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Palladium-Catalyzed C(sp^2 and sp^3)–H Activation/C–O Bond Formation: Synthesis of Benzoxaphosphole 1- and 2-Oxides

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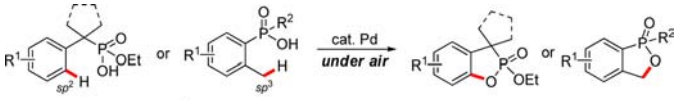
ABSTRACT



An efficient synthetic method of benzoxaphosphole 1- and 2-oxides is reported from phosphonic and phosphinic acids without prefunctionalization through a Pd-catalyzed C(sp^2 and sp^3)–H activation/C–O bond formation under aerobic conditions.

C–H activation catalyzed by transition metals has been recognized as a challenging objective in organic synthesis since unactivated C(sp^2)–H and C(sp^3)–H bonds are omnipresent in organic compounds.[1] Hence, the direct use of C–H bonds as functional groups without prefunctionalization provides new disconnection strategies to approach target molecules from easily obtainable starting materials.[2] In particular, the development of a synthetic method of a C-heteroatom bond through C–H activation is very important due to the ubiquity of heterocycles in nature.[3] Among the many heterocycle-forming reactions, the direct cyclization method between tethered heteroatoms and adjacent nonactivated C–H bonds proved recently to be an interesting and streamlined method.[4] To date, the intramolecular C–H activation/C–N cyclization method has been used for the synthesis of N-containing heterocyclic compounds. However, the preparation of O-containing heterocyclic compounds through intramolecular C–H activation/C–O cyclization has been reported comparatively much less due to the energy gap between the highest occupied molecular orbital (HOMO) of the Pd–O

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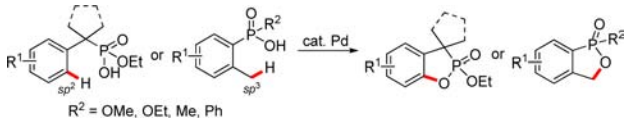
bond and the lowest unoccupied molecular orbital (LUMO) of the Pd−C bond and the substantial ionic character of the Pd−O bond.[5,6] Recently, Martin and co-workers reported Pd-catalyzed C−H activation/C−O bond formation to prepare benzolactones.[7] In addition, Yu and Shi demonstrated Pd-catalyzed C−H activation/C−O bond formation to prepare benzofuranones.[8]

We have recently been interested in the development of novel phosphoryl-related directing groups[9] in C−H activations and application to the synthesis of P-heterocyclic compounds due to a remarkable similarity in reactivity and bioactivity between the carbon species and their phosphorus counterparts.[9a,10] Although the oragnophosphorus compounds have been identified as important compounds in the field of medicinal, material, and agricultural chemistry,[11] their application in transition-metal-catalyzed C−H activations has been rarely explored.[12] Thus, development of efficient C−H activation using a phosphorus-related directing group is important. Herein, we report Pd-catalyzed C(sp^2 and sp^3)−H activation/C−O bond formation for the synthesis of benzoxaphosphole 1- and 2-oxides from phosphonic and phosphinic acids without prefunctionalization under aerobic conditions (Scheme 1).[13]

Scheme 1. Pd-Catalyzed C(sp^2 and sp^3)−H Activation/C−O Bond Formation



We began our studies by examining the C−H activation/C−O bond formation of ethyl hydrogen benzylphosphonate (**1a**) using a variety of oxidants and bases in the presence of $Pd(OAc)_2$ (Table 1). A wide range of oxidants such as $Cu(OAc)_2$, Ag_2O, $K_2S_2O_8$, and BQ (see Supporting Information) failed to give the cyclized product **2a**. However, we found that **2a** could be obtained in 51% yield in DCE with $PhI(OAc)_2$, which is a useful oxidant for the Pd(II)/Pd(IV) catalytic cycle.[6a,14] Next, a multitude of bases were screened in the presence of $PhI(OAc)_2$ in DCE. Although K_2CO_3 was totally ineffective, KPF_6 and K_2HPO_4 provided the cyclized product in 32 and 35% yields, respectively (entries 7 and 8). Also, use of LiH_2PO_4 and CsOAc did not give satisfactory results (entries 9 and 10). Optimal results were obtained with NaOAc (1 equiv) and $PhI(OAc)_2$ (1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) to afford **2a** in 91% yield (isolated yield 87%) under aerobic conditions (entry 12). Among the solvents tested, DCE gave the best result (see Supporting Information). It should be noted that acetoxylation of the C−H bond, which is usually proceeded with this oxidant, did not occur under the optimized reaction conditions. When NaOAc was not used, the reaction did not proceed because the corresponding salt that brings about C−H activation in a similar manner to that of benzoic acid substrates could not be produced in situ (entry 13).[15]

The influence of the Thorpe−Ingold effect on the cyclization was examined. As shown in Table 2, the effect of substitutions at the α-positions of **1** is evident. The existence of the α-hydrogen of the phosphonates suppressed such C−O cyclization (entries 1 and 2). Phosphonate **1e**, having the sterically more bulky *n*-propyl group than methyl and ethyl at the α-position, was smoothly cyclized to the benzoxaphosphole 2-oxide **2e** in quantitative yield (96%, entry 5).

Next, we applied this catalytic system to various **1** to demonstrate the efficiency and scope of the present method. A number of α,α-disubstituted ethyl hydrogen benzylphosphonates were cyclized to produce the corresponding benzoxaphosphole 2-oxides in good to excellent yields (Scheme 2). In contrast to phenyl acetic acid with an *ortho*-substituted group at the phenyl ring,[8a] substrates **1f** with an *ortho*-methyl group produced the benzoxaphosphole 2-oxide

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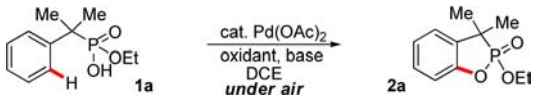
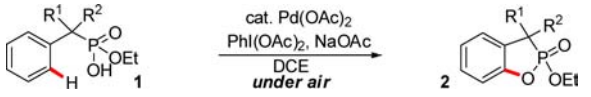
Table 1. Reaction Optimization[a]



entry	oxidant (equiv)	base (equiv)	yield[b] (%)
1	$Cu(OAc)_2$ (2)	KOAc (1.5)	0
2	Ag_2O (2)	KOAc (1.5)	0
3	$K_2S_2O_8$ (2)	KOAc (1.5)	0
4	BQ (2)	KOAc (1.5)	0
5	$PhI(OAc)_2$ (2)	KOAc (1.5)	51
6	$PhI(OAc)_2$ (2)	K_2CO_3 (1.5)	0
7	$PhI(OAc)_2$ (2)	KPF_6 (1.5)	32
8	$PhI(OAc)_2$ (2)	K_2HPO_4 (1.5)	35
9	$PhI(OAc)_2$ (2)	LiH_2PO_4 (1.5)	25
10	$PhI(OAc)_2$ (2)	CsOAc (1.5)	50
11	$PhI(OAc)_2$ (2)	NaOAc (1.5)	91
12	$PhI(OAc)_2$ (1.5)	NaOAc(1)	91 (87)[c]
13	none	NaOAc(1)	0

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), 80 °C, 20 h, DCE (2 mL). [b] ^1H NMR yields using CH_2Br_2 as an internal standard. [c] Isolated yield.

Table 2. Effect of Substituents at the α-Positions on Pd-Catalyzed C−O Cyclization[a]

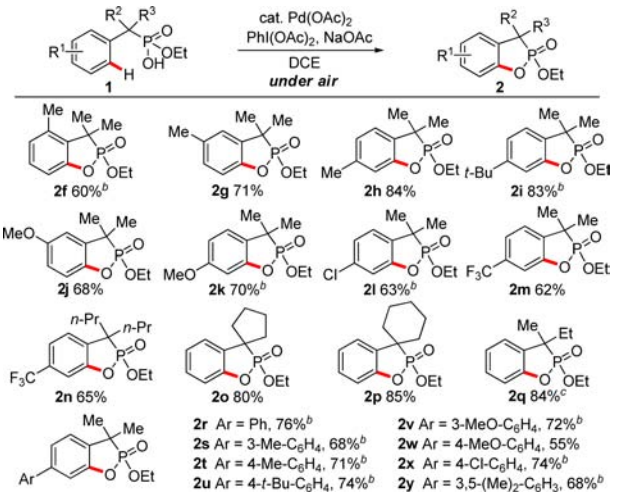


entry	R^1	R^2		product	yield[b] (%)
1	H	H	**1b**	**2b**	NR
2	H	Me	**1c**	**2c**	<1
3	Me	Me	**1a**	**2a**	87
4	Et	Et	**1d**	**2d**	87
5	*n*-Pr	*n*-Pr	**1e**	**2e**	96

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (0.3 mmol), NaOAc (0.2 mmol), 80 °C for 20 h, DCE (2 mL). [b] Isolated yield.

2f in 60% yield under aerobic conditions. As anticipated, *meta*-methyl substrate **1g** underwent Pd-catalyzed C−H activation followed by C−O cyclization regioselectively at the sterically less hindered position to afford benzoxaphosphole **2g** (71%). Ethyl hydrogen benzylphosphonates **1h** and **1i** having *para*-methyl and *para*-*tert*-butyl groups at the phenyl ring afforded the corresponding **2h** and **2i** in 84 and 83% yields, respectively. Electron-donating groups such as *meta*-MeO (**1j**) and *para*-MeO (**1k**) also gave **2j** (68%) and **2k** (70%). In addition, substrates having an electron-withdrawing group underwent the C−H activation/C−O cyclization smoothly. When *para*-chloro-substituted benzylphosphonate **1l** was subjected to the standard conditions, the desired benzoxaphosphole **2l** was obtained in 63% yield. The tolerance of the *para*-chloro group is especially useful, as the following catalytic cross-coupling reactions are

Scheme 2. Scope of Ethyl Hydrogen Benzylphosphonates[a]

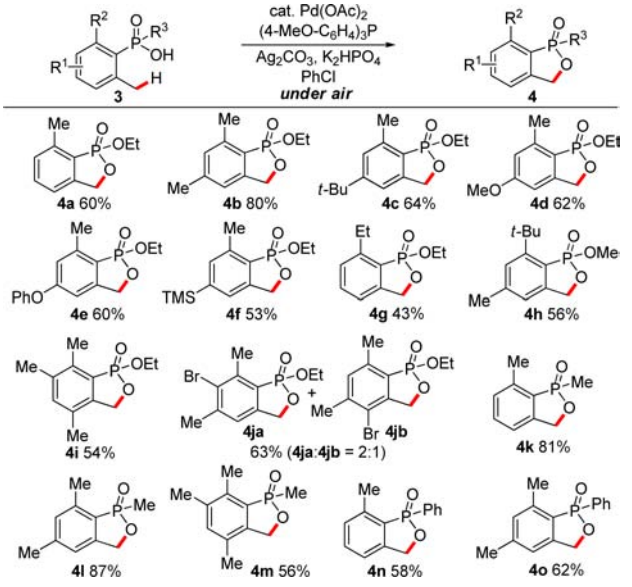


[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (0.3 mmol), NaOAc (0.2 mmol), 80 °C, 20 h, DCE (2 mL). [b] $PhI(OAc)_2$ (0.6 mmol) is used. [c] Diastereomeric ratio = 2:1.

promising. Although a strong electron-withdrawing trifluoromethyl group was located at the *para*-position of the phenyl ring, the cyclized products **2m** and **2n** were obtained in good yield. Both five- and six-membered rings **1o** and **1p** are also excellent substrates toward the C−H activation/C−O cyclization. Furthermore, substitution of nonsymmetrical alkyl groups (Me and Et) furnished **2q** in 84% (dr = 2:1) yield. For biaryl substrates having 3-Me, 4-Me, and 4-*tert*-Bu (**1s-u**) groups, the corresponding products (**2s**−**u**) were produced in good yields. Both electron-donating groups (3-MeO, **1v** and 4-MeO, **1w**) turned out to be compatible with the reaction conditions. Electron-withdrawing chloro group (**1x**) was tolerated on the substituted aryl ring, thus allowing an opportunity for further functionalization. We were pleased to obtain **2y** from 3,5-dimethyl-substituted biaryl compound **1y**. When cyclization of ethyl hydrogen benzylphosphonate **1a** was carried out in the presence of ethyl benzoate or *N*-methyl benzamide, **2a** was selectively obtained (see Supporting Information).

With the newly developed tandem $C(sp^2)$−H activation/C−O cyclization protocol of ethyl hydrogen benzylphosphonates, we attempted more difficult $C(sp^3)$−H activation/C−O cyclization using ethyl hydrogen phenylphosphonates **3**. First, we employed the optimum reaction conditions of $C(sp^2)$−H activation/C−O cyclization to intramolecular cyclization of **3b**, thus obtaining gratifyingly the desired cyclized product **4b** (20%) albeit in low yield. Encouragingly, the second attempt was conducted with the combination of $Pd(OAc)_2$ and K_2HPO_4, which was reported as an efficient catalytic system in the carboxyl-directed C−H/C−O cyclization,[7] producing the corresponding benzoxaphosphole 1-oxide **4b** in 60% yield. Therefore, new optimum reaction conditions were re-examined for $C(sp^3)$−H activation/C−O cyclization with **3b** (see Supporting Information). Because a multitude of carboxylic acids and amino acids as ligand failed to increase

Scheme 3. Scope of Arylphosphonic and Arylphosphinic Acids[a]



[a] Reaction conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), (4-MeO-C_6H_4)$_3$P (0.08 mmol), Ag_2CO_3 (0.6 mmol), K_2HPO_4 (0.5 mmol), 120 °C, 12−36 h, PhCl (2 mL).

the product yield, a wide range of phosphous-related ligands were screened. To our delight, (4-MeO-C_6H_4)$_3$P turned out to be the most effective ligand, resulting in the complete use of **3b** to furnish **4b** in 80% yield in PhCl at 120 °C for 12 h under aerobic conditions.

Stimulated by these results, we investigated the efficiency and scope of Pd-catalyzed C(sp^3)−H activation/C−O cyclization using various ethyl hydrogen arylphosphonates **3** (Scheme 3). Ethyl hydrogen 2,6-dimethylphenylphosphonate **3a** underwent the oxidative cyclization to produce **4a** in 60% yield. When ethyl hydrogen 4-*tert*-butyl-2,6-dimethylphenylphosphonate (**3c**) was subjected to the standard conditions, the desired product **4c** was obtained in 64% yield. Substrates **3d** and **3e** possessing strong electron-donating 4-MeO and 4-PhO groups were cyclized to provide the corresponding benzoxaphosphole 1-oxides **4d** and **4e** in 62 and 60% yields, respectively. 4-Trimethylsilyl-substituted **3f** gave the desired product **4f** in 53% yield. In the case of substrates **3g** and **3h** bearing different alkyl groups at the *ortho*-position of the phenyl ring, C−H activation at the methyl group occurred selectively to produce **4g** and **4h**, indicating that the present method could discriminate methyl, ethyl, and *tert*-butyl groups. 2,3,5,6-Tetramethylphenylphosphonate **3i** was less reactive, and cyclized product **4i** was isolated in 54% yield. 3-Bromo-2,4,6-trimethylphenylphosphonate **3j** was also converted to **4j** in 63% yield (**4ja**/**4jb** = 2:1). Chemoselective cyclization of ethyl hydrogen mesitylphosphonate **3b** was obtained in the presence of ethyl benzoate (see Supporting Information).

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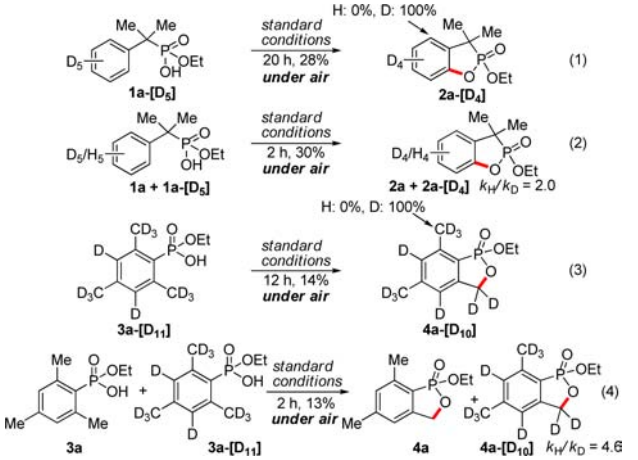
Scheme 4. Studies with Isotopically Labeled Compounds



Interestingly, when 2,6-dimethylphenyl(methyl)phosphinic acid **3k** was used, the reaction proceeded smoothly, yielding the benzoxaphosphole 1-oxide **4k** in 81% yield. 2,4,6-Trimethylphenyl(methyl)phosphinic acid **3l** promoted cyclization considerably, thus producing **4l** in 87% yield. 2,3,5,6-Tetramethylphenyl(methyl)phosphinic acid **3m** showed similar reactivity to **3i**, thus affording **4m** in 56% yield. Phosphinic acids **3n** and **3o** underwent C−H activation/C−O cyclization to give the cyclized products **4n** and **4o** in good yields.

Next, to obtain insight into the reaction mechanism, we conducted kinetic isotope effect (KIE) studies (Scheme 4). A KIE was detected (k_H/k_D = 2.0) (eqs 1 and 2).[16] We also conducted KIE studies of 2,4,6-trimethylphenylphosphonate **3a**. An obvious KIE was observed (k_H/k_D = 4.6), indicating that the C−H bond cleavage at the *ortho*-position of phosphonate is most likely involved with the rate-limiting step (eqs 3 and 4).

In this paper, we have developed an efficient synthetic method of benzoxaphosphole 1- and 2- oxides from phosphonic and phosphinic acids without prefunctionalization through Pd-catalyzed C(sp^2 and sp^3)−H activation/C−O bond formation under aerobic conditions.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.