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Silver-catalyzed 2-isocyanobiaryls insertion/cyclization with phosphine oxides: synthesis of 6-phosphorylated phenanthridines

Jia-Jia Cao, Tong-Hao Zhu, Zheng-Yang Gu, Wen-Juan Hao, Shun-Yi Wang *, Shun-Jun Ji *

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

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ABSTRACT

A silver-catalyzed 2-isocyanobiaryls insertion/cyclization with phosphine oxides was described for the construction of the 6-phosphorylated phenanthridines through radical addition of in situ formed P-centered radical to 2-isocyanobiphenyls and homolytic aromatic substitution process. The reactions could proceed smoothly to give the desired 6-phosphorylated phenanthridines promoted by AgOAc (20 mol %) with $PhI(OAc)_2$ (3.0 equiv).

1. Introduction

Isocyanides have been used as useful building blocks for the synthesis of broad varieties of peptides and peptide mimetics based on the pioneer Ugi reaction.[1] With the new development of isocyanide chemistry, it got a renaissance during the past 15 years.[2] New isocyanide-based multicomponent reactions, transition-metal-catalyzed isocyanide insertion reaction, and somophilicisocyanide insertion reaction have become increasingly popular.[3–5] Phenanthridine derivatives are very important core scaffolds with versatile biological activities such as anti-bacterial, cytotoxic, DNA intercalator, and antitumoral (Fig.1). The remarkable biological profiles stimulated people to explore efficient methods for the synthesis of these compounds.[6] Recently, Chatani's group has reported the synthesis of phenanthridine derivatives by $Mn(acac)_3$ mediated annulation of 2-isocyanobiphenyls with arylboronic acid.[7] Studer's group[8] and Zhou's group[9] have independently reported the formation of 6-trifluoromethyl-phenanthridines through radical trifluoromethylation of 2-isocyanobiphenyls. It's interesting that Yu and co-workers have reported the synthesis of 6-alkylated phenanthridines through photoredox neutral isocyanide insertions almost at the same time.[10]

Yang's group has reported that silver salt could catalyze carbon–phosphorus functionalization of alkenes to synthesis of phosphorylated oxindoles through the in situ generated $Ph_2P(O)Ag$ from $Ph_2P(O)H$.[11] Almost at the same time, Duan group has reported the silver-promoted oxidative C–H/P–H functionalization of arylphosphine oxides with internal alkynes.[12] More recently, Studer's group and Yang's group have reported excess Ag-mediated 2-isocyanobiaryls insertion reactions with phosphine oxides, independently.[13] However, these conditions utilizing stoichiometric amounts of silver salts as the radical initiator and oxidant limited their applications. As a continuation of our works on the construction of 6-alkyl phenanthridines by *tert*-butyl benzoperoxoate

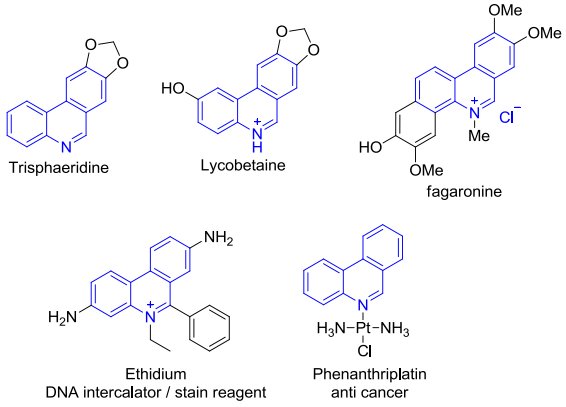

Fig. 1. Selected phenanthridine derivatives.

* Corresponding authors. E-mail addresses: shunjun@suda.edu.cn, chemjsj@suda.edu.cn (S.-J. Ji).

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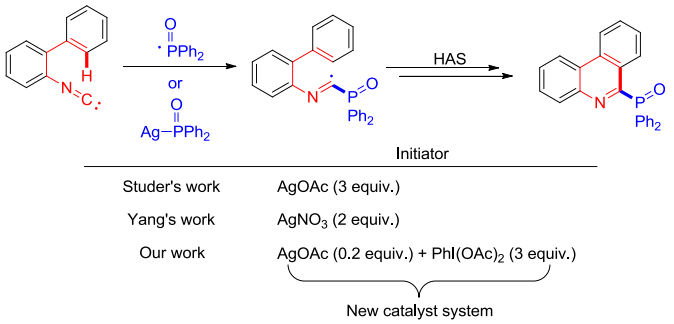
(TBPB) mediated 2-isocyanobiaryls insertion with 1,4-dioxane[14] and a novel phosphinylation of α,α-diarylallylic alcohols via 1,2-aryl migration of an aryl group,[15] herein, we disclose the construction of 6-phosphorylated phenanthridines by 2-isocyanobiaryls insertion/cyclization with phosphine oxides utilizing a catalytic amount of AgOAc in the presence of $PhI(OAc)_2$ (Scheme 1).

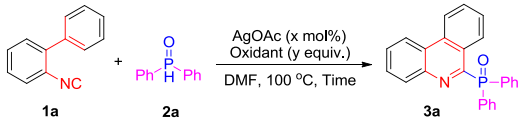


Scheme 1. Phenanthridines synthesis via somophilicisocyanide insertion.

2. Results and discussion

Our initial efforts were focused on using a catalytic amount of AgOAc in the presence of different simple oxidants (Table 1). Excitingly, when the model reaction of **1a** with **2a** catalyzed by 20 mol % AgOAc in the presence of 2.0 equiv $K_2S_2O_8$, the desired product **3a** could be obtained in 34% LC yield (Table 1, entry 1), which was further confirmed by X-ray analysis (Fig. 2). This

Table 1
Screening of reaction conditions in the presence of a catalytic amount of AgOAc[a]



1a 2a 3a

Entry	Cat. (mol %)	Oxidant (equiv)	Time (h)	Yield[b] (%)
1	AgOAc (20)	$K_2S_2O_8$ (2)	3	34
2	AgOAc (20)	$PhI(OAc)_2$ (2)	3	57
3	AgOAc (20)	O_2 (1 atm)	3	29
4	AgOAc (20)	TBHP (2)	3	51
5	AgOAc (20)	TBPB (2)	3	47
6	AgOAc (20)	DTBP (2)	3	33
7	AgOAc (20)	CHP (2)	3	38
8	AgOAc (20)	BQ (2)	3	7
9	AgOAc (20)	TEMPO (2)	3	23
10	AgOAc (20)	$Zn(NO_3)_2·6H_2O$ (2)	3	47
11	AgOAc (20)	$Zn(OAc)_2·H_2O$ (2)	3	36
12	AgOAc (20)	$ZnCl_2$ (2)	3	40
13	AgOAc (20)	ZnO (2)	3	42
14	AgOAc (20)	$Cu(OAc)_2·H_2O$ (2)	3	33
15	AgOAc (20)	$Cu(NO_3)_2·H_2O$ (2)	3	30
16	AgOAc (20)	$PhI(OAc)_2$ (1)	3	56
17	AgOAc (20)	$PhI(OAc)_2$ (3)	3	73
18	AgOAc (15)	$PhI(OAc)_2$ (3)	3	66
19	AgOAc (10)	$PhI(OAc)_2$ (3)	3	54
20	AgOAc (5)	$PhI(OAc)_2$ (3)	3	49
21	AgOAc (0)	$PhI(OAc)_2$ (3)	3	41
22[c]	AgOAc (20)	$PhI(OAc)_2$ (3)	3	52
23[d]	AgOAc (20)	$PhI(OAc)_2$ (3)	3	25
24	*AgOAc (20)*	*$PhI(OAc)_2$ (3)*	*3.5*	*83(61[e])*

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (2.5 equiv), catalyst, and oxidant in DMF (2 mL) with stirring at 100 °C under argon.
[b] Yields were determined by LC with an internal standard (benzophenone) as the ratio between the formed products and the initial amount of limiting reactant.
[c] Under O_2 atmosphere.
[d] Et_3N as solvent.
[e] Isolated yield.

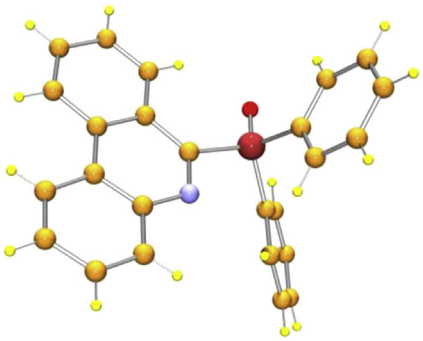
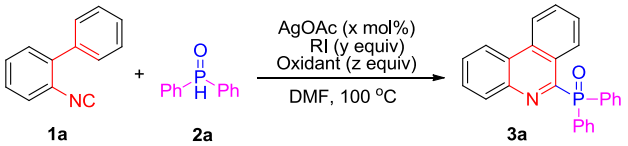


Fig. 2. Crystal structure of **3a**.

promising results push us to try the reaction utilizing other different oxidants such as $PhI(OAc)_2$, O_2, BQ, TEMPO, as well as $Cu(OAc)_2·H_2O$ (Table 2, entries 1–15). The screening results indicated that $PhI(OAc)_2$ (2.0 equiv) was the best oxidant, which leading to **3a** in 57% LC yield (Table 1, entry 2). Further screening of the amount of AgOAc and $PhI(OAc)_2$ established the competitive optimized condition (Table 1, entries 16–21). Compound **3a** could be formed in 73% LC yield catalyzed by 20 mol % AgOAc in the presence of 3.0 equiv $PhI(OAc)_2$ (Table 1, entry 17). When the reaction was conducted under O_2 atmosphere, it was found that **3a** could be produced in only 52% LC yield (Table 1, entry 22). Notably, when the reaction was carried out in an increased time, 83% LC yield of **3a** could be obtained (61% isolated yield) (Table 1, entry 24).

Table 2
Screening of reaction conditions (in situ oxidation of iodo(I)arenes to iodine(III) species)[a]



1a 2a 3a

Entry	Cat. (mol %)	RI (equiv)	Oxidant (equiv)	Yield[b] (%)
1	AgOAc (20)	—	AcOOH (3)	34
2	AgOAc (20)	PhI (1)	AcOOH (3)	45
3	AgOAc (20)	PhI (1)	*m*-CPBA (3)	Trace
4	AgOAc (20)	DIBP (1)	AcOOH (3)	44
5	AgOAc (20)	PhI (1)	AcOOH (2)	39
6	AgOAc (20)	PhI (1)	AcOOH (6)	29
7[c]	*AgOAc (20)*	*PhI (1)*	*AcOOH (3)*	*48*
8[d]	AgOAc (20)	PhI (1)	AcOOH (3)	41
9[c]	AgOAc (20)	PhI (0.1)	AcOOH (3)	37

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (2.5 equiv), AgOAc (20 mol %), RI, and oxidant in DMF (2 mL) with stirring at 100 °C under argon for 3.5 h.
[b] Yields were determined by LC with an internal standard (benzophenone) as the ratio between the formed products and the initial amount of limiting reactant.
[c] The mixture of PhI and AcOOH was stirred for 10 min, then the others were added.
[d] The mixture of PhI and AcOOH was stirred for 30 min, then the others were added. DIBP=2,2′-diiodo-1,1′-biphenyl.

In the light of literature, (diacetoxy)iodobenzene can be achieved by in situ oxidation of iodo(I)arenes to iodine(III) species. We have also tried the reaction in the presence of 1 equiv PhI and 3 equiv peracetic acid instead of 3.0 equiv $PhI(OAc)_2$ (Table 2). To our delight, the desired product **3a** could be formed in up to 48% LC yield (Table 2, entry 7), even the yield is lower than the yield of the reaction utilizing $PhI(OAc)_2$.

With the optimal conditions in hand, we investigated the scope of various substrates. The results are listed in Table 3. Firstly, the 2-isocyanobiaryl substrates **1** bearing electron-withdrawing or