

General and highly active catalyst for mono and double Hiyama coupling reactions of unreactive aryl chlorides in water†

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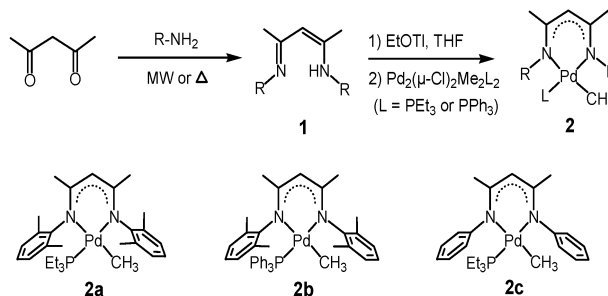
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A new β -diketiminatophosphane Pd catalyst was found to be highly effective in the mono and double Hiyama coupling reactions of unactivated aryl chlorides in water.

The palladium-catalyzed Hiyama coupling reaction of organic halides or sulfonates with organosilanes has become an interesting alternative to the Suzuki and Stille reactions.¹ Compared to organoborons (Suzuki–Miyaura reaction)² and organostannanes (Stille reaction),³ organosilanes are very attractive due to their low toxicity, easy handling and high stability. A variety of palladium catalysts have been extensively studied for the couplings.⁴ Aryl iodides and bromides have been predominantly used as the coupling partners of organosilanes. The use of aryl chlorides would be highly desirable, as they are cost effective and readily available. However, they are much more difficult to activate than any other coupling substrates. So far there are only few examples of the Hiyama coupling with aryl chlorides that proceed under microwave heating or high catalyst loading.⁵ Typically, the Hiyama reaction requires fluoride anion for the activation of the stable silicon–carbon bond and is conducted in organic solvents. Recently, it has been reported that aryl bromides can couple with arylsilanes under fluoride-free conditions.⁶ The mild Hiyama coupling of unreactive aryl chlorides is still challenging. Herein, we present new kinds of β -diketiminatophosphane palladium complexes **2** as highly active catalysts for the fluoride-free Hiyama coupling of unactivated aryl and heteroaryl chlorides in water. Transition metal β -diketimines have been used as precursors for metallo-organic chemical vapor deposition and catalysts for olefin polymerization.⁷ However, they have received little attention in other catalytic processes.

As shown in Scheme 1, the Pd complexes **2** were easily prepared in three steps. Condensation of acetylacetone and primary amines under mild microwave heating (85 °C) gave the desired β -diketimines **1** in high yields. Impressively, this reaction was complete within 30 min in the absence of solvents. Deprotonation of **1** with EtOTf or EtONa in THF, followed by treatment with Pd₂(μ -Cl)₂Me₂L₂ (L = PPh₃, PEt₃) led to the formation of the corresponding Pd complexes **2**.

We initially tested the activity of catalyst **2** for the Hiyama coupling of deactivated 4-chloroanisole with triethoxyphenylsilane under different conditions (Table 1). Water was used as



Scheme 1 Synthesis of β -diketiminatophosphane Pd complexes **2**.

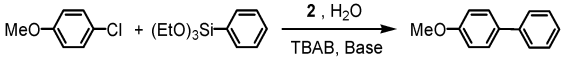
a reaction media for environmental benefit, even though the activity could be accelerated in organic solvents. The reaction took place smoothly in the presence of 1.0 mol% of **2a** and 4 equiv. of NaOH at 60 °C (entry 1). A phase transfer agent, tetrabutylammonium bromide (TBAB) was added to enhance the reactivity. As a consequence, this reaction proceeded very well with 0.5 mol% catalyst to afford the desired product in high yield in 8 h (entries 2 and 3). The catalyst loading could be reduced to 0.1 mol% without a significant impact on the activity, although longer reaction times were needed (entry 4). Besides, this catalyst showed satisfactory performance even at 40 °C (entry 5). The catalytic activity is significantly superior to any previously reported results on the Hiyama reaction. A similar activity was observed with the conventional TBAF activator (entry 6). In contrast, the use of KF, K₃PO₄, and Cs₂CO₃ instead of NaOH was ineffective for this reaction (entries 7–9). Catalysts **2b** and **2c** led to a decrease in the rate (entries 10 and 11). It is worth noting that **2a** exhibits higher catalytic efficiency than **2b** and **2c**. This could be explained by the fact which triethylphosphanyl group has stronger σ -donating ability compared to the triphenylphosphanyl one. The results indicate that electron-donating methyl groups on the phenyl rings also have a beneficial effect on enhancing the reactivity of this coupling.

The coupling reactions of various aryl chlorides with aryltriethoxysilanes were then performed under the optimized reaction conditions (Table 2). Deactivated aryl chlorides including 2-chloroanisole, 2-chlorotoluene and 3-chloroaniline were cross-coupled well with triethoxyphenylsilane or triethoxy-*o*-tolylsilane in the presence of 0.5 mol% of **2a** at 60 °C (**3a–h**). Sterically hindered 2-chloro-1,3-dimethylbenzene and 1-chloro-2,4,6-trimethylbenzene reacted uneventfully to afford the corresponding biaryls in good yields, although a higher temperature and longer time were required (**3i–l**). Regardless of the substituent, all of the coupling reactions were highly efficient and clean in water.

The Hiyama reaction of heteroaryl halides is of interest to the pharmaceutical industry since biologically active biaryls

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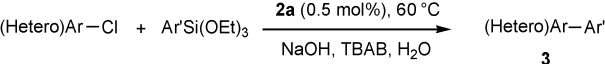
Table 1 Hiyama coupling of 4-chloroanisole with PhSi(OEt)₃^a


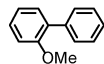
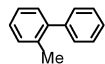
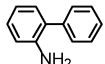
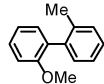
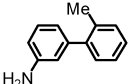
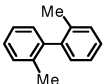
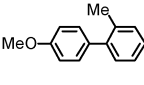
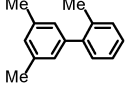
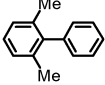
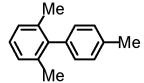
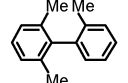
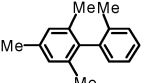
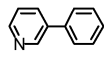
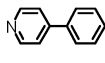
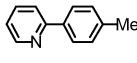
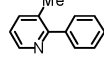
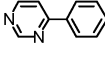
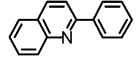
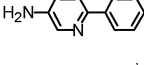
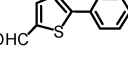
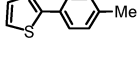
| Entry | 2 (mol%) | Base | T/°C | Time/h | Yield (%) ^b |
|----------------|-----------------|---------------------------------|------|--------|------------------------|
| 1 ^c | 2a (1.0) | NaOH | 80 | 15 | 86 |
| 2 ^d | 2a (0.5) | NaOH | 60 | 8 | 88 |
| 3 | 2a (0.5) | NaOH | 60 | 8 | 93 |
| 4 | 2a (0.1) | NaOH | 60 | 24 | 81 |
| 5 | 2a (0.5) | NaOH | 40 | 24 | 90 |
| 6 | 2a (0.5) | TBAF | 60 | 8 | 91 |
| 7 | 2a (0.5) | KF | 60 | 8 | 53 |
| 8 | 2a (0.5) | K ₃ PO ₄ | 60 | 8 | 27 |
| 9 | 2a (0.5) | Cs ₂ CO ₃ | 60 | 8 | 18 |
| 10 | 2b (0.5) | NaOH | 60 | 8 | 68 |
| 11 | 2c (0.5) | NaOH | 60 | 8 | 80 |

^a Reaction conditions: 4-chloroanisole (1.0 mmol), triethoxyphenylsilane (1.3 mmol), a catalytic amount of **2**, base (4.0 mmol), TBAB (0.5 mmol), H₂O (2 ml). ^b Isolated yields. ^c Without TBAB. ^d With 0.3 mmol of TBAB.

substituted with heteroatoms can be accessed through this methodology.⁸ We next extended the scope of this catalytic system to the coupling of heteroaryl chlorides. The chloropyridines underwent successful couplings to give the desired products in high yields (**3m–p**). The couplings of other heteroaryl chlorides such as 2-chloropyrimidine and 2-chloro-quinoline proceeded very well (**3q** and **3r**). Especially, very basic and electron-rich 5-amino-2-chloropyridine was found to be a suitable coupling partner (**3s**). Catalyst deactivation is often noticed with these types of substrates, because electron-rich pyridines bearing unprotected amino groups have a large potential to bind to the Pd center.⁹ Chlorothiophenes are also challenging substrates due to strong affinity of the sulfur to the Pd.^{9a,e} It is noteworthy, therefore, that the very meaningful activity of **2a** was observed for the coupling of chlorothiophenes (**3t** and **3u**). Interestingly, an aldehyde functional group was tolerated under the present reaction conditions. To the best of our knowledge, this is the first relatively general Hiyama coupling reaction of aryl and heteroaryl chlorides in water.

From the viewpoint of efficiency, a one-pot double Hiyama coupling reaction of inexpensive aryl dichlorides would be highly valuable for the synthesis of symmetrical terphenyls. We tested the activity of **2a** in the double coupling of aryl dichlorides (Table 3). To our great delight, 1,2-dichlorobenzene was dicoupled efficiently with different aryltriethoxysilanes in a single pot (**4a–f**). During the 1,2-diarylations, the unfavorable steric effects may be overcome by the active catalyst. Moreover, highly deactivated dichlorobenzene having a strong electron-donating hydroxy or amino group also showed good reactivity in the double coupling (**4g–i**). Overall, this system displays a high level of reactivity for the double coupling of diverse aryl dichlorides and allows for the preparation of a variety of terphenyls without difficulty. This is the first time that such one-pot double Hiyama reaction has been discovered and applied. Furthermore, the multiple coupling of 1,2,4,5-tetrachlorobenzene with triethoxy(4-methoxyphenyl)silane proceeded to give a two-dimensional oligoarylene in good yield (Scheme 2).

Table 2 Hiyama coupling of aryl chlorides with aryltriethoxysilanes^a


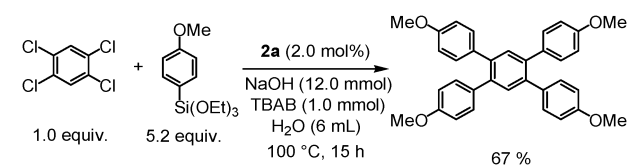
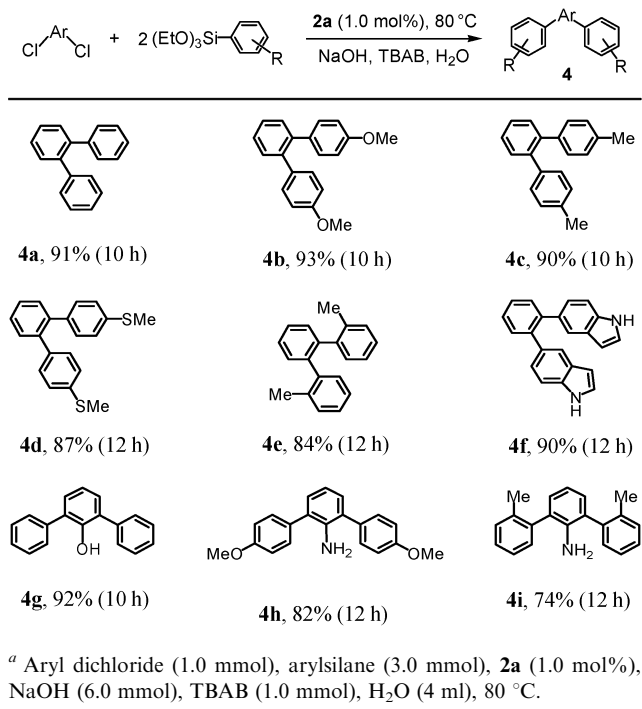
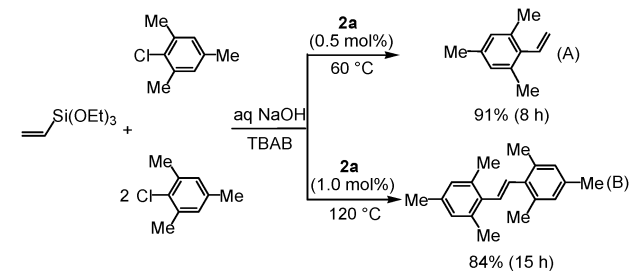
| | | |
|--|--|--|
|  3a , 90% (8 h) |  3b , 86% (8 h) |  3c , 84% (8 h) |
|  3d , 91% (8 h) |  3e , 91% (10 h) |  3f , 90% (10 h) |
|  3g , 92% (10 h) |  3h , 87% (10 h) |  3i , 87% (12 h) ^b |
|  3j , 81% (15 h) ^b |  3k , 68% (15 h) ^b |  3l , 74% (15 h) ^b |
|  3m , 92% (8 h) |  3n , 90% (6 h) |  3o , 84% (10 h) |
|  3p , 83% (10 h) |  3q , 88% (10 h) |  3r , 85% (10 h) |
|  3s , 89% (12 h) ^b |  3t , 92% (8 h) |  3u , 83% (12 h) |

^a Reaction conditions: aryl chloride (1.0 mmol), arylsilane (1.3 mmol), **2a** (0.5 mol%), NaOH (4.0 mmol), TBAB (0.5 mmol), H₂O (2 ml) and 60 °C. Yields are isolated yields. ^b Reaction was performed at 80 °C.

These results represent a significant advancement in the Hiyama coupling reaction.

As shown in Scheme 3, we have achieved the vinylation of 1-chloro-2,4,6-trimethylbenzene with triethoxyvinylsilane (method A). Besides, the catalyst promotes a one-pot Hiyama–Heck double coupling of highly hindered substrates (method B). This method opens the way to the synthesis of (*E*)-1,2-diarylethenes from the readily available aryl chlorides.

The Pd complex **2a** has a unique structure involving triethylphosphine and diketimine ligands on the palladium. Although the mechanism of the present coupling reactions is not obvious, the high catalytic activity is probably attributed to the enhanced nucleophilicity of the catalytically active Pd species which facilitate the cleavage of the inert Ar–Cl bond in the rate-limiting oxidation step.

Table 3 One-pot double Hiyama coupling of aryl dichlorides^a**Scheme 2** One-pot multiple Hiyama coupling of 1,2,4,5-tetrachlorobenzene.**Scheme 3** One-pot Hiyama–Heck double coupling.

In conclusion, we have demonstrated that the β -diketiminatophosphane Pd complex serves as a highly active catalyst for the Hiyama coupling reaction of a wide range of aryl chlorides with aryltriethoxysilanes in water. Notably, the efficient one-pot double Hiyama couplings of aryl dichlorides

were realized for the first time. We anticipate that the application of this catalyst can be extended to other catalytic processes.

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