorotoluene (0.5 mmol), phenyltrimethoxysilane (1.0 mmol), Pd source/L = 1:4 and base (1.0 mmol) were stirred for 3 h at 110 °C under nitrogen. [b] Calibrated GC yields were reported using dodecane as internal standard. [c] Pd source:L = 1:2

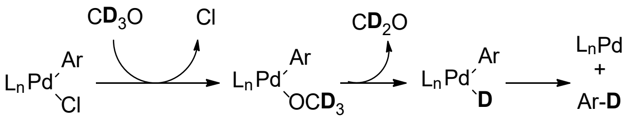
The promising results were obtained using only 0.2 mol% Pd. Indolylphosphine ligands that the phosphino group attached to the 3-position of indole ring (Table 1, entries 1–3) were highly active towards the Hiyama coupling reaction. The results (Table 1, entries 1–5) also showed that the Hiyama coupling reaction was sensitive to the steric (product yield increased with increasing the *ortho* steric hindrance of the indole bottom ring, (**L1**–**L3**)) and electronic factors (product yield significantly decreased if the phosphino group was at the nitrogen position (**L1** and **L4**)) of the phosphine ligands and the 2-arylindole provided an excellent scaffold (**L1** and **L5**) to affect the Hiyama coupling reaction. Commercially available and well recognized ligands such as phosphine ligands **L6** (CataCXiumA), **L7** (dppf), dinitrogen ligand **L8** (DABCO), and NHC carbene ligands **L9** (IMes·HCl), **L10** (IPr·HCl) were examined. However, they were found to be inactive ligands towards the Pd-catalyzed Hiyama coupling reaction. Commonly used fluoride bases were screened (Table 1, entries 1, 11 and 12). $TBAF\cdot 3H_2O$ was found to be the best base while KF and CsF hardly promoted the Hiyama reaction. Upon surveying the Pd sources (Table 1, entries 1, 11 and 12), $Pd(OAc)_2$ afforded the best product yield. It was worthy to note that Pd/**L2** system gave the best result among **L1**–**L10** under solvent-free condition and achieved the lowest catalyst loading for this entry so far in Hiyama coupling reaction (Table1, entry 2).

Sterically hindered di-*ortho*-substituted aryl chlorides were found to be extremely difficult substrates in Hiyama coupling with aryl(alkoxy)silanes. There was only one report about these substrates up to date.[31] With the promising results in hand, we attempted to apply the highly active Pd/**L2** system to the Hiyama coupling of extremely sterically hindered 1-chloro-2,4,6-triisopropylbenzene. To our disappointment, we obtained the reduced 1,3,5-triisopropylbenzene as the sole product, with the absence of any desired coupling products (Scheme 1).



Scheme 1. Deuterium experiment of Hiyama coupling reaction of 1-chloro-2,4,6-triisopropylbenzene.

The result of the complete conversion of the extremely sterically hindered aryl chloride to the 1,3,5-triisopropylbenzene implies that the Pd/**L2** system is able to activate the highly challenging aryl chlorides. However, the slow transmetallation of the phenyltrimethoxysilane to the sterically congested aryl–palladium center allows the competing side reaction to consume the aryl–palladium species smoothly.

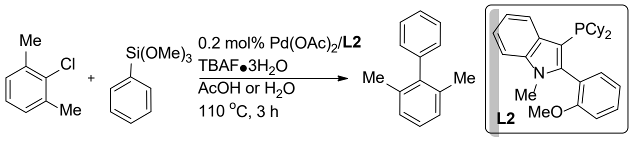


Scheme 2. Proposed mechanism for the generation of reduced arenes.

We proposed that the methoxide anion generated from the phenyl(trimethoxy)silane might compete with the transmetalation step of the corresponding silane to undergo the ligand substitution of chloride anion and following the β-hydride elimination and reductive elimination to give the reduced arene (Scheme 2). We synthesized the $PhSi(OCD_3)_3$ to perform the deuterium experiment and the reduced 1,3,5-triisopropylbenzene has 99%D at the reduction position, an observation that supports our hypothesis (Scheme 1).

We think that the strategic modification of the reaction protocol which supplies proton source to protonate the alkoxy anion is an efficient means to suppress the competing side reaction and enhance the possibility for the slow transmetallation of the aryl(alkoxy)silane to the aryl–palladium species. Addition of 0.25-0.50 equivalent of acetic acid to neutralize the methoxide anion was first attempted; this can successfully suppressed the generation of 1,3-dimethylbenzene and increased the yield of the desired coupling product (Table 2, entries 2–4). Since a certain amount of 1,3-dimethylbenzene was still observable (Table 2, entries 2–4) and excess acetic acid reduced the rate of reaction (Table 2, entries 4 and 5), we attempted to use water as a mild proton source to protonate the methoxide anion meanwhile the reaction rate was able to remain intact (Table 2, entries 6–9). The addition of 10 equivalent of water is highly sufficient to suppress the formation of 1,3-dimethylbenzene so as to greatly improve the yield of desired product by nearly double (Table 2, entries 1 and 8).

Table 2. Water and acid additive effect in Hiyama coupling of ArCl.[a]

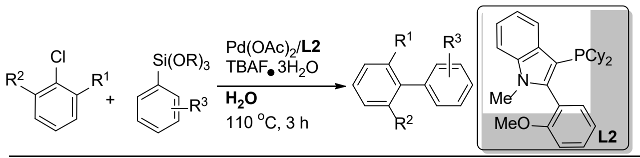


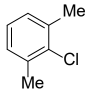
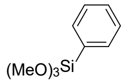
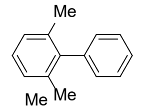
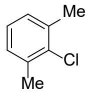
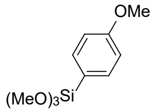
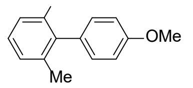
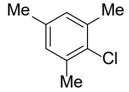
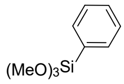
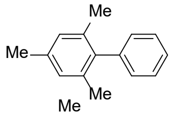
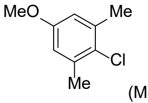
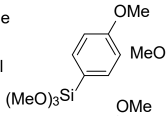
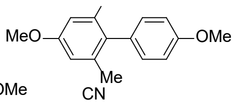
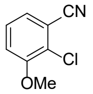
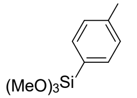
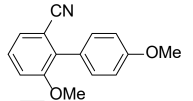
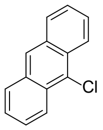
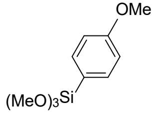
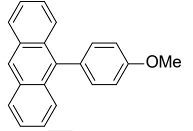
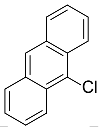
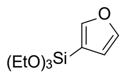
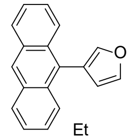
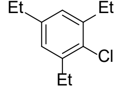
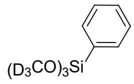
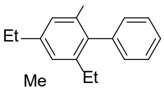
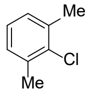
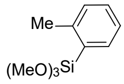
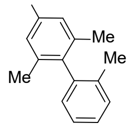
entry	AcOH (equiv.)	H_2O (equiv.)	% yield[b]
1	-	-	56[c]
2	0.25	-	67
3	0.35	-	74[d]
4	0.50	-	73
5	1.0	-	22
6	-	2.5	69
7	-	5.0	81
8	-	10	97
9	-	20	49

[a] Reaction conditions: 1,3-dimethyl-2-chlorobenzene (0.5 mmol), phenyltrimethoxysilane (1.0 mmol), $Pd(OAc)_2$/**L2** =1:4, $TBAF•3H_2O$ (1.0 mmol) and acetic acid or water additive were stirred at 110 °C for 3 h. [b] Calibrated GC yields were reported using dodecane as internal standard. [c] 0.5 mol% $Pd(OAc)_2$. [d] Isolated yield.

A range of extremely sterically congested di-*ortho*-substituted aryl chlorides were tested. With the water addition protocol, 2-chloro-*m*-xylene, 2-chloromesitylene, 2-chloro-1,3,5-triethylbenzene and more electron rich 2,6-dimethyl-4-chloroanisole were able to give the corresponding coupling products in good to excellent yield (Table 3, entries 1–6 and 10). The sterically congested 9-chloroanthracene and functionalized 2-chloro-3-methoxybenzonitrile were also feasible coupling partners (Table 3, entries 7–8). It was worthy to note that the Hiyama coupling of sterically congested aryl chlorides with heteroaryl(triethoxy)silanes was reported for the first time. Fair yield could also be obtained in the tri-*ortho*-subsitiuted biary synthesis through Hiyama coupling reaction (Table 3, entry 11).

Table 3. Palladium-catalyzed Hiyama cross-coupling reaction of steric hindered aryl chlorides with water addition protocol.[a]

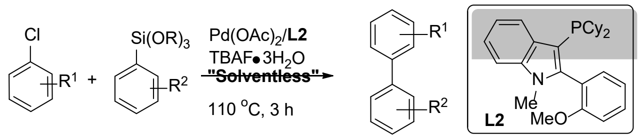


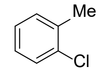
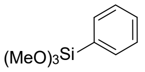
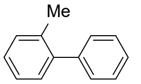
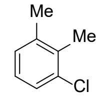
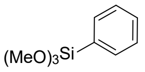
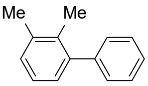
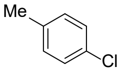
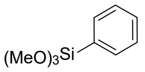
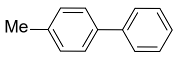
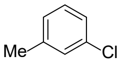
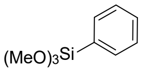
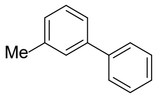
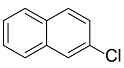
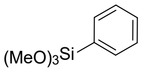
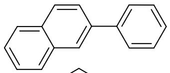
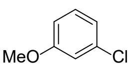
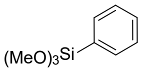
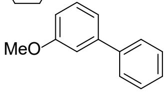
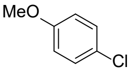
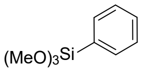
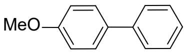
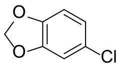
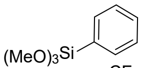
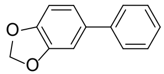
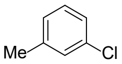
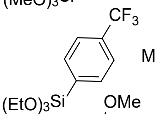
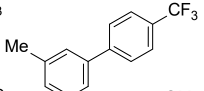
entry	ArCl	Ar'Si(OR)3	product	mol% Pd	% yield[b]
1				0.2	97
2				0.2	74[c]
3				0.2	72
4				0.5	80
5				0.5	70[c]
6				0.5	72
7				1.0	56[d]
8				1.0	58[e]
9				1.0	75[d]
10				1.0	66[f]
11				1.0	36[c,f]

[a] Reaction condition: ArCl (0.5 mmol), Ar'$Si(OR)_3$ (1.0 mmol), $Pd(OAc)_2$/**L2** =1:4, $TBAF•3H_2O$ (1.0 mmol), and 10 equiv. H_2O were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields. [c] 0.35 equiv. AcOH was used instead of H_2O. [d] 30 equiv. H_2O and toluene (1.0 mL) were added. [e] Toluene (0.5 mL) was added. [f] NMR yield.

With the highly active Pd/**L2** system and the water addition protocol in hand, a wide range of electron rich, electron neutral and functionalized aryl chlorides were examined. Sterically hindered, electron neutral and electron rich aryl chlorides were coupled with phenyl(trimethoxy)silane to give excellent yields (Table 4, entries 1–8). Apart from aryl chlorides, electron-deficient and -rich aryltrialkoxysilanes were also able to couple and gave products in good yields (Table 4, entries 9–16). It was noteworthy that the water addition protocol could be widely adopted, efficiently minimized the disadvantages of the inferior reactivity of arylalkoxysilanes and greatly improved the desired

Table 4. Palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides.[a]



entry	ArCl	Ar'Si(OR)$_3$	product	mol% Pd	% yield[b]
1				0.2	86
2				0.2	80
3				0.067	86
4				0.1	99
5				0.1	92
6				0.2	97
7				0.2	98
8				0.2	95
9				0.2	65
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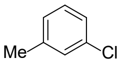
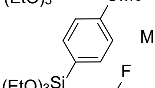
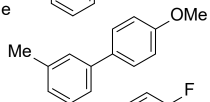
11				0.2	70
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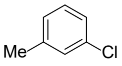
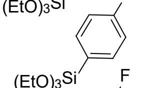
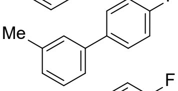
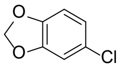
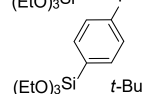
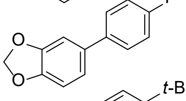
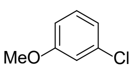
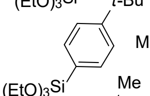
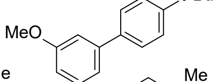
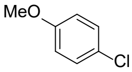
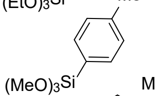
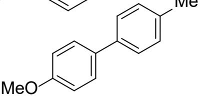
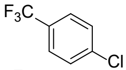
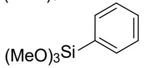
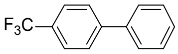
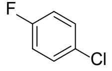
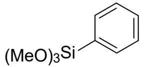
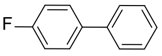
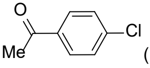
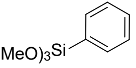
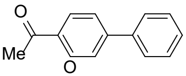
13				0.2	96[c]
14				0.2	99[c]
15				0.2	99[c]
16				0.2	82
17				0.05	93
18				0.05	86
19				0.05	75
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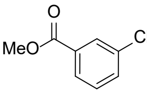
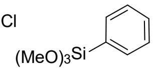
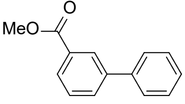
21				0.05	53
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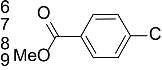
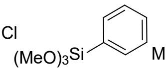
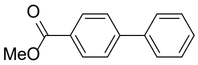
26				0.05	64
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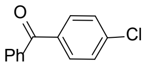
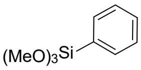
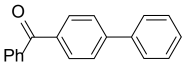
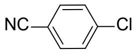
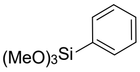
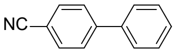
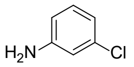
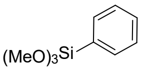
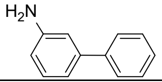
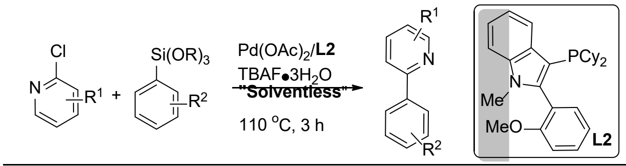
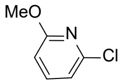
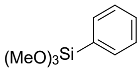
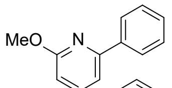
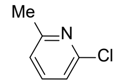
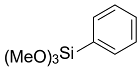
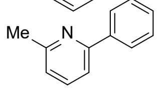
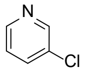
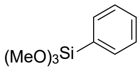
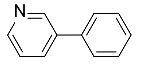
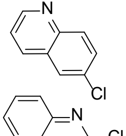
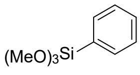
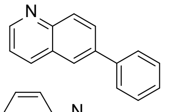
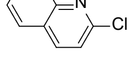
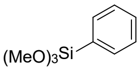
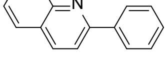
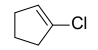
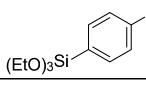
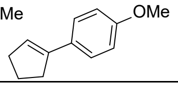
30				0.05	99[h]
31				0.2	88[h]
32				0.2	73

[a] Reaction condition: ArCl (0.5 mmol), Ar'Si(OR)$_3$ (1.0 mmol), Pd(OAc)$_2$/**L2** = 1:4 and TBAF•$3H_2O$ (1.0 mmol) were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields. [c] 10 equiv. H_2O was added. [d] 0.25 equiv. AcOH was added. [e] 0.25 equiv. AcOH and toluene (0.5 mL) were added. [f] 0.50 equiv. AcOH was added. [g] 10 equiv. H_2O and toluene (0.5 mL) were added. [h] Toluene (0.5 mL) was added.

product yields (Table 4, entries 9–12). The aryl chlorides bearing an array of common functional groups such as –CF_3, –F, –COMe, –CO_2Me, –COPh and –CN were compatible and afforded excellent product yields (Table 4, entries 17–31). A free –NH_2 group in 3-chloroaniline remained intact under these optimized reaction conditions (Table 4, entry 32). During the study of the Hiyama reaction, we observed lower yield for the ArCl bearing an ester functional group (Table 4, entries 21 and 26) and corresponding benzoic acid. The addition of acetic acid to the reaction mixture was found to be able to neutralize the methoxide anion, thus reducing the possibility of alkaline hydrolysis of ester group and improving the product yield (Table 4, entries 21–29). The catalyst loading could be down to 0.2-0.05 mol% Pd. To our best knowledge, this is the lowest catalyst loading reported in general for the Hiyama coupling of aryl chlorides with aryl(trialkoxy)silanes.

Table 5. Palladium-catalyzed Hiyama cross-coupling reaction of heteroaryl chlorides and alkenyl chloride with aryltrialkyoxysilanes.[a]



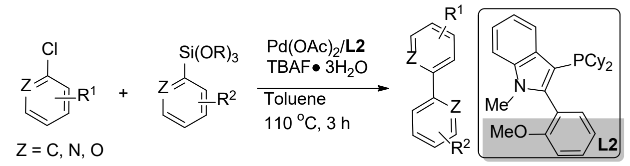
entry	Het-ArCl	Ar'Si(OR)$_3$	product	mol% Pd	% yield[b]
1				0.05	99
2				0.1	97
3				0.2	88
4				0.2	83
5				0.1	81
6				0.2	63

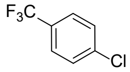
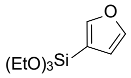
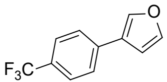
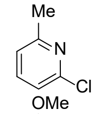
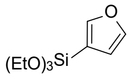
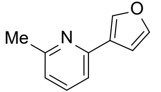
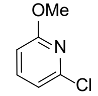
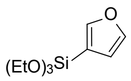
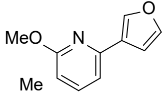
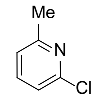
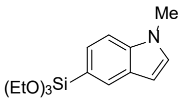
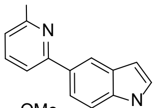
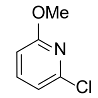
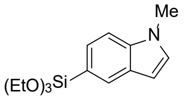
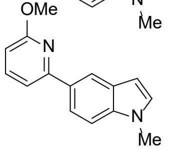
[a] Reaction condition: ArCl (0.5 mmol), Ar'Si(OR)$_3$ (1.0 mmol), Pd(OAc)$_2$/**L2** =1:4 and TBAF•$3H_2O$ (1.0 mmol) were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields.

Apart from electron rich and steric hindered aryl chlorides, heteroaryl chlorides are another class of difficult substrates in Hiyama coupling reaction. In general, even with the help of microwave irradiation, 0.5-1.0 mol% Pd was still necessary to bring about the Hiyama coupling reaction of heteroaryl chlorides to obtain good to excellent product yields. However, using Pd/**L2** system, a range of heteroaryl chlorides could be smoothly coupled with aryltrialkyoxysilanes to afford good to excellent yields of the corresponding products under solvent-free condition and the catalyst loading could be down to 0.05 mol% Pd (Table 5, entries 1–5). Alkenyl chloride was also a feasible coupling partner for the Hiyama coupling reaction (Table 5, entry 6).

Heteroaryl–heteroaryl cross-coupling reaction is found to be one of the most difficult coupling reactions since both of the coupling partners are electron-deficient aromatic compounds. The electron-deficient heteroaryl nucleophiles are usually unstable and often undergo a transmetallation process at a relatively slower rate. With 1 mol% Pd catalyst of the Pd/**L2** system and toluene as solvent[32],electron-deficient aryl and heteroaryl chlorides (Table 6, entries 2–5) were coupled with heteroaryl(triethoxy)silanes for the first time in Hiyama coupling reaction (Table 6, entries 1–5).

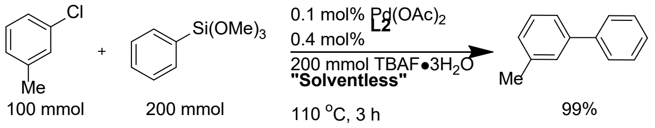
Table 6. Palladium-catalyzed Hiyama cross-coupling reaction of aryl- or hetero- aryl chlorides with heteroaryl trialkyoxysilanes.[a]



entry	Het-ArCl	Het-Ar'Si(OR)$_3$	product	mol% Pd	% yield[b]
1				1	67
2				1	81
3				1	87
4				1	60
5				1	54

[a] Reaction condition: ArCl (0.5 mmol), Ar'Si(OR)$_3$ (1.0 mmol), Pd(OAc)$_2$/**L2** =1:4, TBAF•3H$_2$O (1.0 mmol), and 1 mL toluene were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields.

To test the feasibility of scaling up the current reaction condition and to magnify the advantages of using conventional heating techniques for the routine application, a large scale Hiyama cross-coupling reaction was conducted (Scheme 3). Notably, without any degasification and purification of the reactants, 3-chlorotoluene and phenyltrimethoxysilane was directly scaled up 200 times to give the coupling product without any diminishing of the yield (Table 4, entry 4 and scheme 3).



Scheme 3. Large scale solvent-free Hiyama cross-coupling reaction of 3-chlorotoluene and phenyltrimethoxysilane.

In conclusion, the Pd/**L2** system is highly efficient towards Hiyama cross-coupling reaction. Aryl and heteroaryl chlorides are smoothly coupled with aryltrialkoxysilanes under solvent-free condition to give excellent yields within 3 h. The deuterium experiment reveals the possible pathway for the formation of reduced arenes. The newly developed water addition protocol can in general dramatically improve the product yield of Hiyama coupling not only for sterically hindered aryl chlorides but also for arylalkoxysilanes with inferior reactivity. A wide range of aryl chlorides bearing common functional groups such as cyano, ketone, ester, and amine were compatible to the mild reaction conditions and the catalyst loading can be down to 0.05 mol% Pd for the first time. Particularly noteworthy is that the Hiyama coupling of heteroaryl chlorides with heteroaryltrialkoxysilanes is reported for the first time. Under the conventional heating, the reaction can be easily scaled up 200 times (100 mmol) without any degasification and purification of reactants. We anticipate this highly efficient method can be widely adapted in routine synthesis.

Experimental Section

General procedure for palladium-catalyzed Hiyama coupling of aryl chlorides: Pd(OAc)$_2$ (2.3 mg, 0.010 mmol) with ligand **L2** (17.3 mg, 0.040 mmol) in freshly distilled 10 mL THF (0.2 mol% Pd per 1 mL stock solution) were initially prepared with continuously stirring at room temperature for 1 min. Schlenk tube was charged with magnetic stirrer bar (4 mm x 10 mm) and was evacuated and backfilled with nitrogen (3 cycles). The corresponding volume of stock solution was added by syringe to the tube. The solvent was removed under reduced pressure. TBAF•3H$_2$O (0.32 g, 1.0 mmol) and solid aryl chlorides (0.50 mmol) was added to the tube which was again evacuated and backfilled with nitrogen (3 cycles). Trimethoxyphenylsilane (0.19 mL, 1.0 mmol) was then added to the tube via autopipette and the reaction mixture was allowed stir for 1 min. Liquid aryl chlorides (0.50 mmol) was added to the tube via autopipette. Acetic acid or water and/or toluene (0.50-1.0 mL) were then added via autopipette and syringe respectively (if needed, as indicated in Table 2 and 4). The tube was resealed and magnetically stirred in a preheated 110 °C oil bath for 3 h. The reaction was allowed to reach room temperature. Ethyl acetate (~8 mL), water (~2 mL) were added. The organic layers were combined and concentrated. The crude products were purified by column chromatography on silica gel (230-400 mesh).

Acknowledgements

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Keywords: cross-coupling reaction • palladium • phosphine ligand • aryl(alkoxy)silane • aryl chlorides

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[1] Metal-Catalyzed Cross-Coupling Reactions, Vol. 1–2, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) M. Beller, C. Bolm, Transition Metals for Organic Synthesis Building Blocks and Fine Chemicals, Vol. 1–2, 2nd ed., Wiley-VCH, Weinheim, **2004**; c) Handbook of Organopalladium for Organic Synthesis, Vol. 1–2 (Ed.: E. Negishi), Wiley- Interscience, New York, **2002**; d) J. Hassan, M. Svignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; e) J. Tsuji, Palladium Reagents and Catalysts, 2nd ed., Wiley, Chichester, **2004**; f) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133; g) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; h) A. Roglans, A. Pla-Quintana, M. Moreno-Manas, *Chem. Rev.* **2006**, *106*, 4622.

[2] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, 3437; b) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263; c) A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419; d) J. P. Wolfe, S. P. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413; e) A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, *6*, 1830; f) R. B. Bedford, C. S. J. Cazin, S. J. Coles, T. Gelbrich, P. N. Horton, M. B. Hursthouse, M. E. Light, *Organometallics* **2003**, *22*, 987.

[3] a) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729; b) C. Dai, C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719.

[4] (a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; b) W. A. Herrmann, V. P. W. Bohm, C. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23.

[5] a) J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771; b) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508; c) V. Farina, V. Krishnamurthy, W. Scott, *J. Org. React.* **1997**, *50*, 1; d) J. Hassa, M. Svignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; e) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[6] a) A. O. King, N. Yasuda in Organometallics in Process Chemistry (Ed.: R. D. Larsen), Springer, Berlin, 20**0**4, pp. 205 – 246, and references therein; b) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; c) A. Suzuki in Modern Arene Chemistry (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 53 – 106; d) A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 54.

[7] a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 920; b) K. Gouda, E. Hagiwara, Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1996**, *61*, 7232; c) M. E. Mowery, P. DeShong, *Org. Lett.* **1999**, *1*, 2137; d) J. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 5616; e) S. Riggleman, P. DeShong, *J. Org. Chem.* **2003**, *68*, 8106; f) H. M. Lee, S. P. Nolan, *Org. Lett.* **2000**, *2*, 2053.

[8] C. J. Handy, A. S. Manoso, W. T McElroy, W. M Seganish, P. DeShong, *Tetrahedron* **2005**, *61*, 12201.

[9] K. Shibata, K. Miyazawa, Y. Goto, *Chem. Commun.*, **1997**, 1309.

[10] For reviews, see: a) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, *40*, 4893; b) H. F. Sore, W. R. J. D. Galloway, D. R Spring, *Chem. Soc. Rev.* **2012**, *41*, 1845.

[11] M. E. Mowery, P. DeShong, *Org. Lett.* **1999**, *1*, 2137.

[12] J. -H. Li, C. –L. Deng, Y. –X. Xie, *Synthesis* **2006**, *6*, 969.

[13] M. Murata, S. Yoshida, S. Nirei, S. Watanabe, Y. Masuda, *Synlett* **2006**, *1*, 118.

[14] Y. Monguchi, T. Yanase, S. Mori, H. Sajiki, *Synthesis* **2013**, *45*, 40; (b) T. Yanase, S. Mori, Y. Monguchi, H. Sajiki, *Chem. Lett.* **2011**, *40*, 910.

[15] J. Ju, H. Num, H. M. Jung, S. Lee, *Tetrahedron Lett.* **2006**, *47* ,8673.

[16] L. Ackermann, C. J. Gschrei, A. Althammer, M. Riederer, *Chem. Commun.* **2006**, 1419.

[17] (a) H. M. Lee, S. P. Nolan, *Org. Lett.* **2000**, *2*, 2053; (b) C. Dash, M. M. Shaikh, P. Ghosh. *Eur. J. Inorg. Chem.* **2009**, 1608; (c) J. Yang, L. Wang, *Dalton Trans.* **2012**, *41*, 12031; (d) Z. -S. Gu, L. –X. Shao, J. –M. Lu, *J. Organomet. Chem.* **2012**, 132; (e) S. Modak, M. K. Gangwar, M. N. Rao, M. Madasu, A.C. Kalita, V. Dorcet, M. A. Shejale, R. J. Butcher, R. Ghosh, *Dalton Trans.* **2015**, *44*, 17617.

[18] J. -H. Li, C. -L. Deng, W. -J. Liu, Y. -X. Xie, *Synthesis*, **2005**, *18*, 3039.

[19] (a) D. Domin, D. Benito-Garagorri, K. Mereiter, J. Fröhlich, K. Kirchner, *Organometallics* **2005**, *24*, 3957; (b) D. -H. Lee, J. Y. Jung, M. –J. Jin, *Chem. Commun.* **2010**, *46*, 9046.

[20] Z. -S. Wu, M. Yang, H. -L. Li, Y. –X. Qi, *Synthesis* **2008**, *9*, 1415.

[21] M. Guo, L. Qi, Q. Zhang, Z. Zhu, W. Li, X. Li, *Org. Biomol. Chem.* **2014**, *12*, 7136.

[22] (a) C. Pan, M. Liu, L. Zhao, H. Wu, J. Ding, J. Cheng, *Catalysis communications* **2008**, *9*, 1685; (b) T. Yanase, Y. Monguchi, H. Sajiki, *RSC Adv.* **2012**, *2*, 590.

[23] S. -H. Huang, C. -H. Liu, C. -M. Yang, *Green Chem.* **2014**, *16*, 2706.

[24] S. M. Raders, J. V. Kingston, J. G. Verkade, *J. Org. Chem.* **2010**, 75, 1744.

[25] The catalyst loading for limited examples such as 4-chloroanisole, 4-chloroacetophenone, 4-chlorobenzaldehyde, 4-chloronitrobenzene and 4-chlorobenzotrifluoride could be down to 0.1 mol%Pd with moderate to excellent yields at 90-130 ºC. However, 1.0-1.5 mol%Pd was still essential for heterocyclic and other aryl chlorides to obtain good yields.

[26] For microwave-accelerated Hiyama coupling of aryl chlorides, see: (a) M. L. Clarke, *Adv. Synth. Catal.* **2005**, *347*, 303; (b) E. Alacid, C. Nájera, *Adv. Synth. Catal.* **2006**, *348*, 945; (c) I. Peñafiel, I. M. Pastor, M. Yus, M. A. Esteruelas, M. Oliván, E. Oñate, *Eur. J. Org. Chem.* **2011**, 7174; (d) A. R. Hajipour, F. Rafiee, *Appl. Organometal. Chem.* **2012**, *26*, 51; (e) I. Peñafiel, I. M. pastor, M. Yus, *Eur. J. Org. Chem.* **2013**, 1479; (f) R. Martínez, I. M. Pastor, M. Yus, *Eur. J. Org. Chem.* **2014**, 872; (g) A. R. Hajipour, F. Rafiee, N. Najafi, *Appl. Organometal. Chem.* **2014**, *28*, 217.

[27] M. A. Surati, S. Jauhari, K. R. Desai, *Archives of Applied Science Research* **2012**, *4*, 645.

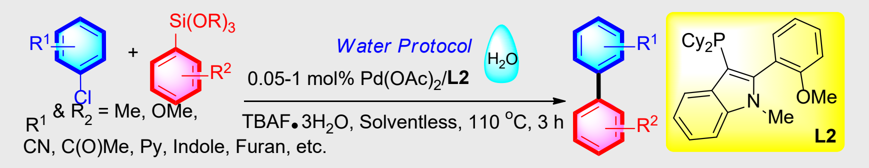
[28] Ligand cost and catalyst loading become the most important factors in production scale catalysis reactions, see: a) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599; b) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177.

[29] For reviews, see: a) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963; (b) S. M. Wong, O. Y. Yuen, P. Y. Choy, F. Y. Kwong, *Coord. Chem. Rev.* **2015**, *293-294*, 158.

[30] (a) H. W. Lee, F. L. Lam, C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *Angew. Chem. Int. Ed.* **2009**, *48*, 7436; (b) O. Y. Yuen, M. Charoensak, C. M. So, C. Kuhakarn, F. Y. Kwong, *Chem. Asian. J.* **2015**, *10*, 857; (c) O. Y. Yuen, S. M. Wong, K. F. Chan, C. M. So, F. Y. Kwong, *Synlett* **2014**, *46*, 2826.

[31] For the steric hindered aryl chlorides coupling, see: ref 19b. Only two di-*ortho*-substituted and two tri-*ortho*-substituted entries were reported.

[32] Using toluene as solvent can minimize the rapid decomposition of heteraryl(alkoxy)silanes during the Hiyama coupling reaction.



Pd/**L2** system is highly active towards the Hiyama coupling of aryl and heteroaryl chlorides. A wide range of aryl chlorides and aryl(alkoxy)silanes including sterically hindered and heterocyclic substrates can be cross-coupled successfully. The catalyst loading can be down to 0.05 mol% Pd for the first time. A new water addition protocol is developed which can dramatically improve the desired product yields.

On Ying Yuen, Chau Ming So, Ho Wing Man and Fuk Yee Kwong**

Page No. – Page No.

A General Palladium-Catalyzed Hiyama Cross-Coupling Reaction of Aryl and Heteroaryl Chlorides