Synthesis of ethoxy dibenzooxaphosphorin oxides through palladium-catalyzed C(sp^2)–H activation/C–O formation
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Abstract
We report an efficient Pd-catalyzed C(sp^2)–H activation/C–O bond formation for the synthesis of ethoxy dibenzooxaphosphorin oxides from 2-(aryl)arylphosphonic acid monoethyl esters under aerobic conditions.

Introduction
Unreactive C(sp^2)–H and C(sp^3)–H bonds are ubiquitous in organic compounds [1-7], so that the development of methods for the transition metal-catalyzed C–H activation is one of the challenging goals in organic synthesis. Especially, the development of synthetic methods of C–heteroatom bond formation via C–H activation has received attention owing to the omnipresence of heterocyclic compounds in nature [8]. Recently, it has been demonstrated that the intramolecular bond formation between a heteroatom and a vicinal unreactive C–H is an efficient method for the synthesis of heterocycles [9-17]. Although C–H activation/C–N formation has been widely used for the synthesis of azaheterocycles, the preparation of oxaheterocycles via C–H activation/C–O formation has been described a lot less, because the energy correlation between the HOMO of the Pd–O bond and the LUMO of the Pd–C bond is unfavorable and the Pd–O bond has a significantly ionic character [18-23]. To expand this scope, we are interested in the development of C–H activation/C–O formation by means of new directing groups. Recently, a variety of C–H activations by using new phosphoryl-related directing groups have been reported by our
[24-32] and other groups [33-41]. More recently, we developed a method allowing for synthetic access to benzoxaphosphole 1- and 2-oxides starting from phosphonic and phosphinic acids via Pd-catalyzed C(sp²)–H activation/C–O formation [42]. In this context, we herein report the synthetic method of alkoxy dibenzooxaphosphorin oxides from 2-(aryl)arylphosphonic acid monoesters via Pd-catalyzed C(sp²)–H activation/C–O formation (Scheme 1).

**Scheme 1:** Synthesis of alkoxy dibenzooxaphosphorin oxides by C(sp²)–H activation/C–O formation.

Results and Discussion

First, a wide range of 2-(aryl)arylphosphonic acid monoethyl esters were efficiently prepared by a Suzuki reaction of 2-bromoiodoarenes with arylboronic acids, a lithium bromide exchange reaction of 2-bromobiaryls followed by diethylphosphinylation with diethyl chlorophosphate, and the C–O cleavage of diethyl 2-(aryl)arylphosphonates by using L-Selectride (Scheme 2).

The C–H activation/C–O formation of 2-(phenyl)phenylphosphonic acid monoethyl ester (1a) was examined with a variety of oxidants and bases in the presence of Pd(OAc)₂. A multitude of oxidants such as K₂S₂O₈, BQ, benzylic peroxide, PhI(TFA)₂, Cu(OAc)₂, CuCl₂, CuBr, AgOAc, Ag₂CO₃ and Ag₂O did not produce the cyclized product 2a (see Supporting Information File 1). However, PhI(OAc)₂, which is an efficient oxidant for the Pd(II)/Pd(IV) catalytic cycle, gave 2a in 30% yield in t-butanol (80 °C for 16 h; Table 1, entry 1) [19,43-47]. In addition, various bases were examined. Although NaOAc, CsOAc, CsF and CsOPiv afforded 2a in yields ranging from 42% to 52%, KOAc gave the best result (57%) in the presence of PhI(OAc)₂ in tert-butanol (see Supporting Information File 1). tert-Butanol gave the best result among the solvents DCE, dioxane, ACN, t-AmOH, DMF, HFIP, THF, toluene, TFA and MeOH (see Supporting Information File 1). With this preliminary result in hand, we investigated a variety of organic acids as ligands in an effort to improve the catalytic efficiency (Scheme 3). However, these attempts provided no improvement (Table 1, entries 2–4). Finally, we discovered that easily accessible monoprotected amino acids, which have recently been established as efficient ligands in C–H activations [48-50], increased the yield (Table 1, entries 5–10). Among the investigated ligands, N-acetyl-L-leucine (L9) gave the best result (Table 1, entry 10). After examination of the reaction temperature (Table 1, entries 11–13) and time (Table 1, entries 14–16), the oxidative cyclization using PhI(OAc)₂ (2 equiv) and KOAc (2 equiv) in the presence of Pd(OAc)₂ (10 mol %) and L9 (30 mol %) gave the best result under aerobic conditions, affording 2a in 61% yield (isolated yield 55%, Table 1, entry 16). Both Pd(TFA)₂ and Pd(OTf)₂·H₂O gave inferior results compared to Pd(OAc)₂ (Table 1, entries 17 and 18).

To ascertain the scope of the Pd-catalyzed C–H activation followed by the C–O formation, a wide range of 2-(aryl)arylphosphonic acid monoethyl esters 1 were examined under the optimized reaction conditions (Scheme 4). Phenylphosphonic acid monoethyl ester 1b with a 2-methyl group on the phenyl ring was transformed to the desired dibenzooxaphosphorin oxide 2b in 53% yield. Phenylphosphonic acid monoethyl esters (1c) with a 3-methyl group were selectively converted to the cyclized products (2c) in 66% yield due to steric effects. In the case of 4-tert-butyl, the desired product
Table 1: Optimization studies for the cyclization of 2-(phenyl)phenylphosphonic acid monoethyl esters.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat. Pd</th>
<th>ligand</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol % Pd(OAc)</td>
<td>—</td>
<td>80</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L1</td>
<td>80</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L2</td>
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<td>16</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L3</td>
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<td>16</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L4</td>
<td>80</td>
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<td>48</td>
</tr>
<tr>
<td>6</td>
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<td>30 mol % L5</td>
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<td>48</td>
</tr>
<tr>
<td>7</td>
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<tr>
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<td>16</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
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<td>30 mol % L8</td>
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<td>16</td>
<td>51</td>
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<tr>
<td>10</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L9</td>
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<td>57</td>
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<td>20</td>
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<tr>
<td>12</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L9</td>
<td>100</td>
<td>16</td>
<td>61</td>
</tr>
<tr>
<td>13</td>
<td>10 mol % Pd(OAc)</td>
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<td>120</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
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<td>30 mol % L9</td>
<td>100</td>
<td>4</td>
<td>45</td>
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<tr>
<td>15</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L9</td>
<td>100</td>
<td>8</td>
<td>51</td>
</tr>
<tr>
<td>16</td>
<td>10 mol % Pd(OAc)</td>
<td>30 mol % L9</td>
<td>100</td>
<td>12</td>
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<td>30 mol % L9</td>
<td>100</td>
<td>12</td>
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<tr>
<td>18</td>
<td>10 mol % Pd(OTf)_2·H_2O</td>
<td>30 mol % L9</td>
<td>100</td>
<td>12</td>
<td>45</td>
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*a*Yields were determined by ^1^H NMR with CH_2Br_2 as an internal standard. The number in parentheses is the isolated yield.

Scheme 3: A variety of organic acids and monoprotected amino acids as ligands.

2e was obtained in 65% yield. Substrate 1f, characterized by an electron-donating 4-methoxy group, was cyclized to dibenzooxaphosphorin oxide 2f in 65% yield under aerobic conditions. The present method worked equally well with 3,4-dimethoxyphenyl-substituted phenylphosphonic acid monoethyl ester 1g. Phenylphosphonic acid monoethyl ester 1h with a 4-phenyl group on the phenyl ring turned out to be compatible with the reaction conditions. As anticipated, 2-naphthyl-substituted phenylphosphonic acid monoethyl ester 1i underwent the Pd-catalyzed oxidative cyclization regioselectively at the sterically less hindered position to afford the desired dibenzooxaphosphorin oxide 2i in 70% yield. We were pleased to
obtain 2j by a Pd-catalyzed oxidative cyclization of 1-naphthyl-substituted phenylphosphonic acid monoethyl ester 1j. 2-(Aryl)phenylphosphonic acid monoethyl esters 1k, 1l and 1m with an electron-withdrawing fluoro or chloro group on the phenyl ring were subjected to the oxidative cyclization to deliver the desired products 2k, 2l and 2m in yields ranging from 54% and 64%. In particular, the tolerance of the chloro groups may be of importance for a subsequent catalytic cross-coupling reaction. Substrate 1n, which contains a 2-thiophenyl moiety, was subjected to the cyclization affording 2n in 52% yield. The preparation of 2-arylphenylphosphonic acid monoethyl esters with a nitro, difluoro, or ethoxycarbonyl group failed.

Next, the Pd-catalyzed oxidative cyclization of 2-(aryl)arylphosphonic acid monoethyl esters 3 were examined to demonstrate the efficiency of the present method (Scheme 5). 4-Methylphenylphosphonic acid monoethyl esters 3a and 3b with a 3-methyl- and 3,4-dimethoxyphenyl group at 2-position turned out to be compatible with the Pd-catalyzed oxidative cyclization. There are no regioisomers formed due to steric effects. Substrate 3c bearing a chloro group was selectively cyclized to afford 4c in 64% yield. To our delight, the present method worked equally well even if a fluoro group on the phenyl ring is present. 3-Fluorophenylphosphonic acid monoethyl esters 3d, 3e and 3f with 3-methyl-, 3,4-dimethoxy and 3-chlorophenyl groups at the 2-position selectively underwent the oxidative cyclization to give the corresponding cyclized products 4d, 4e and 4f in yields ranging from 50% and 63%.

We carried out kinetic isotope effect (KIE) studies to prove the reaction mechanism (see Scheme 8). The required deuterium-labeled 2-(phenyl)phenylphosphonic acid monoethyl ester
Scheme 5: Cyclization of 2-(aryl)arylphosphonic acid monoethyl esters.

1a-[D₅] was efficiently prepared by a Suzuki reaction of deuterated bromobenzene (6) with 2-bromophenylboronic acid (5), a lithium bromide exchange reaction of 2-bromo deuterated biphenyl 7 followed by diethylphosphinylation with diethyl chlorophosphate, and C–O cleavage of diethyl 2-(phenyl)phenylphosphonate by using L-Selectride (Scheme 6). In addition, the deuterium-labeled 2-(phenyl)phenylphosphonic acid monoethyl ester 1a-[D₁] was obtained by the lithium bromide exchange reaction of 2'-bromo-2-iodo-1,1'-biphenyl (10) and the treatment of D₂O, diethylphosphinylation with diethyl chlorophosphate, and C–O cleavage of diethyl 2-(phenyl)phenylphosphonate by using L-Selectride (Scheme 7).

In the case of an intermolecular competition reaction using 1a and 1a-[D₅], a KIE was detected (k_H/k_D = 1.0; Scheme 8, reaction 1) [51,52]. Also, an intramolecular competition reaction...
Scheme 7: Preparation of 1a-[D$_1$].

Scheme 8: Studies with isotopically labelled compounds.

intermolecular competition

\[
\begin{align*}
1a + 1a-[D_2] & \xrightarrow{10 \text{ mol} \% \text{ Pd(OAc)}_2, 2 \text{ equiv Phl(OAc)}_2, 2 \text{ equiv KOAc, 30 mol} \% \text{ L9, 100 °C, t-BuOH, 30 min}} 2a + 2a-[D_2] \\
& \quad k_{H}/k_{D} = 1.0
\end{align*}
\]

intramolecular competition

\[
\begin{align*}
1a-[D_1] & \xrightarrow{10 \text{ mol} \% \text{ Pd(OAc)}_2, 2 \text{ equiv Phl(OAc)}_2, 2 \text{ equiv KOAc, 30 mol} \% \text{ L9, 100 °C, t-BuOH, 30 min}} 2a + 2a-[D_1] \\
& \quad k_{H}/k_{D} = 0.6
\end{align*}
\]

using 1a-[D$_1$] was carried out to give KIE ($k_{H}/k_{D} = 0.6$; Scheme 8, reaction 2). These results indicate that the C–H cleavage at the ortho-position of 2-(phenyl)phenylphosphonic acid monoethyl ester is not involved in the rate-limiting step and the C–H bond metallation is reversible.

To elucidate the mechanism of the present reaction, the reaction was conducted with a stoichiometric amount of Pd(OAc)$_2$ and without the oxidant Phl(OAc)$_2$. However, no cyclized product was observed. This result indicates that the C–O reductive elimination from Pd(II) is not favorable. Because both the intermolecular and intramolecular competition experiments exhibited no significant kinetic isotope effect ($k_{H}/k_{D} = 1.0$ and 0.6; Scheme 8), we hypothesize that the C–O reductive elimination step is the rate-determining step. A feasible mechanism involving the Pd(II)/Pd(IV) catalytic cycle is described in Scheme 9. The C–H activation might be efficiently accelerated by the N–H activation propelled by N-Ac-L-Leu-OH (L9) as a ligand [53-55], resulting in the formation of palladacycle III. Thereafter, ethoxy dibenzooxaphosphorin oxide 2a is obtained from the oxidation of the Pd(II) to Pd(IV) species IV and the subsequent C–O reductive elimination.

Conclusion

In this paper, we have developed an efficient synthetic method for a wide range of ethoxy dibenzooxaphosphorin oxides.
starting from 2-(aryl)arylphosphonic acid monoethyl esters and employing Pd-catalyzed C(sp$^2$)–H activation/C–O formation under aerobic conditions. Oxidative cyclization by means of a Pd(II)/Pd(IV) catalytic cycle might play a role in the mechanism of the present reaction.

**References**


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