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Pd(II)-Catalyzed C(sp^2)−H Hydroxylation with $R_2(O)P$-Coordinating Group

Hong-Yu Zhang,[†] Hong-Ming Yi,[†] Gang-Wei Wang,[†] Bin Yang,[†] and Shang-Dong Yang*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, P. R. China

yangshd@lzu.edu.cn

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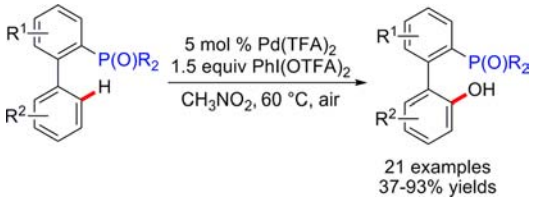
ABSTRACT



A novel $R_2(O)P$-directed Pd(II)-catalyzed C−H hydroxylation to synthesize various substituted 2′-phosphorylbiphenyl-2-ol compounds is described. Notably, the reaction operates under mild conditions and shows good functional group tolerance, high selectivity, and yield.

Phenols bearing functional groups are of great practical value to chemists.[1] Phenols functioning as important building blocks are commonly found subunits in a number of biomolecules and drug molecules.[2] Furthermore, phenols or protected phenols with activating groups such as triflate, nonaflate, mesylate, sulfamate, tosylate, carbonate, and even methyl are attractive for cross-coupling reactions to introduce other functional groups.[3] Various binaphthol derivatives represent ligands or catalysts of particular importance that have seen extensive application in asymmetric catalysis.[4] Recently, as one of several new tactics in practical chemistry, the hydroxyl group has also been used as a directing group to guide the transition-metal-catalyzed ortho-position C−H bond activation.[5] Therefore, the development of a novel and simple method of catalytically hydroxylating arenes to produce phenols represents a considerable task and an important challenge. Indeed, C−H activation is the most straightforward and efficient method for constructing C−O bonds. The method has garnered significant attention over the past several years.[6,7] Versatile ruthenium and palladium catalysts have proved too powerful for hydroxylation as a result of

[†] Lanzhou University.
[‡] Lanzhou Institute of Chemical Physics.

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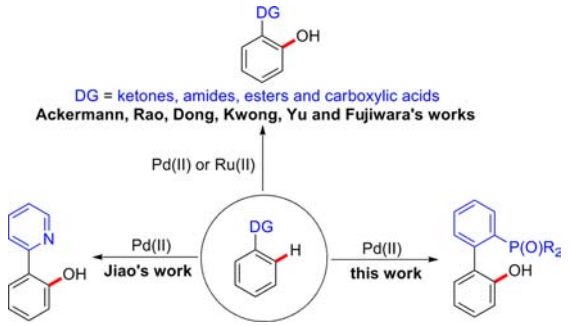
weakly coordinating directing groups (such as ketones, amides, esters, and carboxylic acids).[8,9] Although these present studies exhibit notable advantages, they demonstrate a particular simularity: the directing groups and the new C−OH bond are located on the same aromatic ring. Very recently, Jiao and co-workers have established a method to synthesize various substituted 2-(pyrdin-2-yl)-phenols from 2-phenylpyridines.[10] Herein, we report the first $R_2(O)P$-directed Pd(II)-catalyzed C−H hydroxylation to synthesize various substituted 2′-phosphorylbiphenyl-2-ol compounds (Scheme 1). In contrast to the former directing groups (pyridine, ketone, amides, esters, and carboxylic acids), using the $R_2(O)P$ as a directing group has some unique features: first, organophosphorus molecules play an important part in life sciences and pharmaceuticals.[11] Moreover, the $R_2(O)P$ group not only acts as the directing group but after reduction is also retained as a chelating group in the desired 2′-phosphorylbiphenyl-2-ol products, which are one type of very important *P*,*O*-ligands. In particular, all procedures are easy to handle, the reaction condition is simple to assemble, and the reaction temperature requires 60 °C, which is easily aquired. Furthermore, this reaction provides a pathway for the preparation of substituted 2′-phosphorylbiphenyl-2-ol compounds that is far more concise and effective than previous reports.[12]

Scheme 1. Different Directing Groups Guiding Transition-Metal-Catalyzed C−H Hydroxylation



In the past year, various research groups have reported a series of transition-metal-catalyzed phosphorous acid or phosphate ester directed C−H functionalization.[13] Apart from these developments, our group explored $R_2(O)P$-directed Pd(II)-catalyzed C−H activation that may undergo a seven-membered cyclopalladium pretransition state, followed by successful C−H olefination to synthesize alkene−phosphine compounds.[14] Inspired by this research, we first used 2-(diisopropylphosphoryl)biphenyl (**1a**) as the model substrate in the presence of $Pd(OAc)_2$ (10 mol %) as catalyst in 1,2-dichloroethane (DCE) at 80 °C. The reaction was attempted with various oxidants; ultimately, the desired product **2a** was obtained in 64% yield by using of [bis(trifluoroacetoxy)iodobenzene] ($PhI(OTFA)_2$) (Table 1, entries 1−4). The results were encouraging. We further optimized the reaction conditions. Although the substrate had completely converted in the former reaction condition, we observed a lower yield of **2a**. Considering the decomposition of the substrate or the target molecule, we screened the reaction temperatures and found that depression of the reaction temperature was in fact beneficial for the reaction, and the best yield of **2a** improved to 69% at 60 °C (Table 1, entries 5−6). The loading of the screening showed that the most appropriate oxidant was 1.5 equiv of $PhI(OTFA)_2$, and product **2a** was generated in 73% yield (Table 1, entries 7 and 8). Further screening of different palladium catalysts showed that

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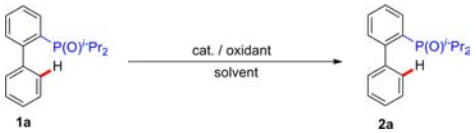
Table 1. Reaction Conditions Screening[a]



1a 2a

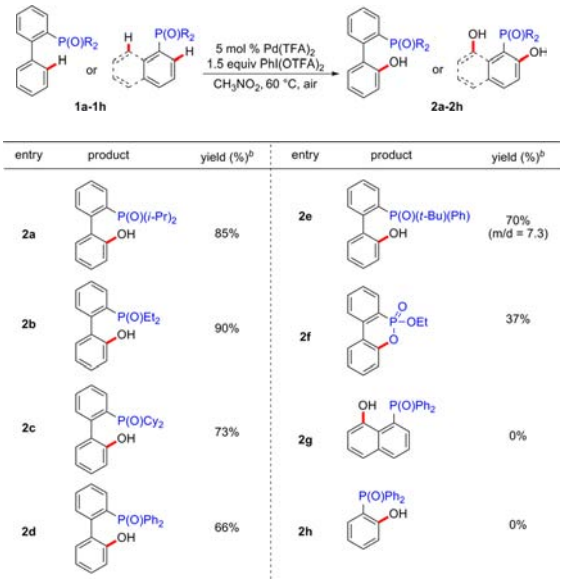
entry	cat. (mol %)	oxidant (equiv)	temp (°C)	solvent	yield[b] (%)
1	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.0)	80	$ClCH_2CH_2Cl$	n.r.
2	$Pd(OAc)_2$(10)	1,4-benzoquinone (2.0)	80	$ClCH_2CH_2Cl$	n.r.
3	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	80	$ClCH_2CH_2CI$	50[c]
4	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$ (2.0)	80	$ClCH_2CH_2Cl$	64
5	$Pd(OAc)_2$(10)	$PhI(OTFA)_2$ (2.0)	60	$ClCH_2CH_2Cl$	69
6	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$ (2.0)	50	$ClCH_2CH_2Cl$	56
7	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	$ClCH_2CH_2Cl$	73
8	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$(1.2)	60	$ClCH_2CH_2Cl$	66
9	$Pd(TFA)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	$ClCH_2CH_2Cl$	81
10	$Pd(NO_3)_2 \cdot 2H_2O$(10)	$PhI(OTFA)_2$(1.5)	60	$ClCH_2CH_2Cl$	75
11	$Pd(CH_3CN)_2(BF_4)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	$ClCH_2CH_2Cl$	58
12	$PdCI_2$(10)	$PhI(OTFA)_2$(1.5)	60	$ClCH_2CH_2Cl$	n.r.
13	$Pd(TFA)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	CH_3NO_2	86
14	$Pd(TFA)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	CF_3COOH	73
15	$Pd(TFA)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	$CHCl_3$	59
16	$Pd(TFA)_2$ (10)	$PhI(OTFA)_2$(1.5)	60	CH_3COOH	53[c]
17	$Pd(TFA)_2$ (5)	$PhI(OTFA)_2$(1.5)	60	CH_3NO_2	85
18	$Pd(TFA)_2$ (3)	$PhI(OTFA)_2$(1.5)	60	CH_3NO_2	79
19	$Pd(TFA)_2$ (0)	$PhI(OTFA)_2$(1.5)	60	CH_3NO_2	n.r.

[a] All reactions were carried out in the presence of 0.3 mmol of **1a** in 2.0 mL of different solvents under air atmosphere. [b] Yield of isolated product. [c] 2′-(Diisopropylphosphoryl)biphenyl-2-yl acetate (**2aa**) was obtained.

$Pd(TFA)_2$ was a better catalyst than $Pd(OAc)_2$, and the yield of **2a** was significantly improved to 81% (Table 1, entry 9). Other Pd(II) catalysts, such as $Pd(NO_3)_2 \cdot 2H_2O$ and $Pd(CH_3CN)_2(BF_4)_2$, could prompt the reaction but were not as efficient as $Pd(TFA)_2$ (Table 1, entries 10 and 11). This was not the case for $PdCl_2$ (Table 1, entry 12), however, likely because chloride ion exchange with trifluoroacetate anions is difficult due to the stable Pd−Cl bonds.[10] Investigation of different solvents indicated that CH_3NO_2 was the best solvent suitable for this reaction, and the product (**2a**) was afforded in 86% yield (Table 1, entries 13−16). Not surprisingly, when $PhI(OAc)_2$ was used as oxidant or CH_3COOH as solvent, the acetoxylated product (**2aa**) was obtained, respectively (Table 1, entries 3 and 16). Finally, when we evaluated the loading of $Pd(TFA)_2$, 5 mol % of $Pd(TFA)_2$ was found to be sufficient to prompt the reaction without an apparent decrease in reaction yield (Table 1, entries 17 and 18). The control experiment thus illustrates that $Pd(TFA)_2$ is indispensable to the reaction (Table 1, entry 19). As our overall experimental results demonstrate, the optimal reaction conditions involve the use of 5 mol % of $Pd(TFA)_2$ and 1.5 equiv of $PhI(OTFA)_2$ as the oxidant in 2.0 mL of CH_3NO_2 for 0.3 mmol of **1a** at 60 °C under an air atmosphere (Table 1, entry 17).

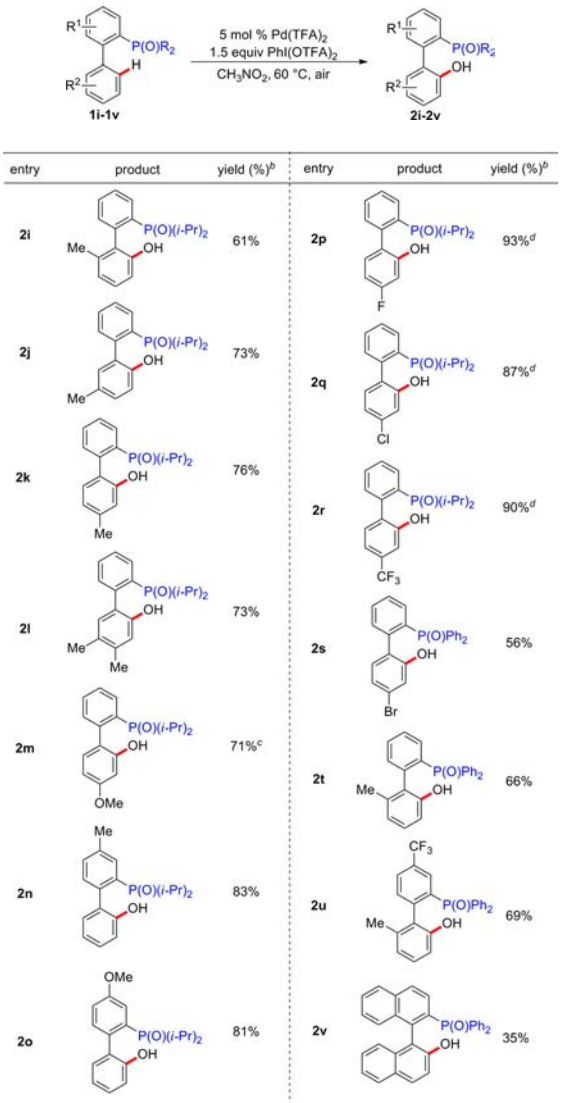
With the optimized conditions in hand, we first examined the scope of substrates by varying the phosphate directing group (Table 2). In addition to 2-(diisopropylphosphoryl)biphenyl, 2-(diethylphosphoryl)biphenyl and 2-(dicyclohexylphosphoryl)biphenyl are also compatible with this reaction, affording their corresponding products in good yields (Table 2, **2b**,**c**). After electron effects are taken into consideration, 2-(diphenylphosphoryl)biphenyl is converted into the desired product of **2d** in a 66% lower yield. Furthermore, 2-(*tert*-butyl(phenyl)phosphoryl)-biphenyl worked smoothly in the reaction; **2e** was obtained

Table 2. Evaluation of Different Directing Groups[a]



[a] All reactions were carried out under the optimal conditions reported in the text. [b] Isolated yields.

Table 3. Scope of Different Substituted Substrate[a]

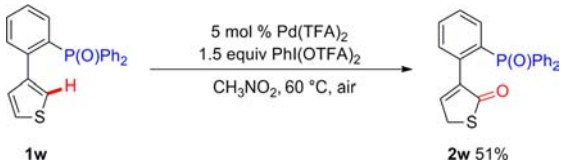


[a] All reactions were carried out under optimal conditions as reported in the text. [b] Isolated yield. [c] 1.4 equiv of $PhI(OTFA)_2$ was used; [d] 10 mol % of $Pd(TFA)_2$ was used at 80 °C.

in the mixture of monohydroxylation and dihydroxylation in a ratio of 7.3:1. Interestingly, when diethylbiphenyl-2-ylphosphonate was used, only phosphoryl lactone **2f** was obtained in 37% yield. Certain phosphates, such as triphenylphosphine oxide and α-diethyl naphthalenyl phosphonate, did not work at all. These results imply, however, that the seven-membered cyclopalladium pretransition state may play a critical role in this transformation.

We next investigated the scope of different substituted 2-(diisopropylphosphoryl)biphenyl derivatives (Table 3). When 2-(diisopropylphosphoryl)-2′-methylbiphenyl was tested, the product of **2i** was obtained in a 61% lower yield as a result of steric hindrance. If the methyl and dimethyl group lie on the meta- or para-position of phenyl phosphate, the corresponding products can be afforded in good yields (**2j**–**l**). Interestingly, if the methoxyl group lies on the para-position of phenylphosphate, the loading of oxidant

Scheme 2. Pd(II)-Catalyzed C−H Oxidation and Rearrangement



must be decreased to 1.4 equiv; otherwise, a lower yield of **2m** will be observed. However, when the methoxyl group lies on the meta-position of the diisopropylphosphoryl group, the reaction progressed very well and the products **2n** and **2o** were obtained in 83% and 81% yields, respectively. We found the electronic effect to be very distinct in these transformations. When electron-withdrawing groups such as F, Cl, and CF_3 lay on the 4′-position, the corresponding products were afforded in excellent yields in the presence of 10 mol % of $Pd(TFA)_2$ at 80 °C (**2p**–**r**). On the other hand, when 2-diphenylphosphino oxide was selected as the directing group, relatively lower yields were observed no matter the electron-donating substituent group or electron-withdrawing group on both aromatic rings (**2s**–**v**).

While in the process of investigating substrates, we discovered that 3-(2-(diphenylphosphoryl)phenyl)thiophene was also compatible with C−H hydroxylation, but an unexpected rearrangement product, 3-(2-(diphenylphosphoryl)-phenyl)thiophen-2(5*H*)-one, was obtained in 51% yield (Scheme 2). As a useful skeleton in the field of medicinal chemistry,[15] this product will provide an efficient and novel pathway for the synthesis of thiophen-2(5*H*)-one derivatives.

In summary, we have developed a novel $R_2(O)P$-directed Pd(II)-catalyzed C−H hydroxylation, which is an effective method to synthesize various substituted 2′-phosphorylbiphenyl-2-ol compounds. Notably, this reaction is easy to handle, can operate under mild conditions, and displays good functional group tolerance. Given its wide utilization in coordination chemistry and the potential value for medicinal chemistry and biochemistry, we anticipate the process described in this paper to be important in practical applications. Further studies into the mechanism and further application of this method into the synthesis of axially chiral phosphines are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.