C–H Phosphonation

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Pyridine-Directed Palladium-Catalyzed Phosphonation of C(sp^2)–H Bonds**

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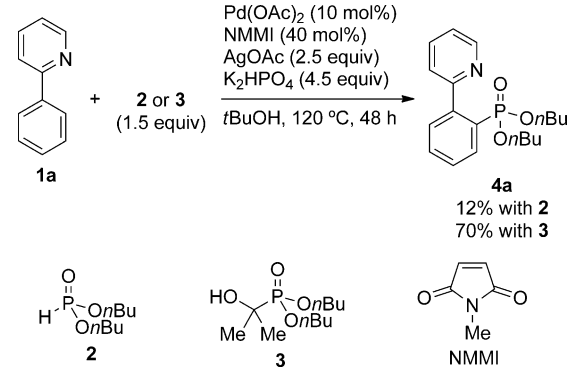
Direct functionalization of carbon–hydrogen (C–H) bonds provides a straightforward means of molecular transformation, and thus has been extensively investigated in the past two decades.[1,2] Although a wide variety of transition-metal-catalyzed reactions for functionalizing C–H bonds are currently available, examples of carbon–phosphorus bond formation are significantly limited, presumably owing to the strong coordinating character of phosphorus reagents.[3,4] Existence of an excess amount of coordinative phosphorus over metal in a reaction media would hamper a process to activate less coordinative C–H bonds. Very recently, Yu and co-workers reported a pyridine-directed C–H phosphonation reaction catalyzed by palladium, in which *H*-phosphonates were directly used.[5] Expeditious deactivation of the catalyst was avoided by adding *H*-phosphonate slowly with a syringe pump. Herein, we describe our independent study of the analogous phosphonation reaction of 2-arylpyridines; an α-hydroxyalkylphosphonate generates *H*-phosphonate upon treatment with a base,[6] which serves as the masked phosphonating reagent[7] to save the catalyst from deactivation. Furthermore, step-by-step stoichiometric reactions clearly delineate the mechanistic features.

2-Phenylpyridine (**1a**) was treated with commercially available *H*-phosphonate **2** in the presence of palladium(II) acetate (10 mol%), *N*-methylmaleimide (NMMI, 40 mol%), silver(I) acetate (2.5 equiv), and K_2HPO_4 (4.5 equiv) at 120°C for 48 h (Scheme 1). The *ortho* C–H bond was phosphonated to give product **4a** in only 12% yield. Next, *H*-phosphonate **2** was replaced by α-hydroxyalkylphosphonate **3**, which was easily prepared from **2** and acetone in one step according to the reported procedure.[8] To our surprise, **4a** was obtained in 70% yield, together with a small amount of diphosphonated product (6%). Thus, α-hydroxyphosphonate **3** proved to be superior to **2** as the phosphonating reagent, probably because it gradually generated *H*-phosphonate **2**.[9] Other reaction conditions were examined using **3** as the masked phosphonating reagent. The use of oxidants such as $Cu(OAc)_2$ and Ag_2CO_3 were less effective. Stronger bases such as K_3PO_4 gave inferior results. Reaction in other solvents, including toluene, dioxane, and acetonitrile, also gave the phosphonated products, but the yields were lower.[10]



Scheme 1. C–H phosphonation of **1a**.

Variously substituted 2-arylpyridines were phosphonated using phosphonating reagent **3** (Scheme 2). The substrate 2-(*o*-tolyl)pyridine (**1b**) allowed the isolation of monophosphonated product **4b** in 66% yield. The *m*-tolyl group was site-selectively phosphonated on the sterically less-hindered side to afford **4c** in 82% yield. Methoxy (**4d**) and chloro (**4e**) groups were tolerated on the phenyl ring. Benzothiophene (**4f**) and alkene (**4g**) were also phosphonated in good yields. Not only pyridine, but also quinoline (**4i**) and pyrimidine (**4k**) were suitable as directing groups.

A proposed mechanism is shown in Scheme 3. Initially, cyclopalladation of **1a** with palladium(II) acetate gives palladacycle **A**.[11] The α-hydroxyalkylphosphonate **3** gradually releases acetone under the reaction conditions to generate a small amount of *H*-phosphonate **2**, which reacts with palladacycle **A** to displace the acetate ligand on palladium. The resulting palladium(II) complex **B** undergoes reductive elimination with the aid of NMMI (see below). Arylphosphonate **4a** is thus produced, along with a palladium(0) species, which is oxidized back into palladium(II) by silver(I) acetate.[12]

We carried out some stoichiometric reactions to corroborate the steps constituting the proposed catalytic cycle. Complex **A** was prepared by treatment of **1a** with palladium(II) acetate (1.0 equiv) in MeOH and isolated in a form of the dimer **5**.[11] Next, a dioxane solution containing complex **5**, phosphonate **3** (2.0 equiv), and K_2HPO_4 (2.2 equiv) was heated at 120°C (Scheme 4). The acetate ligand of **A** was displaced with a phosphonate ligand to afford complex **B**, which was isolated in the dimeric form **6**. Single crystals of **6**,

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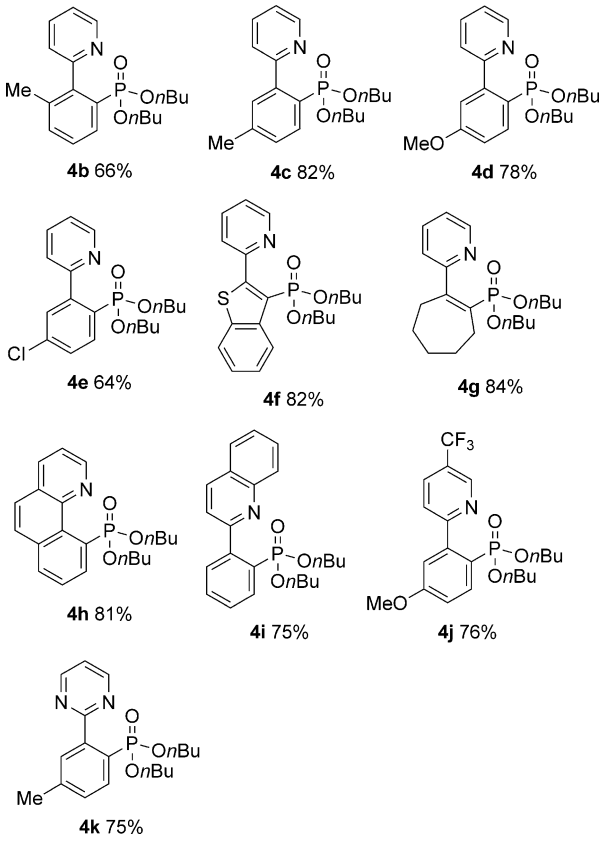
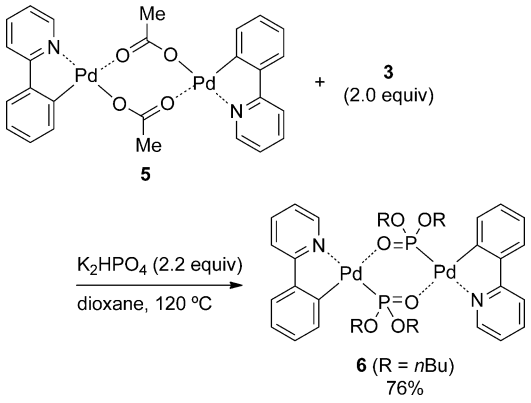


Scheme 2. Palladium-catalyzed phosphonation of **1**. Reaction conditions: **1** (0.20 mmol), **3** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), NMMI (40 mol%), AgOAc (2.5 equiv), K_2HPO_4 (4.5 equiv), *t*BuOH (1.5 mL), 120°C, 48 h. Yields shown are of isolated products.



Scheme 4. Ligand exchange.

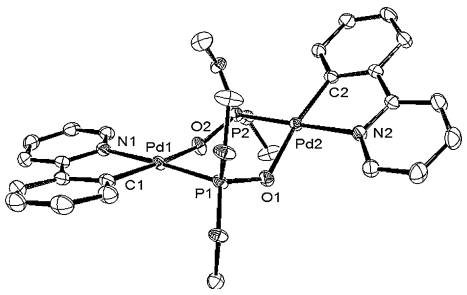
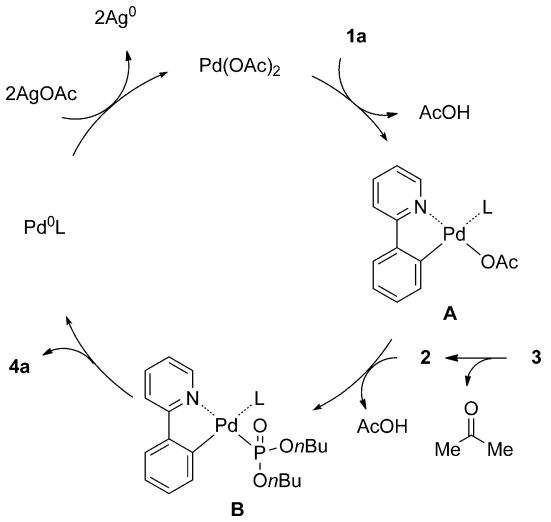


Figure 1. Crystal structure of **6**. Thermal ellipsoids set at 50%. Hydrogen atoms and three carbon atoms of the *n*-butyl groups are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–P(1) 2.227(1), Pd(1)–C(1) 1.998(2), C(1)-Pd(1)-P(1) 96.00(6), O(2)-Pd(1)-P(1)-O(1) 3.54, Pd(1)-P(1)-O(1)-Pd(2) 55.85.

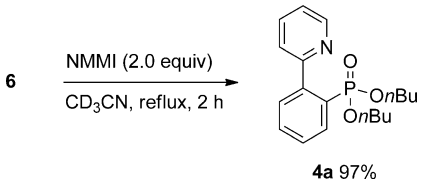
suitable for X-ray crystallographic analysis, were obtained by recrystallization from an ether/hexane solution. The six-membered dinuclear palladacycle is bridged with the phosphonate ligand through its oxygen and phosphorus atoms (Figure 1).[13] It assumes a boat-like form; the O(2), Pd(1), P(1), O(1) atoms are located on a plane [O(2)-Pd(1)-P(1)-O(1) = 3.54°] and the torsion angle of the Pd(1)-P(1)-O(1)-Pd(2) was 55.85°. The phosphorus atom was located *cis* to the phenyl carbon, for which stronger *trans* influence was expected than for the pyridine nitrogen.[14]

The following reductive elimination step was also examined.[15] No reaction was observed upon heating a CD_3CN solution of **6** at reflux. On the contrary, reductive elimination occurred when heated at reflux (bath temperature: 120°C) in the presence of NMMI (2.0 equiv), resulting in the isolation of arylphosphonate **4a** in 97% yield (Scheme 5). The use of benzoquinone and maleic anhydride instead of NMMI was equally effective in inducing reductive elimination. Triphenylphosphine less effectively accelerated reductive elimination (60% after 48 h). These results suggested that electron-accepting ligands are required to facilitate reductive elimination of arylphosphonate **4a** from palladacycle **B**.[16]

The reductive elimination giving **4a** from **6** was accompanied by the formation of black precipitates, presumably an aggregate of palladium(0). The formation of a palladium(0)



Scheme 3. Proposed mechanism.



Scheme 5. Reductive elimination.

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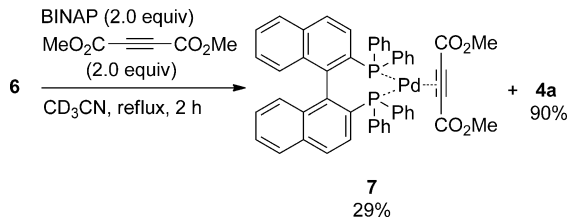

Scheme 6. Detection of palladium(0) complex **7**.

species was confirmed by the reaction in the presence of acetylene dicarboxylate and BINAP (Scheme 6). The palladium(0) complex **7**[17] was isolated in 29% yield together with **4a** (90%). Thus, the mechanistic pathway of the phosphonation of 2-phenylpyridine, proceeding through cyclometallation, ligand exchange, and reductive elimination, was followed step-by-step on the basis of stoichiometric reactions, thus providing an experimental basis for the postulated mechanism depicted in Scheme 3.

In conclusion, we have reported that the palladium-catalyzed phosphonation of a $C(sp^2)$–H bond occurs by the use of a pyridyl group as the directing group. This work demonstrates the potential of α-hydroxyalkylphosphonates as masked phosphonating agents to save the catalyst from deactivation.

Experimental Section

Palladium-catalyzed phosphonation of **1a**: $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *N*-methylmaleimide (8.8 mg, 0.08 mmol), AgOAc (84 mg, 0.5 mmol), and K_2HPO_4 (156 mg, 0.9 mmol). *t*BuOH (1.5 mL), α-hydroxyalkylphosphonate **3** (75 mg, 0.30 mmol), and 2-phenylpyridine **1a** (31 mg, 0.20 mmol) were added by syringe into a 25 mL screw-capped tube equipped with a magnetic stir bar. The reaction tube was capped in the air and heated at 120°C for 48 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of celite, using ethyl acetate as the eluent. The solvent was removed under reduced pressure and the residue was then purified by chromatography to afford **4a** (48.6 mg, 70%).

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[14] The crystal structure of palladacycle **5**[2e] indicates stronger *trans* influence of the phenyl carbon than the pyridine nitrogen; the Pd–O bond *trans* to carbon (avg. 2.158 Å) is longer than that trans to pyridine (avg. 2.061 Å).

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