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Ruthenium-Catalyzed C–H Bond Alkylation of Arylphosphine Oxides with Alkenes: A Straightforward Access to Bifunctional Phosphorous Ligands with a Pendent Carboxylate

Chang-Sheng Wang,[a] Pierre H. Dixneuf[a] and Jean-François Soulé*[a]

Abstract: An efficient approach for the fast modification of arylphosphine oxides involving ruthenium(II)-catalyzed C–H bond alkylation with functional alkenes versus alkenylation has been developed depending on the acidic reaction conditions. A few examples of desymmetrization of diarylphosphine oxides containing three different substituents were prepared using this methodology. After reduction of the phosphate oxide, this method allows the formation of aryl phosphines bearing a flexible pendent carboxylate.

Arylphosphine oxides play a central role in organophosphorus chemistry. This motif is embedded in organic molecular materials, especially in the design of blue phosphorescent organic light-emitting diodes.[1] In addition, phosphorus (V) is an important bioisostere in medicinal chemistry,[2] and among this class of compounds some aryl phosphate oxides have displayed useful biological activity.[3] They are also essential in catalysis whether as organocatalysts[4] or as precursors of phosphine-metal catalysts.[5]

One of the most general methods for the preparation of arylphosphine oxides involves C–P bond formation.[6] Since the discovery of transition-metal catalyzed C–H bond functionalizations, novel synthetic schemes have been proposed for the preparation of complex molecules.[7,8] In this context, Shibata reported, the first example of C–H bond ortho-alkenylation of ferrocenylphosphine oxide using an alkyne in the presence of an iridium catalyst (Scheme 1.a).[9,10] Then, Satoh and Miura demonstrated that the P=O bond of arylphosphine oxides could be more efficiently used as a directing group in rhodium(III)-catalyzed ortho-C–H bond alkenylation with alkenes in the presence of AgOAc as oxidant (Scheme 1.b).[11] Glorius has applied thus alkenylation to arylphosphonates and phosphonamides.[12] Related transformations involving P-OH[13] or P-N[14] directed C–H bond activation have also been reported. Other functionalizations of arylphosphine oxides such as C–H bond amination,[15] arylation,[16] cyanation,[17] are reported using noble transition metals. Ruthenium(II)-catalyzed direct alkenylation of arylphosphine oxides with internal alkynes was further reported by Miura (Scheme 1.c).[18] These pioneering results allowed new synthetic pathways for the preparation of bifunctional phosphine ligands containing a flexible pendent functionality, provided that alkylation selectivity with alkenes, rather than alkenylation, can be controlled. Ruthenium(II)-catalyzed functionalization of C–H bonds with alkenes has preferentially led to alkenylation[19] but some examples of alkenylation,[20] mostly directed by a pyridine group, have been reported. We report now the control and understanding of alkylation versus alkenylation of unreactive C–H bond with phosphate oxide as directing group and their potential for the synthesis of functionalized phosphorous ligands (Scheme 1.d).

a. Ir-catalyzed ortho-alkenylation of ferrocenylphosphine oxide (Shibata)[9]

b. Rh-catalyzed ortho-alkenylation of arylphosphine oxides (Miura)[11]

c. Ru-catalyzed ortho-alkenylation or alkylation of arylphosphine oxides (Miura)[18]

d. Ru-catalyzed ortho-alkylation versus alkenylation of arylphosphine oxides (this work)

Scheme 1. Previous examples of TM-catalyzed direct alkenylation and/or alkylation of arylphosphine oxides

Miura and co-workers have reported beside alkenylation with alkyn (Scheme 1.c) one example of the alkylation using triphenylphosphine oxide (1a) and n-butyl acrylate (2a) catalyzed by [RuCl₂(μ-cymene)]₂ in concert with AgSbF₆ in

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the presence 4 equivalents of 1-adamantane carboxylic acid (AdCO₂H) in diglyme (Table 1, entry 1). We investigated the reaction parameters to influence the selectivity of the alkylation or alkenylation of 1a with the acrylate 2a. Dichlororethane (DCE) as solvent displayed the best reactivity with the formation of 3aa in a higher yield of 65% without formation of 4aa (Table 1, entries 2-4). When pivalic acid was used a comparable yield in 3aa was observed (Table 1, entry 5). However, using simple acetic acid, the yield of 3aa enhanced up to in 80%. Ru(OAc)₃(η-cymene) as the catalyst is inefficient (Table 1, entry 7). The alkylation of 1a with 2a was conducted on a gram scale to afford 1.9 g of 3aa (Table 1, entry 8). Having succeeded to obtain the alkylation product 3aa in both high yield and selectivity, we turned our attention the formation of the alkenylation product 4aa, which was not reported yet using ruthenium(II) catalysis albeit similar transformations were reported using rhodium(III) catalysis.[12, 21] In the presence of Cu(OAc)₂ as oxidant, 4aa was formed in low yield but 3aa remained the major product (Table 1, entry 9). Changing the acid by a base, the formation of 3aa was inhibited and 4aa was obtained as the major product (Table 1, entries 10-14). NaHCO₃ was selected as the best base to afford the alkenylated product 4aa in 48% yield (Table 1, entry 14).

**Table 1. Optimization of the reaction conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive 1 (x)</th>
<th>Additive 2</th>
<th>Solvent</th>
<th>3aa (%)</th>
<th>4aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[1][2]</td>
<td>AdCO₂H (4)</td>
<td>diglyme</td>
<td>58</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>AdCO₂H (4)</td>
<td>toluene</td>
<td>13</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>65</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>58</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>80</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>7[1][2]</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>8[1][2]</td>
<td>AcOH (4)</td>
<td>DCE</td>
<td>63</td>
<td>(1.9 g)</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>AcOH (4)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>71</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>KH₂PO₄ (1)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>11</td>
<td>K₂PO₄ (1)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>Li₂CO₃ (1)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>K₂CO₃ (1)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>trace</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>NaHCO₃ (1)</td>
<td>Cu(OAc)₂H₂O</td>
<td>DCE</td>
<td>trace</td>
<td>53</td>
</tr>
</tbody>
</table>

[1] Determined by GC-analysis using n-dodecane as internal standard, isolated yield is shown in parentheses.
[2] Ru(OAc)₃(η-cymene) was used instead of [RuCl₂(η-cymene)]₂ and AgSbF₆.
[3] Reaction performed from 1a (15.6 mmol, 4.3 g) and 2a (7.8 mmol, 1 g).

With the best conditions in hand (i.e. entry 6), we then investigated the scope of the alkylation of aryl phosphate oxides (Scheme 2). First, we explored the reactivity of some substituted triarylphosphate oxides with n-butyl acrylate. Tris-(p-substituted phenyl)phosphate oxides with an electron-donating group such as methyl or methoxy allowed the formation of the ortho-alkylated triarylphosphate oxides 3ba and 3ca in 58% and 64% yields, respectively. Tris(4-fluorophenyl)phosphate oxide was also ortho-alkylated giving 3da in good yield. However, the reaction seems to be very sensitive to the steric hindrance, as tri-o-tolylphosphate oxide was not reactive. Similarly to triarylphthosphate oxides, benzyl(diphenyl)-phosphate oxide 1e and alkyl(diphenyl)-phosphate oxide 1f underwent ortho-alkylation to afford the desired phosphine oxides 3ea and 3fa in 63% and 47% yields, respectively. Methyl diphenylphosphinate 1g was ortho-alkylated to give 3ga in 53% yield. In these three examples, such late-stage modification affords a stereogenic phosphorus center which bears three different substituents, and provides a new synthetic pathway for the desymmetrization of arylphosphine oxides with the direct access to a potential new class of chiral phosphate. The reactivity of various electrophilic alkenes (2b-d) with 1a or 1e were also examined. Good yields of 62% and 65% in ortho-alkylated arylphosphine oxides 3ab and 3eb were obtained from methyl acrylate (2b) and triphenylphosphate oxide (1a) and benzyl(diphenyl)-phosphate oxide (1e). Reaction of triphenylphosphine oxide (1a) with acrylonitrile (2c) gave a mixture of ortho-alkylation product 3ac and ortho-alkenylation product 4ac in a 1:4 ratio. This lack of reactivity of acrylonitrile might be due to its strong coordination ability, which could prevent the P=O coordination on the ruthenium. We also evaluated the reactivity of ethyl 3-phenylpropionate (2d) and showed that the hydroxylation occurred to allow the regioselective formation of the ortho-alkenylation arylphosphate oxide 3ad in 67% yield. In this case, only the E-isomer of 3ad was selectively obtained. This procedure offers a straightforward access to phosphine ligands containing a shorter (i.e., 4 carbons instead of 5) flexible pendant carbamate.

![Scheme 2. Scope of Ru(II)-catalyzed C-H bond alkylation of arylphosphate oxides](image)

Scheme 2. Scope of Ru(II)-catalyzed C-H bond alkylation of arylphosphate oxides.

We next examined the possibility of accessing bifunctional phosphine ligands with a pendent carbamate, as some...
hemiaminal phosphine carboxylates have been used in catalysis. Free carboxylic acids have been shown to be critical in metal-catalyzed C–H bond activation. The phosphine oxide carboxylate compound 5aa was obtained in 75% yield through a saponification of the ester moiety using KOH. The reduction of phosphine oxide is well documented and we selected the conditions described by Werner; using phenylsilane as reducing agent in the presence of catalytic amount of triflic acid, the phosphine oxide carboxylate compound 5aa was converted into the phosphine carboxylate 6aa in 67% yield (Scheme 3). Using this protocol, additional phosphine carboxylates 6ba and 6ca were prepared in 42% and 63% overall yields over the two steps.

Using the second set of ruthenium conditions favouring the formation of the alkenylation pathway (i.e., NaHCO₃ in concert with Cu(OAc)₂·H₂O), we synthesized a couple of alkylated aryl phosphine oxides (Scheme 4). Reaction of triphenylphosphine oxide (1a) with ethyl acrylate (2e) gave the ortho-alkenylation product 4ae in 42% yield. The alkenylation reaction seems to be slightly sensitive to the electronic factors. Indeed tris(p-substituted phenyl)phosphine oxide with an electron-donating group such as methyl was alkynylated in the presence of n-butyl acrylate to deliver the 4ba in only 38% yield. Whereas, an electron-withdrawing group on the aryl phosphine oxide such as a fluoro substituent allowed the formation of 4da in 47% yield. For this alkenylation in basic media, it was known that the use of Cu(OAc)₂·H₂O is required.

Based on our observation and the literature, we propose the mechanism shown in Scheme 5. The reaction of [RuCl₂(p-cymene)]₂ with AgSbF₆ in the presence of AcOH generates ionic ruthenium(II) complex ([RuL₂(OAc)]X). The oxygen atom coordination of phosphine oxide leads to the 16-electron intermediate B, and subsequent external acetate-promoted deprotonation allows the formation of the ruthenacycle C and AcOH. Coordination of alkene in D and insertion into the Ru–C bond affords the intermediate E. In absence of base and due to the coordination ability of the P=O bond, avoiding classical β-H elimination, protodemetalation affords the linear alkylation product 3 and regenerates the salt [RuL₂(OAc)]X. On the other hand, in the presence of base (NaHCO₃) the intermediate E undergoes a base-assisted β-H deprotonation to form the alkenylation product 4. This deprotonation in basic medium generates Ru(0) species and Cu(OAc)₂ reoxidize it into Ru(II) species. Starting from a ketone as directing group (see SI), the corresponding intermediate E could undergo a decoordination of the ketone oxygen atom to make possible the classical β-H elimination and thus alkenylation.

**Scheme 3.** Preparation of bifunctional phosphine ligands.

**Scheme 4.** Scope of Ru(II)-catalyzed C–H bond alkenylation of arylphosphate oxides.

**Scheme 5.** Proposed Mechanism
An interesting ruthenium(II)-catalyzed C–H bond alkylation of aryl phosphine oxides with different Michael acceptors has been developed. The reaction requires the presence of acid to selectively obtain the alkylation products without reoxidizing agent, whereas the presence of a base promotes the formation of alkenylation products. Notably, after phosphine oxide reduction, phosphine carboxylate derivatives were obtained in good yields. Further applications in catalysis of bifunctional phosphine ligands bearing a pendent carboxylate are on-going in our laboratory.

Acknowledgements

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Keywords: Aryl phosphine oxides • C–H bond Activation • Alkylation • Ruthenium(II) • Bifunctional phosphine ligands


Ruthenium(II)-catalyzed C–H bond alkylation of arylphosphine oxides with functional alkenes has been developed. The use of acetic acid was found to be critical to favor the formation of the alkylation products while the use of NaHCO₃ affords alkenylation products. This method allows the desymmetrization of diarylphosphine oxides. After reduction of the phosphine oxide, novel phosphines bearing a flexible pendent carboxylate were synthetized.