Room temperature Stille cross-coupling reaction of unreactive aryl chlorides and heteroaryl chlorides†

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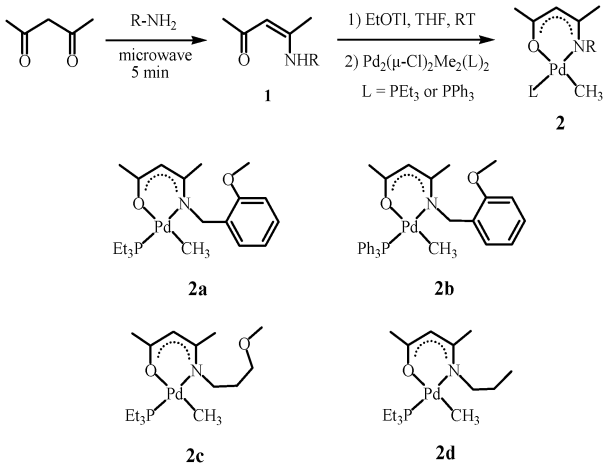
Received (in Cambridge, UK) 1st September 2009, Accepted 20th October 2009
First published as an Advance Article on the web 12th November 2009
DOI: 10.1039/b917711f

Phosphanyl-β-ketoiminate Pd complexes serve as highly effective catalysts in the Stille coupling reaction of aryl chlorides and heteroaryl chlorides with organostannanes at room temperature.

The palladium-catalyzed Stille reaction of organohalides with organostannanes represents one of the most important cross-couplings for the formation of carbon–carbon bonds.[1] This coupling reaction has been used in the synthesis of biaryl compounds that are important intermediates in natural products, polymers, and pharmaceuticals.[2] Much attention has been made to develop efficient catalysts for the Stille reaction. Aryl iodides and bromides have been widely employed as substrates in the coupling reactions.[3] From a practical point of view, the use of aryl chlorides is highly desirable because aryl chlorides are readily available and inexpensive. However, they are much more difficult to activate than aryl iodides and bromides.[4] Recently, attention has been directed towards coupling reactions employing aryl chlorides as one of the coupling partners.[5] Although significant progress has been achieved with highly active Pd catalysts in this area, the successful examples with aryl chlorides are rare.[6] Moreover, most of the reactions require a high loading of the catalyst and elevated reaction temperature. To the best of our knowledge, the coupling of aryl chlorides at room temperature has not been reported. The efficient coupling of unreactive aryl chlorides is still challenging.

Herein, we present phosphanyl-β-ketoiminate palladium complexes **2** as useful catalysts for room temperature Stille coupling of aryl and heteroaryl chlorides. β-Ketoimines are interesting compounds in coordination chemistry due to their resonance stability and easy modification to tailor the electronic and steric factors by changing the substituent on the N atom.[7] β-Ketoiminate complexes have been used as precursors for metalloorganic chemical vapor deposition[8] and as catalysts for olefin polymerization.[9] In contrast, they have received little attention in other catalytic processes. Recently, Pd catalyst **2b** was found to be highly active for the Suzuki–Miyaura coupling reaction in our laboratories.[10] Similar to the previous method, Pd complexes **2** were easily prepared from 2,4-pentanedione as shown in Scheme 1. Condensation of 2,4-pentanedione and primary amines under microwave heating gave

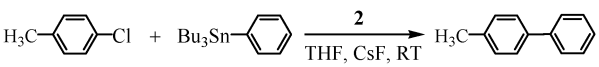


Scheme 1 Synthesis of phosphanyl-β-ketoiminate Pd complexes **2**.

β-ketoimines **1** in 5 min in quantitative yield. Deprotonation of **1** with EtOTl in THF, followed by treatment with $Pd_2(\mu\text{-}Cl)_2Me_2(PEt_3)_2$[11] which led to the formation of the corresponding Pd complexes, respectively.

With the Pd catalysts **2** in hand, we tested Stille coupling of 4-chlorotoluene with tributylphenylstanne as a model reaction (Table 1). The reaction was initially performed in the presence of 1.0 mol% of catalyst **2a** and 2.0 equiv. of CsF in THF. Both excellent conversion and good yield were obtained in 5 h (entry 1). High catalytic activity was still maintained in the presence of 0.5–0.1 mol% of **2a** (entries 2 and 3). Such activities obtained with this catalyst are remarkably superior

Table 1 Stille coupling of 4-chlorotoluene with tributylphenyltin[a]



Entry	**2** (mol%)	Solvent	Time/h	Yield (%)[b]
1	**2a** (1.0)	THF	5	97 (94)
2	**2a** (0.5)	THF	5	95 (93)
3	**2a** (0.1)	THF	8	90
4	**2a** (0.5)	Acetonitrile	5	87
5	**2a** (0.5)	Toluene	5	79
6	**2a** (0.5)	NMP	5	92
7	**2a** (0.5)	DME	5	93 (85)
8	**2a** (0.5)	1,4-Dioxane	5	88 (82)
9	**2b** (0.5)	THF	5	86
10	**2c** (0.5)	THF	5	87
11	**2d** (0.5)	THF	5	72

[a] Reaction conditions: 1.0 mmol of 4-chlorotoluene, 1.1 mmol of tributylphenylstanne, 2.0 mmol of CsF, and a catalytic amount of **2**. [b] GC yield was determined using *n*-dodecane as an internal standard. Isolated yield is given in parenthesis.

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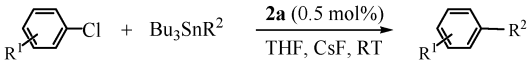
† Electronic supplementary information (ESI) available: General experimental procedures, synthesis and characterization details. See DOI: 10.1039/b917711f

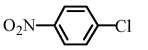
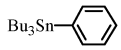
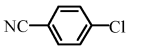
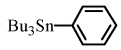
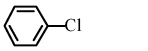
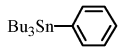
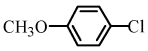
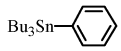
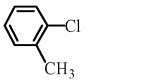
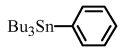
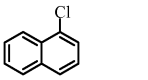
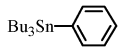
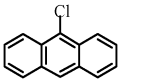
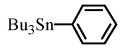
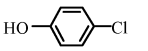
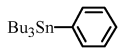
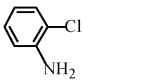
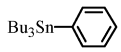
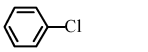
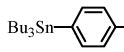
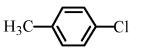
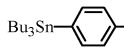
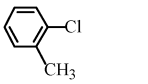
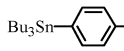
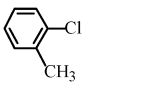
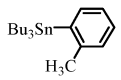
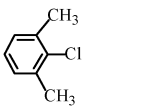
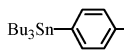
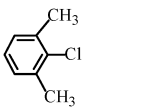
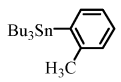
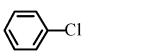
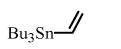
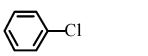
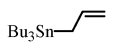
to any previously reported results on Stille coupling. It is noteworthy that the catalyst shows outstanding performance at room temperature. The solvent effect on the activity was examined with different solvents. When the reaction was conducted in acetonitrile, toluene, NMP, DME and 1,4-dioxane instead of THF, the catalytic activity was somewhat reduced under the same conditions (entries 4–8). Similar catalysts **2b–d** were also tested in the coupling of 4-chlorotoluene with tributylphenylstanne (entries 9–11). In this process, the use of **2b–d** led to a decrease in the rate. Consequently, Pd complex **2a** stood out as the most effective catalyst. It is interesting that **2a** exhibits a catalytic activity that is superior to **2b**. This could be explained by the fact that the triethylphosphanyl group has stronger σ-donating ability compared to that of the triphenylphosphanyl one.[12] In addition, the results reveal that the alkoxybenzyl moiety as a hemilabile arm has a beneficial effect in enhancing the reactivity of this Stille coupling. Less change of the activity was observed on exposure of the system to air and water in the reaction.

To further expand the scope of our catalytic system, we next investigated the coupling of substituted aryl chlorides with various organostannanes in the presence of 0.5 mol% of **2a** at room temperature (Table 2). Excellent catalytic activity was observed in the coupling of chlorobenzene, activated 1-chloro-4-nitrobenzene, and 4-chlorobenzonitrile (entries 1–3). Deactivated aryl chlorides possessing electron-donating substituents were found to furnish the corresponding biaryl products in high yields (entries 4 and 5). 1-Chloro-naphthalene and 9-chloroanthrancene coupled well with tributylphenyltin in high yields (entries 6 and 7). Importantly, the catalyst was found to be active for the coupling of unprotected 4-chlorophenol and 2-chloroaniline (entries 8 and 9). Furthermore, the catalyst system was also efficient for the couplings of aryl chlorides with electron-rich arylstannanes (entries 10–13). It is noteworthy that deactivated and sterically hindered 2-chloro-1,3-dimethylbenzene could be coupled in good yield, although elevated temperature and longer time were required (entries 14 and 15). One of the most useful applications of the Stille reaction is the coupling with vinyl- and allylstannanes. Similar results were also obtained in the reaction of chlorobenzene with tributylvinylstanne and allyltributylstanne at room temperature (entries 16 and 17). Regardless of the substituents, most of the coupling reactions were very clean and highly efficient under mild conditions. To our knowledge, our catalyst **2a** showed the highest catalytic activity reported for the Stille coupling of aryl chlorides.

Stille coupling of heteroaryl halides is of particular interest to the pharmaceutical industry since many biologically active compounds are accessed through this methodology.[13] Despite their importance, the coupling of heteroaryl chlorides remains a challenge, especially at low temperature. Development of effective catalysts are thus highly desired in this area. We therefore attempted the coupling of heteroaryl chlorides at room temperature (Table 3). Chloropyridines bearing a chloride in the 2-, 3-, or 4-position underwent the coupling with tributylphenylstanne in high yields (entries 1–3). A somewhat decreased yield was obtained for the reaction of 2-chloropyridine with tributyl(*p*-toly)stannane (entry 4). Satisfyingly, sterically hindered 2-chloro-3-methylpyridine could be coupled with a prolonged reaction time (entry 5). Other heteroaryl chlorides such as 4-chloropyrimidine and 2-chloroquinoline also gave promising results under the mild conditions (entries 6 and 7). Chlorothiophenes in the coupling reaction are challenging substrates due to the strong affinity of the sulfur for the Pd.[14] 2-Chlorothiophene or 3-chlorothiophene were converted to the corresponding products in satisfactory yields (entries 8 and 9).

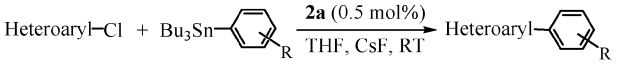
Table 2 Stille coupling of aryl chlorides with organostannanes[a]

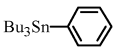
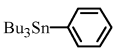
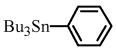
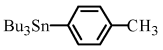
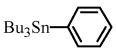
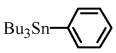
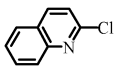
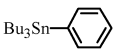
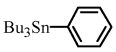
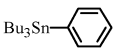
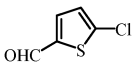
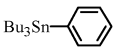
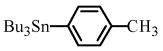


Entry	Aryl chloride	Organostannane	Time/h	Yield (%)[b]
1			3	96 (92)
2			3	94 (92)
3			4	93 (91)
4			5	92 (90)
5			6	95 (91)
6			5	93 (90)
7			5	90 (83)
8			5	87 (81)
9			6	94 (91)
10			5	92 (88)
11			6	92 (90)
12			8	90 (85)
13			8	83 (80)
14[c]			15	84 (81)
15[c]			15	75 (70)
16			6	84 (81)
17			6	91 (90)

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.1 mmol of organostannane, 2.0 mmol of CsF, and 0.5 mol% of **2a**. [b] GC yield was determined using *n*-dodecane as an internal standard. Isolated yield is given in parenthesis. [c] Reaction performed at 50 °C.

Table 3 Stille coupling of heteroaryl chlorides with organostannanes[a]



Entry	Heteroaryl chloride	Organostannane	Time/h	Yield (%)[b]
1			4	90 (86)
2			5	92 (89)
3			4	97 (91)
4			6	84 (80)
5			8	87 (81)
6			8	93 (90)
7			8	90 (85)
8			6	91 (88)
9			6	84 (80)
10			5	93 (91)
11			10	81 (79)

[a] Reaction conditions: 1.0 mmol of heteroaryl chloride, 1.1 mmol of organostannane, 2.0 mmol of CsF, and 0.5 mol% of **2a**. [b] GC yield was determined using *n*-dodecane as an internal standard. Isolated yield is given in parenthesis.

As expected, 2-chlorothiophene showed higher reactivity than deactivated 3-chlorothiophene. The important aldehyde functional group was tolerated under the present conditions (entry 10). 2-Chlorothiophene was also coupled with tributyl(*p*-toly)-stannane in good yield (entry 11). This is the first example of the Stille coupling of aryl and heteroaryl chlorides at room temperature as well as one of the most powerful catalysts.

In conclusion, we have achieved the general Stille reaction of aryl chlorides at room temperature. The catalyst **2a** is highly active with structurally and electronically diverse aryl and heteroaryl chlorides. We envisage the application of these catalysts could be extended to a wide range of catalytic processes.

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (2009–0072013).

Notes and references

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