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Silver-mediated radical 5-*exo-dig* cyclization of 2-alkynylbenzonitriles: Synthesis of phosphinylated 1-indenones

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A new silver-mediated 5-*exo-dig* cyclization of 2-alkynylbenzonitriles with disubstituted phosphine oxide and H_2O has been developed. The reaction enables multiple bond-forming events including C–P, C–C and C–O bonds under air conditions, leading to the concise and direct formation of 28 examples of phosphorus-containing 1-indenones with generally good yields.

Functional 1-indenones are ubiquitous substructure in natural products (Figure 1, type I)[1] and synthetically bioactive molecules (Figure 1, type II and III),[2] which display a broad spectrum of extraordinary biological and pharmaceutical properties[3] and also behave as key intermediates in the preparation of natural products[4] and pharmaceuticals.[5] Consequently, substantial efforts have been made to develop powerful and reliable methods for the construction of indenone frameworks. Known procedures for indenone formation include traditional intramolecular Friedel–Crafts acylations,[6] Grignard reactions,[7] and Heck–Larock annulation[8] and related process[9] as well as recently well-developed metal-catalyzed C(sp^2)–H activation of arenes.[10] Besides, Zhang and Zhou et al. reported manganese(III)-mediated phosphonation-cyclization of ynones for 1-indenone preparation (Scheme 1a).[11a,b] Despite these significant advances achieved in this field, new protocols for the assemble of diverse functionalized indenones with readily available substrates under mild conditions are still highly desirable.[11c,d]

Meanwhile, organophosphorus compounds have been extensively utilized in organic synthesis, medicinal chemistry, and materials science.[12] Their synthesis has been attracted considerable attention. Specifically, P-centered radical-triggered addition to unsaturated systems provides direct and

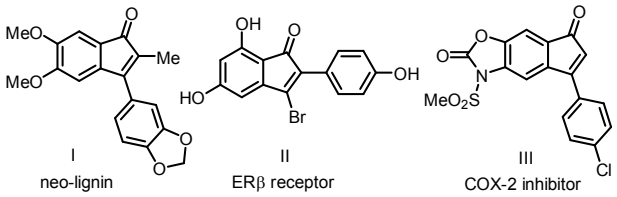
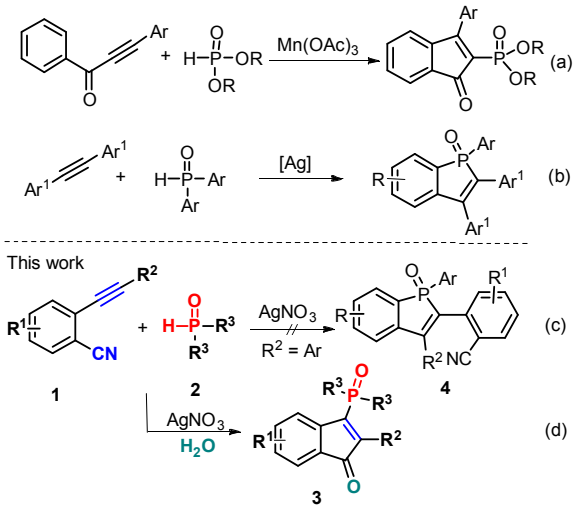


Figure 1. Some bioactive 1-indenone derivatives



Scheme 1. Profiles for P-centered radical-triggered cyclization

atom economic approaches toward organophosphorus compounds with good functional group compatibility.[13] Among them, di-substituted phosphine oxide radicals, in situ generated from HP(=O)R^1R^2 precursor, have exhibits high reactivity with unsaturated bonds and gradually become an ideal radical partner for forming organophosphorus compounds.[14] For instance, Miura[14a] and Duan[14b] et al. independently reported the Ag-mediated arylphosphine oxide radical cyclization of symmetrical diarylalkynes for the direct preparation of benzo[*b*]phosphole oxides (Scheme 1b). On the basis of these studies, we questioned whether the reaction selectivity could be harnessed to establish a regioselective [3+2] cyclization by using unsymmetrical diarylalkynes (Scheme 1c). Interestingly, we found the expected

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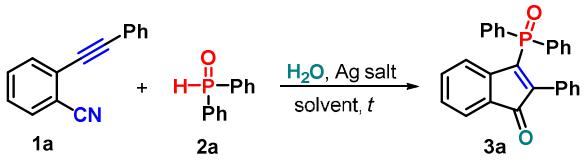
benzo[*b*]phosphole oxides cannot be generated as we originally planned. Instead, unexpected Ag-mediated 5-*exo-dig* cyclization occurred under oxidative conditions in the presence of water, leading to the direct formation of 3-phosphoryl 1-indenones in a functional-group compatible manner (Scheme 1d). To the best of our knowledge, this arylphosphine oxide radical-induced carbocyclization of 2-alkynylbenzonitriles for the construction of 1-indenones is virtually unexplored so far. Herein, we would like to elaborate this interesting transformation. This protocol represents the first domino procedure for the direct synthesis of these new 3-phosphorylinden-1-ones through a mild Ag-mediated carbonylphosphinylation of internal alkynes.

Table 1. Optimization of Reaction Condition for Product 3a[a]



entry	Ag salts (equiv)	solvent	*t* /(°C)	yield (%)[b]
1	$AgNO_3$ (2.0)	CH_3CN	80	42[c]
2	$AgNO_3$ (2.0)	CH_3CN	80	67
3	AgTFA (2.0)	CH_3CN	80	20
4	Ag_2CO_3 (2.0)	CH_3CN	80	NR[d]
5	AgOAc (2.0)	CH_3CN	80	trace
6	Ag_2O (2.0)	CH_3CN	80	NR
7	$AgNO_3$ (1.5)	CH_3CN	80	48
8	$AgNO_3$ (2.5)	CH_3CN	80	51
9	$AgNO_3$ (2.0)	DCE	80	40
10	$AgNO_3$ (2.0)	DCM	80	33
11	$AgNO_3$ (2.0)	1,4-dioxane	80	52
12	$AgNO_3$ (2.0)	THF	80	trace
13	$AgNO_3$ (2.0)	MeOH	80	40
14	$AgNO_3$ (2.0)	EtOH	80	38
15	$AgNO_3$ (2.0)	CH_3CN	100	43
16	$AgNO_3$ (2.0)	CH_3CN	70	31
17	$AgNO_3$ (2.0)	CH_3CN	80	36[e]
18	$AgNO_3$ (2.0)	CH_3CN	80	44[f]
19	$AgNO_3$ (0.1)	CH_3CN	80	37[g]
20	$AgNO_3$ (0.1)	CH_3CN	80	26[h]
21	$AgNO_3$ (0.1)	CH_3CN	80	35[i]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), Ag salt (X equiv), solvent (1.5 mL) and water (0.5 mL) for 4.0 hours, air conditions. [b]Isolated yield of product **3a** based on **1a**. [c]Without additional water. [d]NR= No reaction. [e]The ratio of **1a**:**2a** in 1:3. [f]The ratio of **1a**:**2a** in 1:5. [g]Use of TBHP (2.0 equiv). [h]Use of DTBP (2.0 equiv). [i]Use of O_2 (1.0 atm).

Initially, 2-(phenylethynyl)benzonitrile (**1a**) and diphenylphosphine oxide (DPPO, **2a**) were selected as the model substrates to identify the optimal reaction conditions, with different silver salts as radical promoters and acetonitrile (CH_3CN) as the solvent. The results are summarized in Table 1. In the presence of 2.0 equivalents of silver nitrate, the reaction at 80 °C generated the unexpected 1-indenone product **3a** in 42% yield (Table 1, entry 1). Obvious improvement in the yield of **3a** was achieved (67%) when the co-solvent of CH_3CN and H_2O was used as reaction media (entry 2), indicating water could facilitate this radical transformation. Other attempted silver salts like silver trifluoroacetate (AgTFA), silver carbonate (Ag_2CO_3), silver acetate (AgOAc) and silver oxide (Ag_2O) all showed a lower catalytic capability and gave unsatisfactory results (entries 3-6). A decrease of the loading of silver nitrate resulted in a remarkably dropped yield of **3a** and the similar outcome was observed with increase of the amount of silver nitrate (entries 7-8). Next, the investigation of the solvent effect revealed that other aprotic solvents, such as 1,2-dichloroethane (DCE), dichloromethane (DCM), 1,4-dioxane, THF, MeOH, and ethanol (EtOH) proved to be far less effective than CH_3CN. Besides, the reaction efficiency shows an important dependency on temperature. A lower conversion was observed with the reaction temperature at either 70 °C or 100 °C (entry 2 vs. entries 15 and 16). Changing the substrate ratio to 1:3 or 1:5 did not improve the reaction process (entries 17 and 18). Next, we attempted to combine the catalytic amount of $AgNO_3$ and additional oxidants such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP) and O_2[15] to improve the reaction efficiency (entries 19-21). The results revealed that all these attempts did not show any improvements with respect to the reaction yield.

Having the optimized conditions in hand (Table 1, entry 2), we next investigated Ag-mediated 5-*exo-dig* cyclization of various alkynes with disubstituted phosphine oxide to evaluate the generality of the methodology. Upon repeating the reaction with diphenylphosphine oxide (**2a**), substrates **1** with different functional groups on the arylalkynyl moiety all work well, efficiently delivering the corresponding functionalized inden-1-ones **3** with yields ranging from 54% to 76%. A variety of substituents on the aryl ring of the arylalkynyl moiety, such as fluoro (**1b**), chloro (**1c-d**), bromo (**1e**), methyl (**1f-g**), ethyl (**1h**), *t*-butyl (**1i**), and methoxy (**1j-1k**, PMP = *p*-methoxyphenyl) groups, can tolerate the oxidative conditions well. Generally, substrates bearing electron-poor groups showed better reactivity and higher yields than electron-donating ones. Alternatively, a sterically encumbered 4-chloronaphthalen-1-yl (4-ClNp) counterpart was proven to be a suitable reaction component, which underwent a similar diarylphosphine oxide-enabled cyclization process toward 1-indenone **3l** in 61% yield. However, an *n*-butyl substrate **1m** proved to be ineffective for this reaction, which may be caused by its relative instability of the vinyl radical intermediate. Next, we evaluated the electronic nature of the internal arene ring of 2-alkynylbenzonitriles. Different substituents like methyl, fluoro and chloro located at the 4- or 5-position of benzonitrile ring were compatible in these radical cyclization reactions, and the corresponding inden-1-ones **3n-x** were afforded in 50%-73% yields. Regarding the scope of diaryl phosphine oxides, besides phenyl substrate, 4-methyl (**2b**) and 3,5-dimethylphenyl (**2c**) analogue could also be accommodated, thus confirming the reaction efficiency, as 1-indenones **3y-3bb** were generated in good yields. Additionally, the reaction is also applicable to

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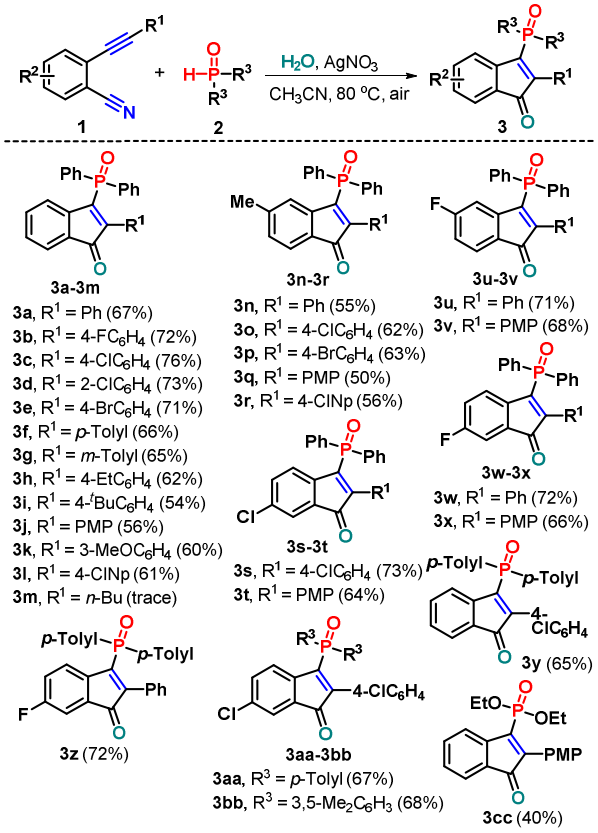
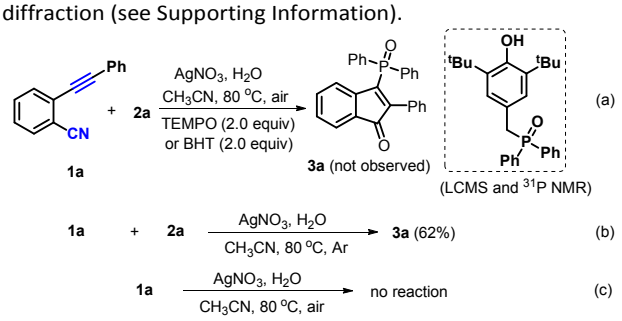
diethyl phosphite, delivering the corresponding product **3cc** in 40% yield. Obviously, the current radical 5-*exo-dig* cyclization can tolerate structurally distinct substrates with steric bulk and a different electronic property, which provides a straightforward and practical pathway for forming richly decorated 1-indenones with generally good yields



Scheme 2. Synthesis of 3-phosphoryl 1-Indenones (*i*) Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $AgNO_3$ (0.4 mmol), H_2O (0.5 mL), and CH_3CN (1.5 mL) in the seal reaction tube under air conditions at 80 °C for 4.0 hours. (*ii*) Isolated yields based on **1**.

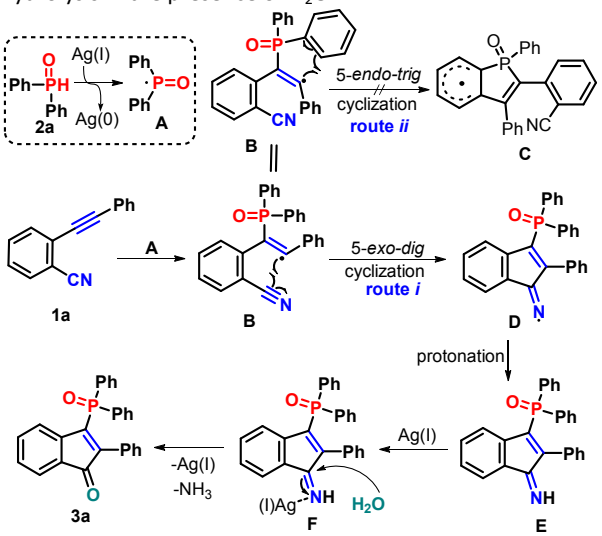
The structures of the resulting 1-indenones **3** were determined by carrying out their NMR and HRMS analysis. Furthermore, in the case of **3f**, its structure was further confirmed by X-ray diffraction (see Supporting Information).



Scheme 3. Control experiments

To gain mechanistic insight of this transformation, $AgNO_3$-mediated reaction of **1a** with **2a** in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylhydroxytoluene (BHT), a radical scavenger, were performed under the standard condition (Scheme 3a), but no expected product **3a** was observed. Among them, a BHT-P adduct was detected by LC-MS and ^{31}P NMR analysis,[16] indicating the reaction involves a radical mechanism. Subsequently, the reaction was carried out under Ar conditions to access a 62% yield of **3a** (Scheme 3b), suggesting that oxygen atom at the carbonyl unit comes from water. The reaction of **1a** did not work without DPPO (**2a**) under the standard conditions, showing that phosphine oxide radicals triggered 5-*exo-dig* cyclization (Scheme 3c).

On the basis of above observations and the literature survey,[14] a tentative mechanism for this transformation was proposed in Scheme 4. First, diphenylphosphine oxide (**2a**) reacts with $AgNO_3$ to form diphenylphosphine oxide radical **A** through a single electron transfer (SET).[14] After that, intermolecular addition of **A** into **1a** gives the alkenyl radical **B**, which undergoes 5-*exo-dig* cyclization to give intermediate **D** (route *i*) rather than 5-*endo-trig* cyclization to form intermediate **C** (route *ii*). The reason may be that the polarized triple bond (cyano group) favors as radical acceptor more than phenyl ring because of its easy π-band breaking.[17] Subsequently, the protonation of **D** occurs to yield intermediate **E**, which is converted into the target product **3a** *via* silver(I)-catalyzed hydrolysis in the presence of H_2O.[18]



Scheme 4. Plausible Reaction Pathway

In summary, we have developed a new P-centered radical-triggered addition-cyclization that offers a direct protocol toward phosphorus-containing 1-indenones *via* carbonylphosphinylation of 2-alkynylbenzonitriles. This transformation consists of P-centered radical addition, 5-*exo-dig* cyclization and hydrolysis process, resulting in the successive multiple bond-forming events including C–P, C–C and C–O bonds in a one-pot manner. This reaction features flexible structural modification, broad substrate scope and high functional group tolerance as well as mild reaction conditions. Currently, experiments toward further biological application are underway in our laboratory.

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Silver-mediated radical 5-*exo-dig* cyclization of 2-alkynylbenzonitriles: Synthesis of phosphinylated 1-indenones

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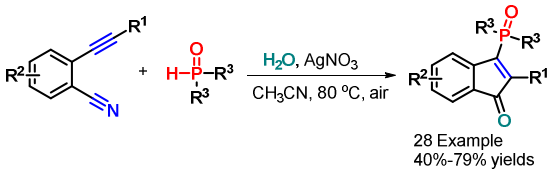

A new silver-mediated 5-exo-dig cyclization of 2-alkynylbenzonitriles with di-substituted phosphine oxide and H_2O has been developed.