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Communication

Pyridine-directed palladium-catalyzed electrochemical phosphonation of C(sp_2)–H bond

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ABSTRACT

A new electrocatalytic method for the phosphonation of 2-phenylpyridine was developed. The joint electrochemical oxidation of a mixture of palladium acetate, 2-phenylpyridine, and H-diethylphosphonate affords the *ortho* C–H phosphonation product. The electrocatalytic synthesis proceeds under mild conditions (room temperature) at potentials that clearly generate high oxidation state of palladium complexes without any specially added oxidizing agents. An intermediate dipalladium [(PhPy)Pd$(EtO)_2$P(O)]$_2$ complex was isolated, the structure was confirmed by X-ray analysis. Cyclic voltammetry studies reveal the [(PhPy)Pd$(EtO)_2$P(O)]$_2$ complex to be oxidized at more positive potentials compared with the acetate palladacycle [(PhPy)Pd(OAc)]$_2$. Preparative oxidation of the diethylphosphonate palladium complex affords 2-phenylpyridine C–H bond phosphonation product.

Introduction

Direct functionalizations of C–H bonds provide the most effective way of organic molecules transformations, that attracts great attention to this field. Transition metal-catalyzed carbon–phosphorus bond formation represents an important method for obtaining diverse organophosphorus compounds. Many such methods have found widespread applications in organic synthesis [1–6], medicinal chemistry [7–9] and materials science [10–12]. Although a wide range of such reactions has been developed including those catalyzed by transition metals, there are just few examples of the direct phosphonation of carbon–hydrogen bonds, apparently due to the strong coordination character of phosphorus reagents [13–21], and first catalytic methods, being nowadays especially important due to the requirements of “green chemistry”, were developed quite recently, and there are just few good examples of them [22,23].

Not so long ago, Yu [22] and Murakami [23] reported examples of catalytic ligand-directed C–H phosphonation of aromatic substrates in 12–66% yields, and showed that H-dialkylphosphonates and α-hydroxyphosphonate were phosphorylating reagents. However, these reactions required high temperatures, an excess of oxidants (expensive silver salts), bases, and additives to promote a reductive elimination step. One of the main problems arising in the chemistry of Pd(II)/Pd(IV) compounds consists in the fact that the applied co-oxidizing agents are either expensive (Ag or other metals salts are frequently used) or hardly separating from the reaction mixture (organic oxidizers with high molecular weight). At that, all of them are insufficiently selective. There is no phenylpyridine phosphonation method in one step at room temperature with high yield. The development of new C–H phosphonation methods remain an important ongoing field of research.

An electrochemical approach has several advantages over conventional organic syntheses. Typically, electrochemical syntheses can be carried out under mild conditions and without any oxidizing/reducing agents that often complicate product separations, resulting in higher operational costs. The ability to dial in redox potentials in electrochemical methods might also be important for controlling $Pd^{II}/Pd^{III}/Pd^{IV}$ redox shuttles in more

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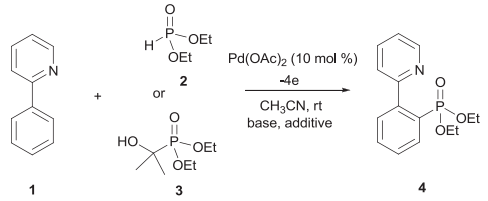
sophisticated palladium catalysis. We recently exploited the advantages of electrochemical syntheses in developing electrochemical and ligand-directed C–H acetoxylation and perfluoroalkylation reactions [24–26]. The aim of the present study is to develop electrocatalytic phosphonations and to obtain mechanistic insights into the reaction that may aid in future reaction optimizations.

Results and discussion

Our initial investigations focused on achieving the electrooxidative Pd-catalyzed phosphonation of 2-phenylpyridine **1**. Both *H*-phosphonate HP(O) $(OEt)_2$ **2** and α-hydroxyphosphonate **3** were examined as phosphorylating agents. For optimization of the reaction conditions, a set of electrolysis was carried out with various bases and additives, such as N-methylmaleimide (NMMI), 1,4-benzoquinone (BQ), and 2,2′-bipyridine (bpy), which are known reagents for facilitating reductive elimination reactions. The electrolysis results are presented in Table 1.

The joint electrochemical oxidation of **1** and **2** (1.0:1.1 ratio) in the presence of palladium acetate $Pd(OAc)_2$ (10 mol %) afforded the desired *ortho* C–H substitution product **4** in moderate or good yields in the presence of a base, even in the absence of any other additives. The target product **4** was formed under electrochemical oxidation at room or enhanced temperature (80°C) even in the absence of NMMI, BQ or bpy (entries 1, 4, 6, 10, 14). The base was found to be the only critical additional component for the C–P coupling, as the reaction does not occur without it (entries 11, 15).

Table 1
Optimization of reaction conditions.[a]



Entry	Phosphonating agent	Base	Additive	4[b], [%]
1	2	Na_2HPO_4	–	20
2	2	Na_2HPO_4	BQ (2 equiv.)	43
3[c]	2	Na_2HPO_4	NMMI (4 equiv.)	42
4	2	$(EtO)_2PONa$	–	48
5	2	$(EtO)_2PONa$	BQ (2 equiv.)	45
6[d]	2	$(EtO)_2PONa$	–	15
7	2	NaOAc	BQ (2 equiv.)	78
8[e]	2	Lutidine	bpy(1 equiv.)	72
9	2	Lutidine	bpy(1 equiv.)	48
10[f]	2	Lutidine	–	12
11	2	–	bpy(1 equiv.)	n.r.
12	3	Lutidine	bpy(1 equiv.)	n.r.
13	3	Na_2HPO_4	BQ (2 equiv.)	n.r.
14	3	NaOH	–	30
15[g]	2	–	–	n.r.

[a] Unless otherwise noted, reactions were carried out with **1** (7.0 mmol), $Pd(OAc)_2$ (0.7 mmol, 10 mol%) and a corresponding base (4 equiv.) in CH_3CN (25 mL) at room temperature. Reagents **2** or **3** (7.7 mmol) were dissolved in 5 ml acetonitrile and added dropwise to the electrolysis mixture (Q = 4*F*).
[b] Isolated yields.
[c] The reaction was carried out at 80 °C.
[d] AmOH was the solvent, the reaction was carried out at 80 °C.
[e] An equimolar amount of $Pd(OAc)_2$ was used.
[f] The reaction was carried out under refluxing conditions.
[g] [PhPyEt][EtOP(O)(H)O] was the main product.

However the best result was obtained in a reaction with BQ and sodium acetate or lutidine as a base (entry 7). Replacing *H*-diethylphosphonate **2** with α-hydroxyethylphosphonate **3** does not produce the desired product **4** both at room temperature and at refluxing within the electrolysis (entries 12, 13). However, addition of a strong base NaOH to the reaction mixture resulted in a moderate yield of **4** (entry 14). In the absence of electricity no phosphonation of 2-phenylpyridine was observed.

To get insight into the process, the putative palladacycle intermediate $[(PhPy)Pd(EtO)_2P(O)]_2$ (**5**), similar to the $[(PhPy)Pd(BuO)_2P(O)]_2$ complex described by Murakami and co-workers [23], was synthesized, and its reactivity and electrochemical properties were explored. The stirring of the dimeric acetate palladacycle **6** [27] and **2** (1:2.4 ratio) for an hour at room temperature affords the desired complex **5** as a white precipitate in 90% yield (Scheme 1). This procedure, involving a ligand exchange reaction, is more straightforward than the one described for the synthesis of $[(PhPy)Pd(BuO)_2P(O)]_2$ complex, which involved reaction of α-hydroxybutylphosphonate and complex **6** at 120 °C with excess of K_2HPO_4 [23].

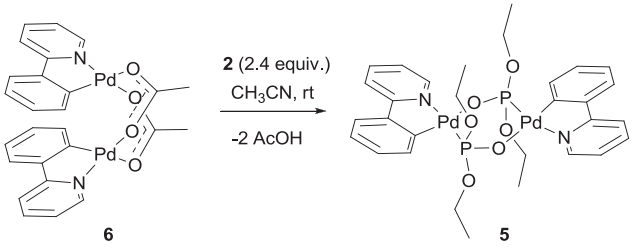
An X-Ray single diffraction study revealed that the structure of complex **5** (Fig. 1) with diethylphosphonate ligands differs from the previously described dipalladium complex with dibutylphosphonate ligands. The central metal containing cycle of complex **5** is nearly planar with the dihedral angle between two phenylpyridine fragments being equal 19°. The complex with dibutylphosphonate ligands [23] has a folded metal containing cycle with a considerably distorted tricyclic moiety.

A cyclic voltammetry study (Fig. 2) reveals the complex **5** to be oxidized in two irreversible steps at more positive potentials (1.18 and 1.69 V) compared with the acetate complex **6** (0.62 and 1.60 V).

The Murakami reaction [23] was carried out with complex **5** (Scheme 2A). The procedure involved refluxing the reagents in CD_3CN in the presence of NMMI (2 equiv.) for 4 h at 120 °C. In this way, only half of the initial complex was transformed into the product **4**. By comparison, the isolated complex **5** was electrochemically oxidized (Scheme 2B) in CH_3CN at room temperature under air-free conditions at the first oxidation peak potential, the complete conversion giving a single product **4** (^{31}P NMR spectrum revealed the only signal with δ_P 18 ppm) which was isolated in 90% yield. Thus, the electrochemical oxidation more effectively promoted elimination of product from intermediate complex **5**.

Importantly, the phosphonation reaction described in Scheme 2 did not require any additional reagents (such as NMMI, BQ, etc.) to promote the reductive elimination of product. We speculate that the AgOAc oxidant in the reported [22, 23] chemical C–H phosphonations does not transform the Pd(0) species into Pd(II) in the catalytic cycle, but rather oxidizes the intermediate phosphonate palladacycle to release the desired product of C–H substitution.

Comparing the oxidation potentials of the intermediate complexes **5** and **6** of catalytic C-H phosphonation, it is found, that the phosphoric complex **5** is more difficult to oxidize. Under the reaction conditions (chemical or electrochemical) the acetate complex



Scheme 1. Synthesis of $[(PhPy)Pd(EtO)_2P(O)]_2$ palladacycle.

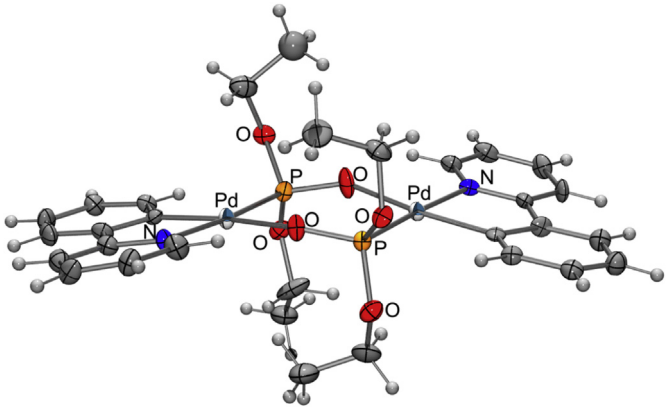


Fig. 1. ORTEP drawing of **5**.

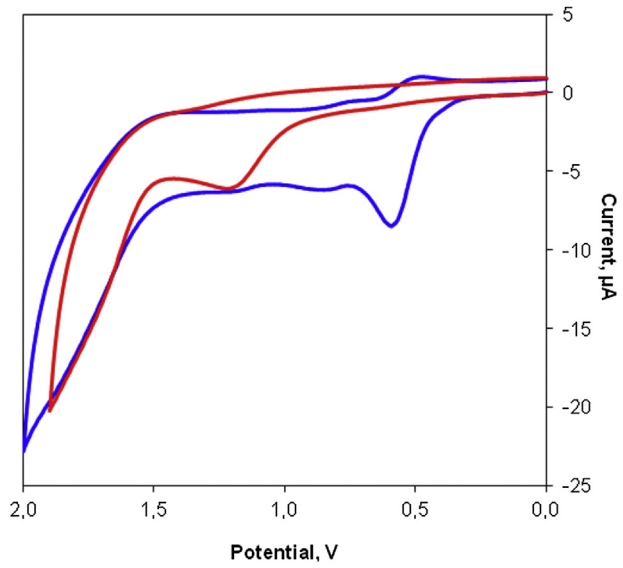
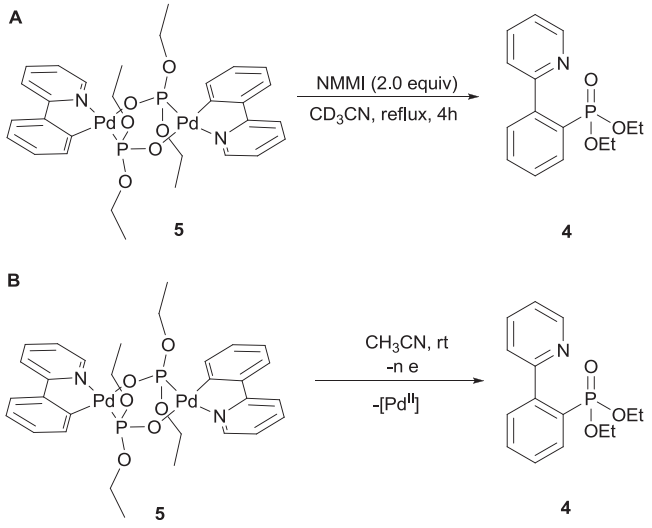
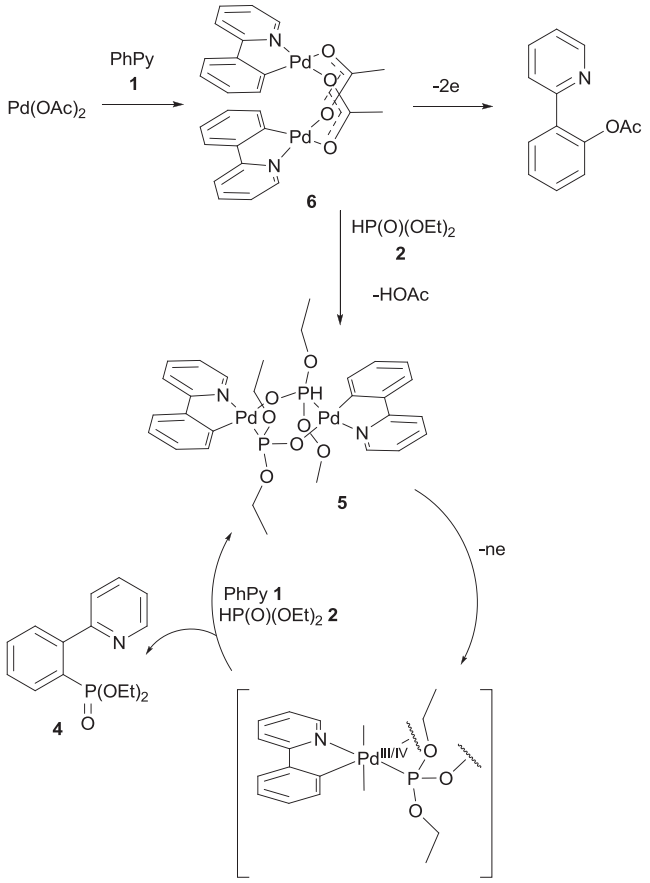


Fig. 2. Cyclic voltammograms of $[(PhPy)Pd(\mu\text{-}OAc)]_2$ **2** (blue) and $[(PhPy)Pd(EtO)_2P(O)]_2$ **3** (red) vs. $Ag/AgNO_3$ in CH_3CN. Scan rate 100 mV/s. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Scheme 2. Convertion of **5** into **4** in Murakami's reaction and under electrochemical oxidation.



Scheme 3. Proposed catalytic cycle.

6 oxidation is faster. An undesirable off–cycle reaction can afford an *ortho*-acetoxylated byproduct. To get the target product **4** in good yields it is necessary either to maintain high concentrations of **5** through protonation of **6** with $HP(O)(OEt)_2$ or to provide conditions for preferred oxidation of complex **5**. With regard to providing conditions for the preferred oxidation of complex **5**, additives that are known to facilitate reductive elimination (BQ, NMMI) might also facilitate the reaction by modulating the oxidation potentials of **5** and **6**. The greatest success, as it is seen from Table 1, was achieved in the reaction with BQ. A proposed scheme for catalytic C–H phosphorylation can be presented in Scheme 3 (see attached scheme that I included in e-mail).

In conclusion, a new electrocatalytic approach to C–H phosphonation of 2-phenylpyridine was developed. An intermediate binuclear phosphonate palladacycle $[(PhPy)Pd(EtO)_2P(O)]_2$ (**5**) was isolated, and its structure was confirmed by X-ray single crystal analysis. Electrochemical oxidation of **5** can quantitatively eliminate phosphonation product, suggesting **5** is a key intermediate of the catalytic cycle in the selective formation of the desired C–H phosphonation product in good yield.

Acknowledgements

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Appendix A. Supplementary material

CCDC 1031219 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from

The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2015.03.001.

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