ORGANIC
LETTERS

2011
Vol. 13, No. 20
5540–5543

# An Efficient and General Method for the Heck and Buchwald–Hartwig Coupling Reactions of Aryl Chlorides

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**Received August 22, 2011**

## ABSTRACT

**The $\beta$-diketiminatophosphane Pd complex acted as a powerful catalyst for the Heck coupling of aryl chlorides with alkenes. Various aryl and heteroaryl chlorides were coupled efficiently under relatively mild conditions. Furthermore, this catalytic system also proved to be highly active in the Buchwald–Hartwig coupling of deactivated and sterically hindered aryl chlorides at room temperature.**

Palladium-catalyzed coupling reactions have remarkably advanced organic synthesis over the past few decades.[1] Among them, the Heck coupling is one of the most valuable and familiar methods for the construction of carbon–carbon bonds.[2] A variety of palladium catalysts has been extensively studied for efficient and general Heck coupling.[3] It seems limited to aryl bromides and iodides as useful coupling substrates. The use of aryl chlorides would be more attractive for industrial applications because of their low cost and wide availability. However, deactivated aryl chlorides are reluctant to undergo catalytic reactions due to their strong C–Cl bonds. It has been recognized that palladium complexes derived from sterically bulky electron-rich phosphines,[4] *N*-heterocyclic carbenes,[5] and carbocyclic carbenes[6] facilitate the Heck reaction of aryl chlorides, a substrate class that had previously been inaccessible. Despite these significant advances, there are only a few successful examples in the coupling of deactivated aryl chlorides.[7] However, these methods require harsh reaction conditions such as high reaction temperatures,

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(1) For reviews, see: (a) deMeijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 2; Wiley-VCH: Weinheim, 2004. (b) Mitchell, T. N. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.

(2) For general reviews on the Heck reaction, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Trzecoak, A. M.; Ziółkowski, J. J. *Coord. Chem. Rev.* **2005**, *249*, 2308. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (d) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.

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(5) (a) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031. (b) Yen, S. K.; Koh, L. L.; Hahn, F. E.; Huynh, H. V.; Hor, T. S. A. *Organometallics* **2006**, *25*, 5105. (c) Lee, J.-Y.; Cheng, P.-Y.; Tsai, Y.-H.; Lin, G.-R.; Liu, S.-P.; Sie, M.-H.; Lee, H. M. *Organometallics* **2010**, *29*, 3901.

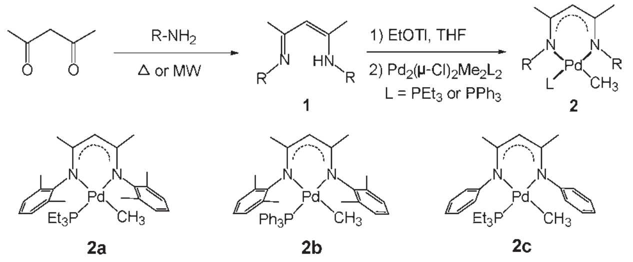
(6) (a) Herrmann, W. A.; Ofele, K.; Schneider, S. K.; Herdtweck, E.; Hoffmann, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3859. (b) Yao, Q.; Zabawa, M.; Woo, J.; Zheng, C. *J. Am. Chem. Soc.* **2007**, *129*, 3088.

(7) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Yi, C.; Hua, R. *Tetrahedron Lett.* **2006**, *47*, 2573. (c) Srinivas, P.; Likhar, P. R.; Maheswaran, H.; Sridhar, B.; Ravikumar, K.; Kantam, M. L. *Chem.—Eur. J.* **2009**, *15*, 1578. (d) Röhlich, C.; Köhler, K. *Chem.—Eur. J.* **2010**, *16*, 2363.

10.1021/ol202177k

high catalyst loadings, and long reaction times. Therefore, there is still significant room for improvement in catalyst performance. We recently reported $\beta$-diketiminatophosphine Pd catalysts **2** for the Suzuki coupling reactions of aryl chlorides.[8]

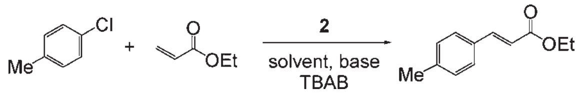
**Scheme 1.** Synthesis of $\beta$-Diketiminatophosphane Pd Catalyst **2**



As shown in Scheme 1, the Pd complexes **2** were readily prepared in three steps. They are air- and moisture-stable and can therefore be easily stored and handled. To evaluate the catalytic activity of **2** in the Heck coupling, we initially tested the reaction of deactivated 4-chlorotoluene with ethyl acrylate as a model system (Table 1). The reaction in aqueous DMF took place smoothly in the presence of 1.0 mol % **2a** and 2.0 equiv of $K_3PO_4$ at 85 °C (entry 1). A phase transfer agent, tetrabutylammonium bromide (TBAB), was added to enhance the reactivity. As a consequence, this reaction proceeded very well to afford the product in high yield (entry 2). A catalyst loading as low as 0.1 mol % was also shown to be effective, though a somewhat long reaction time was required (entry 3). It was possible to achieve this coupling even at 60 °C (entry 4). When the reaction was conducted in aqueous DMSO, DMA, NMP, and EtOH instead of aqueous DMF, the catalytic activity was reduced under the same conditions (entries 5–8). The use of $K_2CO_3$, $Na_2CO_3$, $Cs_2CO_3$, and KO$^t$Bu as a base gave inferior results under the same conditions (entries 9–12). Interestingly, precatalysts **2b** and **2c** led to significant drops in the rate (entries 13 and 14). This difference reflects the fact that a more electron-rich triethylphosphine ligand increases the electron density on the palladium center compared to triphenylphosphine,[9] accelerating the formation of the active Pd catalyst or the rate-limiting oxidative addition of the active Pd species to the substrate. It can also be supposed that the methyl groups have beneficial electronic and steric effects in enhancing the reactivity of this coupling. However, the diketiminate and the triethylphosphane both simultaneously would not coordinate on active palladium species through the catalytic cycle.

The Heck coupling of aryl chlorides with various alkenes was then performed with 1.0 mol % of **2a** at 85 °C (Table 2). As expected, activated aryl chlorides and chlorobenzene could be coupled efficiently with ethyl or butyl acrylate, affording the desired products in excellent yields (entries 1–4). More remarkable was that extremely electron-rich aryl chlorides, including 3-chloroanisole and 2-chlorotoluene, were coupled efficiently under relatively mild conditions (entries 5 and 6). This finding is of particular interest in view of the fact that Heck reactions of unactivated aryl chlorides using previously reported catalysts require high catalyst loadings, elevated reaction temperatures, and prolonged reaction times. Moreover, sterically hindered 1-chloro-2,6-dimethylbenzene was successfully coupled by increasing the temperature to 100 °C (entry 7).

**Table 1.** Heck Coupling of 4-Chlorotoluene with Ethyl Acrylate[a]



| entry | **2** (mol %) | solvent | base | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1[c] | **2a** (1.0) | DMF-$H_2O$ | $K_3PO_4$ | 12 | 78 |
| 2 | **2a** (1.0) | DMF-$H_2O$ | $K_3PO_4$ | 8 | 90 |
| 3[d] | **2a** (0.1) | DMF-$H_2O$ | $K_3PO_4$ | 18 | 70 |
| 4[e] | **2a** (2.0) | DMF-$H_2O$ | $K_3PO_4$ | 18 | 62 |
| 5 | **2a** (1.0) | DMSO-$H_2O$ | $K_3PO_4$ | 8 | 88 |
| 6 | **2a** (1.0) | DMA-$H_2O$ | $K_3PO_4$ | 8 | 82 |
| 7 | **2a** (1.0) | NMP-$H_2O$ | $K_3PO_4$ | 8 | 74 |
| 8 | **2a** (1.0) | EtOH-$H_2O$ | $K_3PO_4$ | 8 | 56 |
| 9 | **2a** (1.0) | DMF-$H_2O$ | $K_2CO_3$ | 8 | 81 |
| 10 | **2a** (1.0) | DMF-$H_2O$ | $Na_2CO_3$ | 8 | 73 |
| 11 | **2a** (1.0) | DMF-$H_2O$ | $Cs_2CO_3$ | 8 | 61 |
| 12 | **2a** (1.0) | DMF-$H_2O$ | KO$^t$Bu | 8 | 52 |
| 13 | **2b** (1.0) | DMF-$H_2O$ | $K_3PO_4$ | 8 | 52 |
| 14 | **2c** (1.0) | DMF-$H_2O$ | $K_3PO_4$ | 8 | 80 |

[a] General conditions: 4-chlorotoluene (1.0 mmol), ethyl acrylate (1.3 mmol), **2** (1.0 mol %), base (2.0 mmol), TBAB (0.5 mmol), 85 °C, and DMF–$H_2O$ (3 mL, 1:4). [b] Yields determined by GC/MS. [c] In the absence of TBAB. [d] At 120 °C. [e] At 60 °C.

High catalytic activity was observed in the arylation of styrene or methylstyrene (entries 8–10). Acrylamides were also suitable partners for the reaction of aryl chlorides (entries 11–13). Similarly, chloronaphthalene reacted efficiently with ethyl acrylate and styrene (entries 14 and 15). We were pleased to find that highly hindered 1-chloro-2,4,6-trimethylbenzene could smoothly couple with hindered 2,4,6-trimethylstyrene (entry 16). The catalyst system proved to be active with disubstituted olefins. Aryl chlorides were easily coupled with ethyl methacrylates (entries 17–19) and methacrylamides (entries 20–22) in high yields. Furthermore, catalyst **2a** worked well for the challenging coupling with ethyl cinnamate or *trans*-4-methoxystilbene without any problems (entries 23 and 24). During the arylations, the dicoupled adducts were scarcely formed. It is also noteworthy that excellent stereoselectivity ($E/Z > 25:1$) was observed in all cases. Overall, regardless of the substituents, most of the coupling reactions of aryl chlorides proceeded very selectively in acceptable yields.

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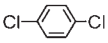
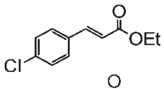
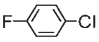
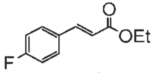
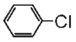
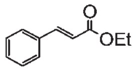
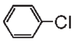
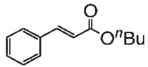
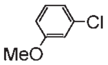
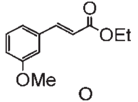
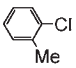
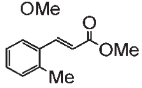
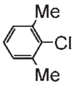
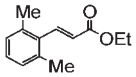
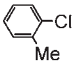
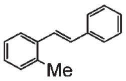
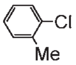
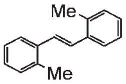
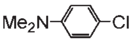
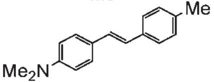
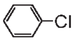
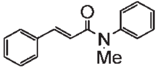
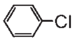
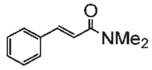
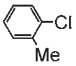
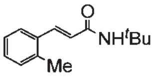
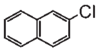
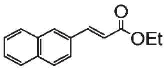
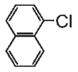
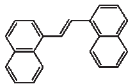
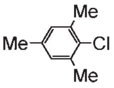
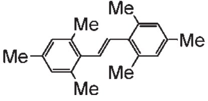
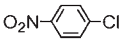
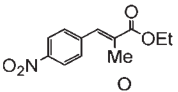
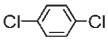
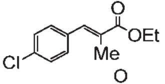
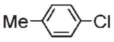
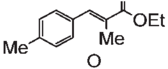
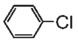
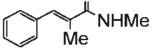
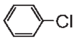
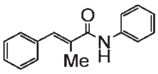
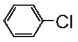
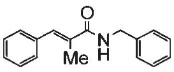
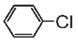
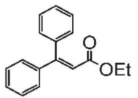
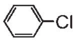
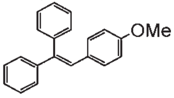
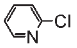
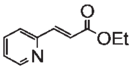
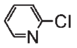
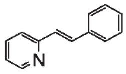
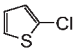
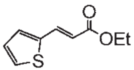
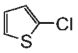
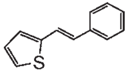
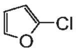
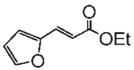
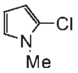
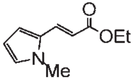
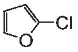
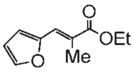
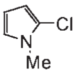
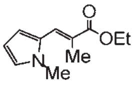
[8] (a) Lee, D.-H.; Jin, M.-J. *Org. Lett.* **2011**, *13*, 252. (b) Lee, D.-H.; Jung, J.-Y.; Jin, M.-J. *Chem Commun.* **2010**, *46*, 9046.

[9] Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555.

**Table 2.** Heck Coupling of Aryl(Heteroaryl) Chlorides with Alkenes[a]

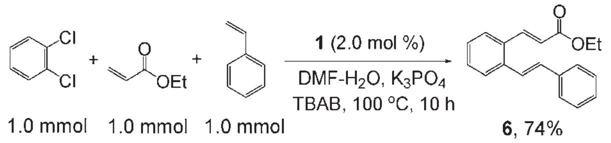
| entry | aryl chloride | product | | time (h) | yield (%)[b,c] |
|---|---|---|---|---|---|
| 1 |  |  | 3b | 5 | 89 |
| 2 |  |  | 3c | 5 | 87 |
| 3 |  |  | 3d | 8 | 94 |
| 4 |  |  | 3e | 8 | 93 |
| 5 |  |  | 3f | 10 | 85 |
| 6 |  |  | 3g | 12 | 81 |
| 7[d] |  |  | 3h | 12 | 80 |
| 8 |  |  | 3i | 12 | 83 |
| 9 |  |  | 3j | 15 | 82 |
| 10 |  |  | 3k | 12 | 81 |
| 11 |  |  | 3l | 10 | 91 |
| 12 |  |  | 3m | 10 | 80 |
| 13 |  |  | 3n | 12 | 74 |
| 14 |  |  | 3o | 8 | 87 |
| 15 |  |  | 3p | 10 | 86 |
| 16[d] |  |  | 3q | 24 | 81 |
| 17 |  |  | 4a | 4 | 91 |
| 18 |  |  | 4b | 6 | 82 |
| 19 |  |  | 4c | 8 | 83 |
| 20 |  |  | 4d | 8 | 83 |
| 21 |  |  | 4e | 8 | 88 |
| 22 |  |  | 4f | 8 | 85 |
| 23 |  |  | 4g | 6 | 82 |
| 24 |  |  | 4h | 6 | 78 |
| 25[e] |  |  | 5a | 8 | 80 |
| 26[e] |  |  | 5b | 8 | 85 |
| 27[e] |  |  | 5c | 10 | 73 |
| 28[e] |  |  | 5d | 10 | 82 |
| 29[e] |  |  | 5e | 10 | 87 |
| 30[e] |  |  | 5f | 8 | 84 |
| 31[e] |  |  | 5g | 12 | 79 |
| 32[e] |  |  | 5h | 10 | 84 |

[a] General conditions: aryl chloride (1.0 mmol), alkene (1.3 mmol), $K_3PO_4$ (2.0 mmol), DMF$-$$H_2O$ (3 mL, 1:4), TBAB (0.5 mmol), **2a** (1.0 mol %), and 85 °C . [b] Isolated yield. [c] (*E*)-Isomer selectivity is more than 96%. [d] At 120 °C. [e] At 100 °C.

Encouraged by these results, we next performed the Heck coupling of heteroaryl chlorides in the presence of 1.0 mol % **2a** at 100 °C. The reaction of 2-chloropyridine with ethyl acrylate or styrene furnished the desired product in 80−85% yields (entries 25 and 26). Even 2-chlorothiophene was a capable substrate for the coupling reaction by this catalyst (entries 27 and 28). Similar results were also obtained in the reactions of 2-chlorofuran and 2-chloro-*N*-methlypyrrole (entries 29 and 30). The catalyst system was found to be active with disubstituted olefins. The heteroaryl chlorides also underwent coupling with ethyl methacrylate to give exclusively (*E*)-heteroarylated alkenes in good yields (entries 31 and 32). In terms of scope and mildness, the results represent a significant advancement in the Heck coupling reaction.

From the viewpoint of efficiency, a one-pot double coupling of widely available aryl dichlorides would be very desirable for the synthesis of unsymmetrically divinylated arenes. We performed a one-pot double Heck reaction of *o*-dichlorobenzene with a mixture of ethyl acrylate and

**Scheme 2.** One-Pot Double Heck Coupling Reaction of *o*-Dichlorobenzene

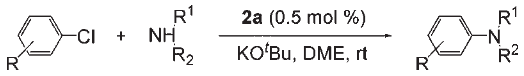


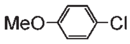
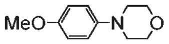
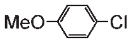
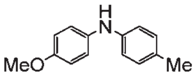
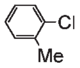
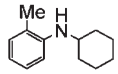
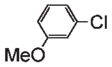
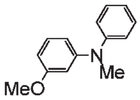
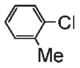
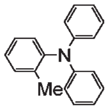
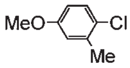
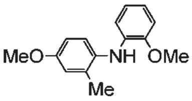
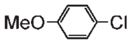
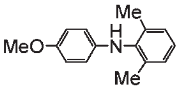
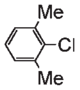
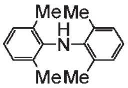
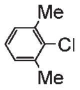
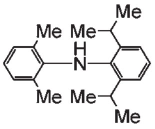
styrene (Scheme 2). To our great delight, this catalyst system allowed the hindered double coupling to afford the dicoupled product in good yield. The result demonstrates clearly the exceptional activity of **2a** in the reaction. This is the first example of a one-pot double Heck coupling of aryl dichlorides.

Recently, highly active Pd complexes have been developed for the Buchwald–Hartwig coupling reaction.[10] Limited examples have been reported for the coupling with aryl chlorides at room temperature.[11] Our catalytic system was further extended to this coupling of aryl chlorides with amines (Table 3). The reaction was carried out in the presence of only 0.5 mol % of **2a** and 2.0 equiv of KO$^t$Bu as a base. A wide array of amines were effectively coupled to electron-rich deactivated aryl chlorides, providing the corresponding products in high yields (entries 1–7). We were pleased to find that this catalyst system performed well for the coupling of highly hindered 1-chloro-2,6-dimethylbenzene with highly hindered 2,6-dimethylaniline or 2,6-diisopropylaniline even at room temperature (entries 8 and 9).

In conclusion, we have demonstrated that *β*-diketiminatophosphane Pd complex **2a** acts as a highly active and general catalyst for the Heck and Buchwald–Hartwig couplings of aryl chlorides. Structurally and electronically diverse aryl and heteroaryl chlorides were coupled very well under mild conditions. We envision the application of these catalysts could be extended to a wide range of catalytic processes.

**Table 3.** Buchwald–Hartwig Coupling of Aryl Chlorides with Amines[a]



| entry | aryl chloride | product | | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | **7a** | 5 | 92 |
| 2 |  |  | **7b** | 8 | 86 |
| 3 |  |  | **7c** | 10 | 82 |
| 4 |  |  | **7d** | 8 | 91 |
| 5 |  |  | **7e** | 10 | 84 |
| 6 |  |  | **7f** | 10 | 81 |
| 7 |  |  | **7g** | 12 | 87 |
| 8 |  |  | **7h** | 15 | 81 |
| 9 |  |  | **7i** | 15 | 73 |

[a] General conditions: aryl chloride (1.0 mmol), amine (1.2 mmol), KO$^t$Bu (2.0 mmol), DME (2 mL), **2a** (0.5 mol %), and rt. [b] Isolated yield.

**Acknowledgment.** This work was supported by a National Research Foundation of Korea Grant funded by the Korean Government (2011-0003169) and an Inha University Research Grant (Inha-2011).

**Supporting Information Available.** General experimental procedures, synthesis characterization details, and copies of $^1$H, $^{13}$C, and $^{31}$P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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