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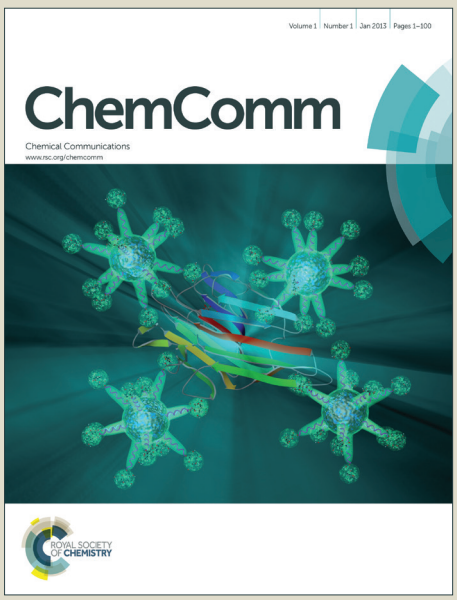

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Palladium-Catalyzed $R_2(O)P$ Directed C(sp^2)-H Acetoxylation

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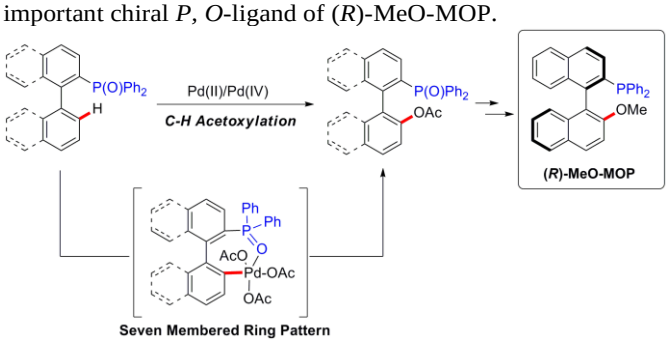
A novel and efficient Pd-catalyzed C-H acetoxylation is described. The approach uses $R_2(O)P$ as directing group to synthesize various substituted 2'-phosphorylbiphenyl-2-OAc compounds. Notably, the reaction exhibits smooth operation under mild conditions and shows good functional group tolerance. Products are obtained with high selectivity and yields.

The development of a catalytic method for the transition-metal-catalyzed oxidation of unactivated C-H bonds represents a considerable research goal to the chemical industry and to synthetic chemists more generally.[1,2] In the past few years, the method of C-H oxidation by transition-metal-catalyzed *ortho*-functional groups has been applied as a powerful weapon to transform arenes and alkanes directly into new products in catalytic reactions.[3] Among the efficient directing groups that have been developed, nitrogen-containing directing groups such as amides,[4] imines,[5] and *N*-heterocycles,[6] carboxyl and hydroxyl directing groups[7,8] contribute to C-H acetoxylation. Furthermore, this strategy has also been applied to the synthesis of several natural products and to the functionalization of other steroids.[9] Despite good progress so far, the application of innovative directing groups with improved directing qualities, such as tunable functional groups with increased levels of reactivity and selectivity, remains an important challenge. Very recently, we selected diphenylphosphine oxide [$Ph_2(O)P$] as a directing group and have succeeded in applying it to the palladium-catalyzed C-H olefination, hydroxylation, and arylation.[10] In our transformations, the $R_2(O)P$ not only acts as a directing group, but also as a useful composition of product. In contrast to the phosphonic acid or phosphate ester directed C-H functionalizations,[11] our reactions featured an unique seven-membered cyclopalladium intermediate. We all know that organphosphorus compounds are most famous for their unusual roles in various aspects of organic synthetic areas. For example, these compounds will act as ligands in asymmetric catalysis and in transition-metal-catalyzed cross-coupling reactions.[12] On the basis of these comprehensions, we wished to use the $R_2(O)P$ as directing group in order to achieve the C-H acetoxylation and afford various substituted 2'-phosphorylbiphenyl-2-OAc compounds, which serve as a kind of *P, O*-ligands precursor. Our endeavors have resulted in the development of a new method of $Pd(OAc)_2$-catalyzed $R_2(O)P$-directed C-H acetoxylation (Scheme 1). Furthermore, the $R_2(O)P$ and OAc groups can be transferred into trivalent phosphorus and –OH easily, which lead to the synthesis of the important chiral *P, O*-ligand of (*R*)-MeO-MOP.

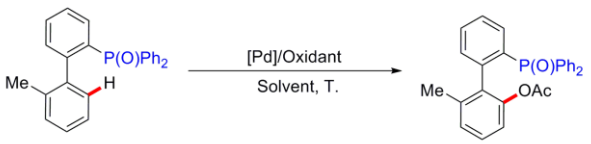


Scheme 1. P=O directed C-H acetoxylation through seven–membered cyclopalladium intermediate

Our first study in this area focused on the Pd (Ⅱ)-catalyzed 2-diphenylphosphino-2'-methylbiphenyl (**1a**). A possible acetate source, (Diacetoxyiodo)- benzene was selected as the oxidant at the same time. We discovered that the combination of 1.0 equiv of substrate 2-diphenylphosphino-2'-methylbiphenyl (**1a**) with 10 mol% $Pd(OAc)_2$ and $PhI(OAc)_2$ (2.0 equiv) in $ClCH_2CH_2Cl$ (DCE) at 90 ℃ for 16 h produced the desired product **2a** in 44% isolated yield (Table 1, entry 1). Encouraged by this result, we attempted to further optimize the reaction conditions. Different solvents were tested first, and the expected product (2**a**) was obtained in a low yield when

CH_3NO_2 was used as solvent (Table 1, entry 2). When the reaction proceeded in CF_3CH_2OH (TFE), the product was obtained in 52% yield (Table 1, entry 5). Similar result was obtained when HOAc was used as the solvent, giving 50% yield (Table 1, entry 6). We hypothesized that Ac_2O would acetylate the Pd–OR complex and regenerate $Pd(OAc)_2$, thereby complying with this reaction catalytic. Different mixed solvents were also tested, and the desired products were obtained in a moderate yield when HOAc + Ac_2O and CF_3CH_2OH + Ac_2O were used as solvents (Table 1, entries 7-8). Further studies indicated that higher reaction temperature gave a better result in 59% yield (Table 1, entry 9). Significant improvement was achieved when 3.0 equiv of $PhI(OAc)_2$ was used at 100 °C for 7 h, giving an 86% yield of the product (Table 1, entry 10). These results seemed to suggest that higher temperatures and more $PhI(OAc)_2$ were advantageous to both the rate of the reaction and its yield. Furthermore, conducting the reaction at 110 °C showed similar results (Table 1, entry 11). Further increasing temperatures provided moderate yield, however, indicating that perhaps the starting materials or the product decomposed at a high temperature (Table 1, entries 12-13). Some other Pd (Ⅱ) catalysts, such as $PdCl_2$, $PdBr_2$, $Pd(TFA)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2(CH_3CN_3)_2$, could also produce good results (Table 1, entries 14-18). No product was detected in the absence of $Pd(OAc)_2$.

Table 1. Screening for Reaction Conditions [a,b]



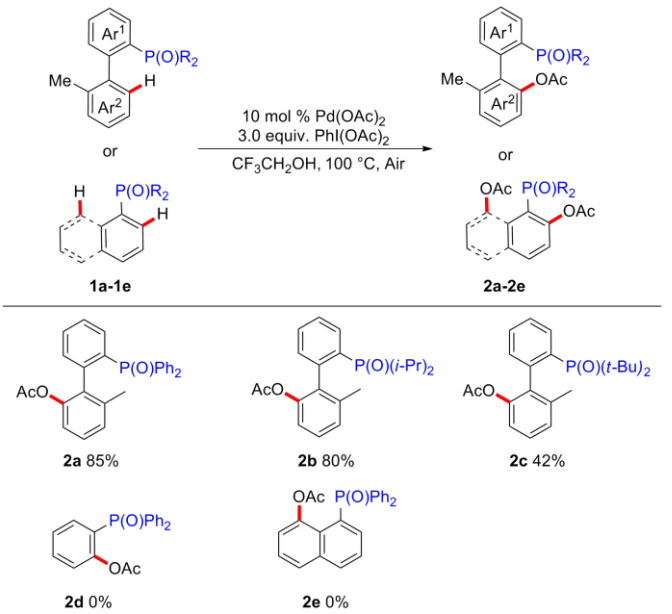
1a **2a**

Entry	[Pd] (10 mol%)	$PhI(OAc)_2$	Solvent	T (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	2.0 equiv	$ClCH_2CH_2Cl$	90	44
2	$Pd(OAc)_2$	2.0 equiv	CH_3NO_2	90	25
3	$Pd(OAc)_2$	2.0 equiv	CH_3CN	90	0
4	$Pd(OAc)_2$	2.0 equiv	THF	90	0
5	$Pd(OAc)_2$	2.0 equiv	CF_3CH_2OH	90	52
6	$Pd(OAc)_2$	2.0 equiv	HOAc	90	50
7	$Pd(OAc)_2$	2.0 equiv	HOAc	90	40[c]
8	$Pd(OAc)_2$	2.0 equiv	CF_3CH_2OH	90	51[d]
9	$Pd(OAc)_2$	2.0 equiv	CF_3CH_2OH	100	59
10	$Pd(OAc)_2$	3.0 equiv	CF_3CH_2OH	100	86
11	$Pd(OAc)_2$	3.0 equiv	CF_3CH_2OH	110	87
12	$Pd(OAc)_2$	3.0 equiv	CF_3CH_2OH	120	63
13	$Pd(OAc)_2$	3.0 equiv	CF_3CH_2OH	130	61
14	$PdCl_2$	3.0 equiv	CF_3CH_2OH	100	67
15	$PdBr_2$	3.0 equiv	CF_3CH_2OH	100	66
16	$Pd(TFA)_2$	3.0 equiv	CF_3CH_2OH	100	76
17	$PdCl_2(PPh_3)_2$	3.0 equiv	CF_3CH_2OH	100	80
18	$PdCl_2(CH_3CN)_2$	3.0 equiv	CF_3CH_2OH	100	75

[a] All reactions were carried out in the presence of 0.2 mmol of **1a** in 2.0 mL different solvents under air atmosphere. [b] Yield of isolated product. [c] HOAc (1 mL) +Ac_2O (1 mL). [d] CF_3CH_2OH (1 mL) + Ac_2O (1 mL).

With optimized conditions (Table 1, entry 10) in hand, we examined the scope of substrates first by varying the phosphate directing group (Table 2). Beside the diphenylphosphine oxide, diisopropylphosphine oxide and di-*tert*-butylphosphine oxide were also involved in the smooth direction of the C-H acetoxylation. Corresponding products were afforded in 80% and 42% yields, respectively (Table 2, **2b** and **2c**). However, other phosphorus compounds, such as triphenylphosphine oxide and α-diethyl naphthalenyl phosphine oxides, were entirely inactive, implying first that this palladium-catalyzed $R_2(O)P$ directed C-H acetoxylation undergoes a seven-member cyclopalladium intermediate in the procedure, and second that palladium should be coordinated with the oxygen of the $R_2(O)P$ group.

Table 2. Evaluation of Different Directing Groups[a,b]

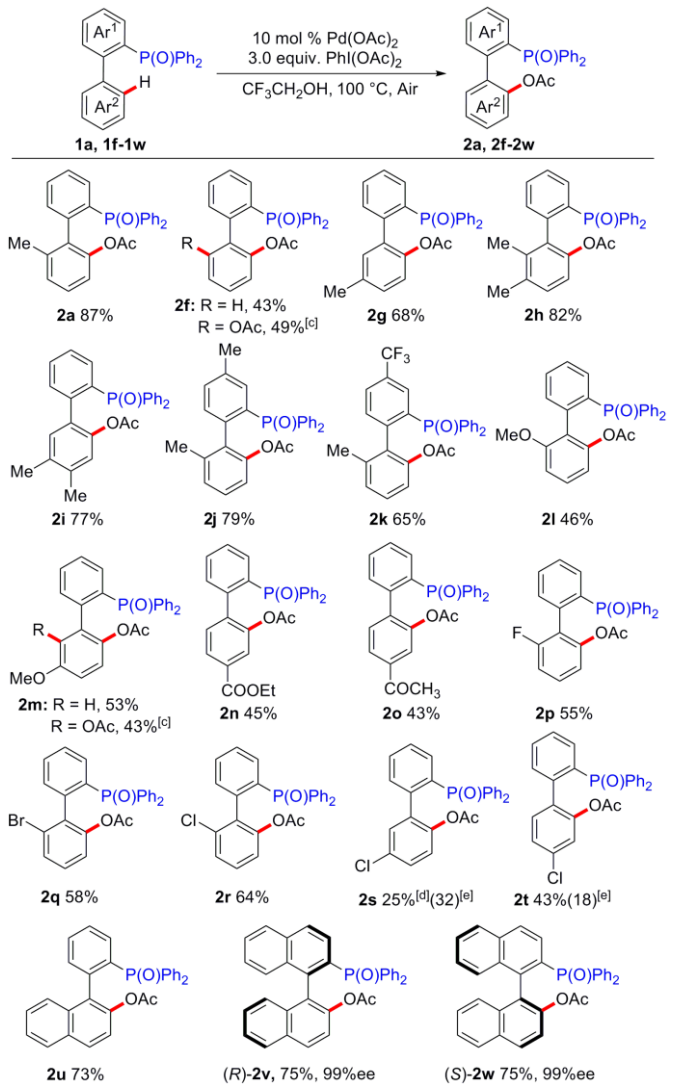


[a] Reaction conditions :**1a-1e** (0.2 mmol), $PhI(OAc)_2$ (3.0 equiv), $Pd(OAc)_2$ (10 mol %), CF_3CH_2OH (2.0 mL), air atmosphere, 100 °C. [b]Isolated yields of products.

Next, we investigated different substituted 2-(diphenylphosphine) biphenyl derivatives (Table 3). When 2-(diphenylphosphine) biphenyl was used as the substrate, the reaction occurred very smoothly and the product of **2f** was obtained in 92% highest yield with a mixture of acetoxylated and diacetoxylated product. Following this result, we focused our investigation on various substituted 2-(diphenylphosphine) biphenyls. Although methyl or dimethyl groups lie on the Ar^2 aromatic ring, the reaction proceeded smoothly and the corresponding product was obtained in good yields (**2a**, **2g**-**2k**). However, the substituent at the *ortho*-position was changed into the methoxyl group; the desired product of **2l** was afforded in only 46% yield. When the methoxyl group lay on the *meta*-position, however, the mixture of acetoxylated and diacetoxylated products (**2m**) was obtained in 53% and 43% yields. These results indicate that the steric effect is the main factor leading to lower yields. This reaction displayed good functional group tolerance, but the electronic effect was also quite evident. When the electron-withdrawing groups ester, ketone, fluoride, bromide, and chloride were located in the Ar^2 aromatic ring, the corresponding product was generally

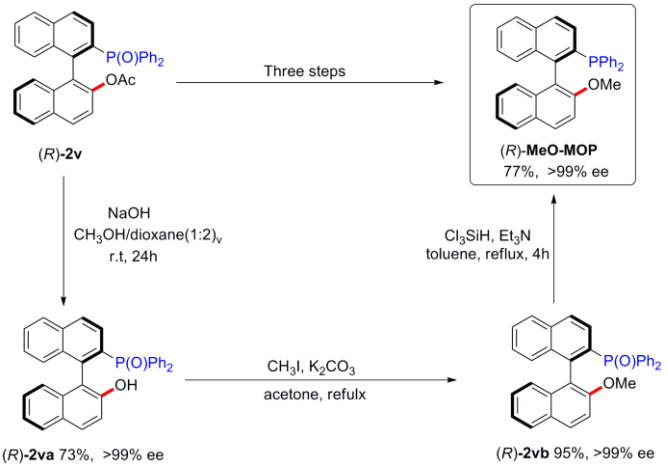
obtained in lower yields (**2n-2r**). The chloride group in particular at the *meta*- and *para*-position gave the desired product of **2s** 25% and **2t** 43% yields and a low conversion led to the recovery of the remaining starting material (**1s-1t**). Furthermore, we also found that the reaction was sensitive to substituents on the Ar^1 aromatic ring. For example, the electron-neutral group of methyl achieved the product with higher yield than electron-withdrawing group of CF_3 (**2j-2k**). Finally, the reaction saw a smooth execution with naphthalene derivatives. When the optically pure 2- diphenylphosphine oxide-1,1'-binaphthyl was used as the substrate, the *R*- and *S*-configuration products were obtained in 75% yields, respectively and accompanied by excellent ee values (**2v-2w**).

Table 3. The investigation of different substituted (2-biphenyl)diphenyl phosphine oxide derivatives [a,b]



[a] Reaction conditions:**1a**, **2f-2w** (0.2 mmol), $PhI(OAc)_2$ (3.0 equiv), $Pd(OAc)_2$ (10 mol %), CF_3CH_2OH (2.0 mL), air atmosphere, 100 °C. [b]Isolated yields of products. [c]Yield of diacetoxylated product. [d]The reaction was carried out at 110 °C. [e]Recovery yield of staring material.

Phosphorus-based ligands play an important role in many metal-catalyzed organic reactions, including various asymmetric transformations.[13] To demonstrate the potential synthetic utility of the $Ph_2(O)P$ directed $C(sp^2)$-H activation to form C-O bond, we selected the acetoxylation product of 2'-(diphenylphosphoryl)-1,1'-binaphthyl-2-yl acetate (*R*)-**2v** as starting material to synthesize the chiral ligand of (*R*)-**Meo-MOP**. According to pioneering reports, acetoxylation can be hydrolyzed in order to afford the (2'-hydroxy-[1, 1'-binaphthalen])-2-yl)diphenylphosphine oxide (*R*)-**2va** in 73% yield with 99% ee.[13e] Then, under basic conditions the methylation of hydroxyl group is formed using the methyl iodide; (*R*)-**2vb** is thus obtained in 95% yield. Finally, deoxidation of (*R*)-**2vb** is carried out in the presence of Cl_3SiH and Et_3N under inert gas and the chiral ligand of (*R*)-**MeO-MOP** is obtained in a 77% yield.[14] To our delight, the excellent ee value persisted throughout the conversion process.



Scheme 2. The utility for the synthesis Chiral Ligand (*R*)-**MeO-MOP**

In summary, we have developed a novel $R_2(O)P$-directed Pd (Ⅱ) –catalyzed C-H acetoxylation of diphenyl phosphine oxide compounds. Notably, the reaction is easy to handle, shows good functional group tolerance, and generates high yields with high selectivity. Various diphenyl phosphine oxide compounds could be synthesized under standard conditions. Further applications based on this research to synthesize biologically active compounds as well as detailed mechanism studies are currently in progress.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/ c3cc

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