



# Synthesis of phenanthridin-6-ylidiphenylphosphine oxides by oxidative cyclization of 2-isocyanobiphenyls with diarylphosphine oxides



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## ABSTRACT

A Mn(III)-promoted oxidative cyclization of 2-isocyanobiphenyls with diarylphosphine oxides is reported, providing phenanthridin-6-ylidiphenylphosphine oxides in good yields. Radical phosphonation and isocyanide insertion are believed to be involved in the reaction process.

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## 1. Introduction

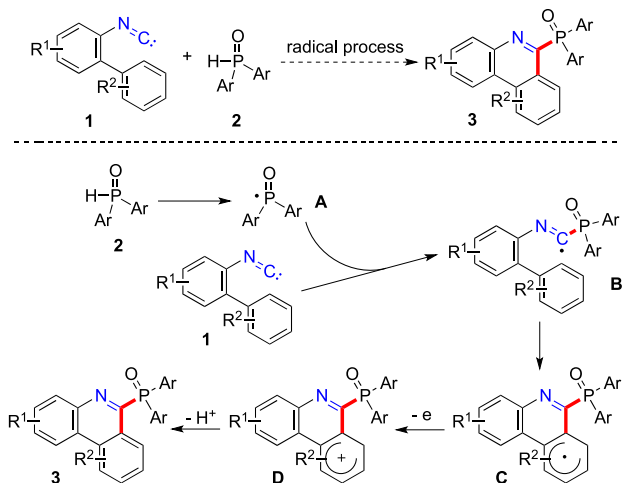
Phosphine-containing compounds are widely found in medicines<sup>1</sup> and organo-ligands.<sup>2</sup> Consequently, tremendous effort has been focused on the incorporation of phosphorus atom into targeted molecules with the aim of improving their properties. To date, it is generally accepted that cross-couplings of electrophiles<sup>3,4</sup> with H-phosphonates in the presence of transition metals (such as palladium, copper, and nickel salts)<sup>4d,5,6</sup> have become practical and powerful methods to construct C(sp<sup>2</sup>)-P bonds, as represented by Hirao reactions. Recently, the alternatives for the formation of C(sp<sup>2</sup>)-P bonds through C-H activation have been developed, where substrates with a directing group were crucial for the final outcome.<sup>7</sup> In particular, radical phosphonation triggered by Mn(III) or silver salt was demonstrated to be a facile route for the preparation of the phosphine-containing products with high efficiency.<sup>7e,8,9</sup> Considering the remarkable significance of phosphonations, we anticipated that radical phosphonation would

be employed in our program for the synthesis of natural products-like compounds.

So far, isocyanide insertion has been attracted growing emphasis in the community of chemistry due to its contributions into palladium-catalyzed imidoylative and cyanative reactions.<sup>10</sup> Our continuous interest in isocyanide insertion prompted us to focus on the radical process of isocyanide insertion. Recently, 2-isocyanobiphenyl **1** was identified as a versatile building block for the construction of nitrogen-containing heterocycles.<sup>11</sup> As a privileged structure, the phenanthridine core is one of common structural units existed widely in many natural alkaloids, which show antibacterial, antitumor, and antileukemic activities.<sup>12</sup> For example, Trisphaeridine<sup>12b</sup> is used as DNA intercalator and Fagaronine was reported as protein kinase C and DNA topoisomerase 1 inhibitor.<sup>12c</sup> Inspired by the radical phosphonation and the advances of isocyanide insertion, we envisioned that phosphated phenanthridines **3** could be generated through a reaction of 2-isocyanobiphenyls **1** with diarylphosphine oxides **2**, which would combine radical phosphonation and isocyanide insertion in a one-pot procedure (Scheme 1).<sup>13</sup>

As mentioned above, we reasoned that a phosphonate radical **A** would be afforded under proper conditions by the treatment of

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**Scheme 1.** A proposed route to phenanthridin-6-ylidiphenylphosphine oxides by oxidative cyclization of 2-isocyanobiphenyls with diarylphosphine oxides.

Mn(III) or silver salt with diarylphosphine oxide **2**. Since the aryl phosphonate radical would be easily trapped by 2-isocyanobiphenyl, this species would undergo a radical addition into 2-isocyanobiphenyl leading to imidoyl radical **B**. Subsequently, an oxidative cyclization would be happened to generate intermediate **C**. The following transformation would furnish cyclohexadienyl cation **D**, which would be ultimately aromatized to produce the targeted product **3** (Scheme 1).

## 2. Results/discussion

Therefore, to verify the feasibility of the projected route as illustrated in Scheme 1, we started to explore the practicability of this transformation. Initially, the reaction of 2-isocyanobiphenyl **1a** with diphenylphosphine oxide **2a** was selected as the model. The preliminary screening results were summarized in Table 1. At the outset, the reaction was performed in the presence of silver oxide in toluene at 70 °C (Table 1, entry 1). However, only a trace amount of the desired product **3a** was detected. The result could not be

**Table 1**  
Initial studies for the oxidative cyclization of 2-isocyanobiphenyl **1a** with diphenylphosphine oxide **2a**

Entry	Additive (equiv)	Solvent	T (°C)	Yield (%) <sup>a</sup>
1	Ag <sub>2</sub> O/2.0	Toluene	70	trace
2	Ag <sub>2</sub> CO <sub>3</sub> /2.0	Toluene	70	Trace
3	AgOAc/2.0	Toluene	70	24
4	PhI(OAc) <sub>2</sub> /2.0	Toluene	70	nd
5	Cu(OAc) <sub>2</sub> /2.0	Toluene	70	19
6	Mn(acac) <sub>3</sub> /2.0	Toluene	70	38
7	Mn(OAc) <sub>3</sub> /2.0	Toluene	70	63
8	Mn(OAc) <sub>3</sub> /2.0	DCE	70	62
9	Mn(OAc) <sub>3</sub> /2.0	CH <sub>3</sub> CN	70	47
10	Mn(OAc) <sub>3</sub> /2.0	THF	70	46
11	Mn(OAc) <sub>3</sub> /2.0	DMF	70	Trace
12	Mn(OAc) <sub>3</sub> /2.0	1,4-Dioxane	70	53
13	Mn(OAc) <sub>3</sub> /2.0	CH <sub>3</sub> OH	70	Trace
14	Mn(OAc) <sub>3</sub> /3.0	Toluene	70	73
15	Mn(OAc) <sub>3</sub> /3.0	Toluene	90	70
16	Mn(OAc) <sub>3</sub> /3.0	Toluene	50	73
17	Mn(OAc) <sub>3</sub> /3.0	Toluene	40	80
18	Mn(OAc) <sub>3</sub> /3.0	Toluene	25	67

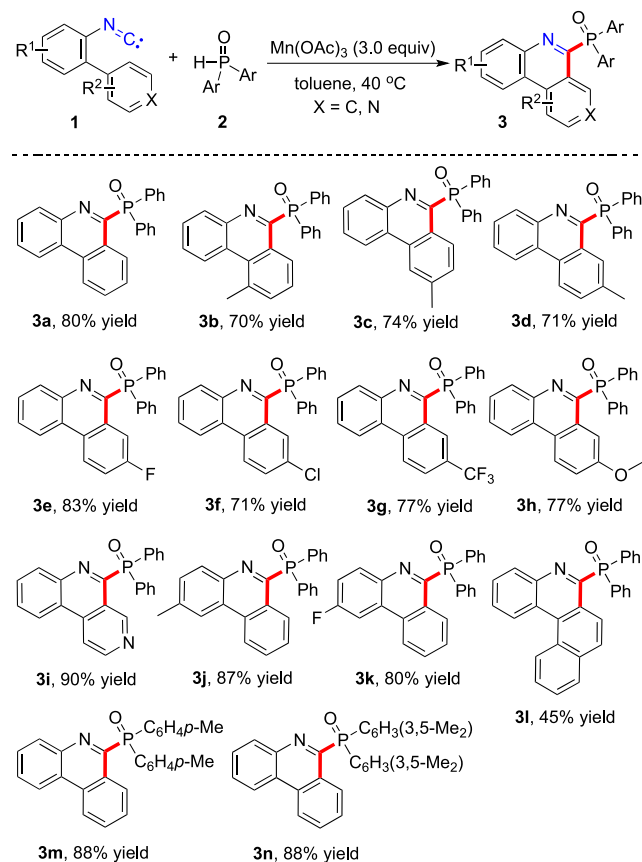
<sup>a</sup> Isolated yield based on 2-isocyanobiphenyl **1a**.

improved by switching the additive to Ag<sub>2</sub>CO<sub>3</sub>, or PhI(OAc)<sub>2</sub> (Table 1, entries 2 and 4). To our delight, the expected phosphonated phenanthridine **3a** was obtained when anhydrous Cu(OAc)<sub>2</sub> or silver(I) acetate was used as an additive (Table 1, entries 3 and 5). Further evaluation found that Mn(OAc)<sub>3</sub> was the best choice, leading to the desired product **3a** in 63% yield (Table 1, entry 7). Other solvents were examined subsequently (Table 1, entries 8–13). However, no better yields were afforded, and toluene was still the most efficient one. The loading of additive made great impact on the outcome, and the desired product **3a** was isolated in 73% yield when the amount of Mn(OAc)<sub>3</sub> was increased to 3.0 equiv (Table 1, entry 14). The reaction temperature was evaluated as well. Gratifyingly, a satisfied yield (80%) was obtained when the reaction was conducted at 40 °C (Table 1, entry 17).

After obtaining the optimized reaction conditions, we started to explore the substrate scope of this transformation. The results are shown in Table 2. The 2-isocyanobiphenyls **1** bearing either electron-rich or electron-deficient substituents on the aromatic ring were all compatible under the standard conditions, and the expected phenanthridin-6-ylidiphenylphosphine oxides **3** were afforded in good yields. The reaction proceeded with excellent regioselectivity. For example, compound **3c** was generated exclusively when the 2-isocyanobiphenyl **1c** with two non-equivalent *ortho* hydrogen atoms was employed. Additionally, 4-(2-isocyanophenyl)pyridine **1i** and 1-(2-isocyanophenyl)naphthalene **1l** were suitable substrates as well in this annulation reaction. Moreover, other diarylphosphites were used in the reaction, and the corresponding products (**3m** and **3n**) were furnished in good yields.

**Table 2**

Synthesis of phenanthridin-6-ylidiphenylphosphine oxides **3** by oxidative cyclization of 2-isocyanobiphenyls **1** with diphenylphosphine oxides **2**<sup>a</sup>



<sup>a</sup> Isolated yield based on 2-isocyanobiphenyl **1**.

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