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Silver-Promoted Oxidative Cyclization of 1,6-Enynes: Highly Regioselective Synthesis of Phosphorated Fluorene Derivatives

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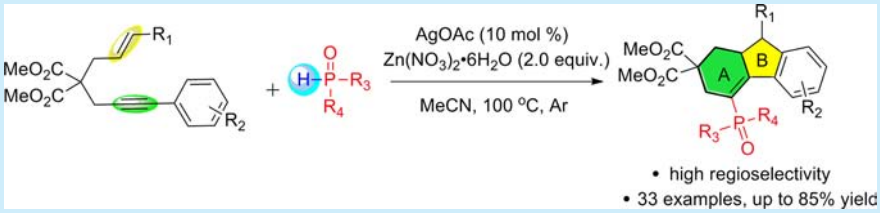
Supporting Information



ABSTRACT: A silver-promoted oxidative cyclization of 1,6-enynes with disubstituted phosphine oxides is developed for the synthesis of fluorene derivatives. The reaction proceeds with high regioselectivity by constructing one C−P bond and two C−C bonds in one step. Moreover, reduction of the pentavalent phosphine enlarges the application scope of the product.

Organophosphorus compounds occupy an important field in organic chemistry because of their varied applications in organic synthesis,[1] pharmacy chemistry,[2] and material science.[3] Among these compounds, the stable ones featuring a C−P(=O) bond have attracted considerable attention. Traditional synthesis methods include employing electrophilic reagents such as $POCl_3$,[4] $PhPCl_2$,[5] or Ph_2POCl[6] and transition-metal-catalyzed coupling reactions.[7] However, highly active substrates or harsh reaction conditions limit their application. Recently, with the development of radical chemistry, HP(=O)R_1R_2 has gradually become an ideal moderate radical precursor.[8] Since the phosphorus radical exhibits high reactivity with unsaturated bonds, it provides an alternative method to construct the C−P bond.

Oxidative radical aromatic cyclization represents a classical method for rapidly constructing cyclic compounds.[9] It avoids using prefunctional aromatic ring substrates or expensive transition metals and the condition could be mild, which shows excellent functional groups compatibility. Not long ago, our group had successfully applied this strategy to the synthesis of hydroxyl-containing oxindoles under metal-free conditions.[10] In the past two years, phosphorus radical participating oxidative aromatic cyclization reaction experienced great development. Yang,[11] Zou,[12] and Wu[13] reported aromatic cyclization with intramolecular alkenes and alkynes, respectively. Studer et al. extended this process by employing isocyanide as a radical acceptor.[14] In the meantime, Duan[15] and Miura[16] developed a simple method to synthesize benzo[*b*]phosphole oxides. But to date, oxidative radical cyclization of 1,6-enynes containing a P-radical has rarely been reported,[17] partly due to the radical being easily captured during the long process and its poor addition selectivity toward alkenyl and alkynyl. Thus, regioselective addition with 1,6-enynes accompanied by radical cyclization is highly challenging. Here, we describe the first example of phosphorus radicals participating in the oxidative cyclization reaction of 1,6-enynes to synthesize fluorene derivatives, which are present in many pharmaceutical compounds and functional materials[18] (Scheme 1).

As an electronic-rich radical, the regioselectivity of a phosphorus radical with enynes was determined by different nucleophilicity toward two radical acceptors.[19] Thus, we chose moderate nucleophile radical precursor diphenylphosphine oxide **2a** and 1,6-enyne **1a** as our model substrates. The reaction was carried out in the presence of 2.0 equiv of $AgNO_3$ in MeCN at 100 °C under argon. Gratifyingly, regioselective addition starting from the less hindered side of alkynyl completed after 24 h and **3a** was isolated in 51% yield (Table 1, entry 1). Encouraged by this result, we further tested solvents and metal salts (see Supporting Information). The result indicated that AgOAc (3.0 equiv) and MeCN could remarkably improve the yield to 71% (Table 1, entries 2−6). It is worth noting that $Fe_2(SO_4)_3$ could also promote the reaction smoothly, which was rarely reported before.[11,15] Considering the cost of silver salt, we tried to decrease its loading by using an additive. To our delight, when $Mg(NO_3)_2{\cdot}6H_2O$ was employed, only a catalytic amount of AgOAc was necessary to finish the total conversion, though the yield was just 52% (Table 1, entry 7). After screening other nitrates and oxidants, we gained a higher yield of 81% with $Zn(NO_3)_2{\cdot}6H_2O$ (Table

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Scheme 1. Phosphorus Radical Participating in Oxidative Aromatic Cyclization Reaction

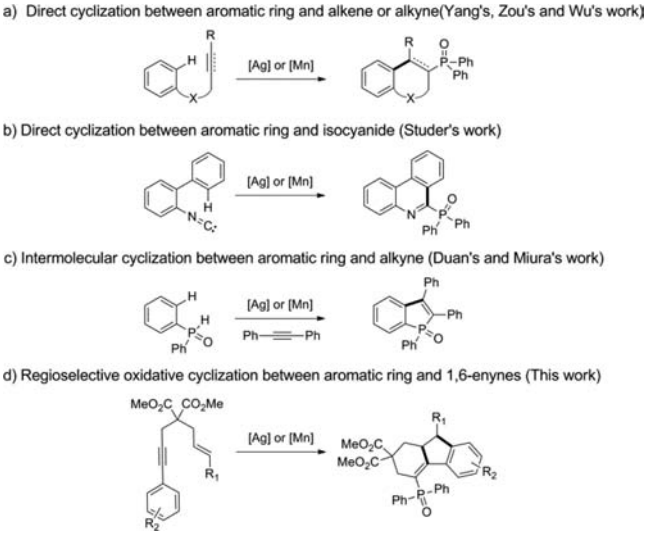
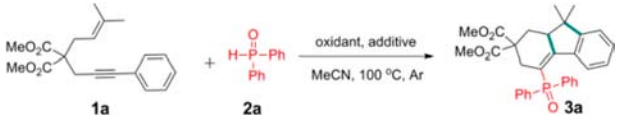


Table 1. Optimization of Reaction Conditions[a]



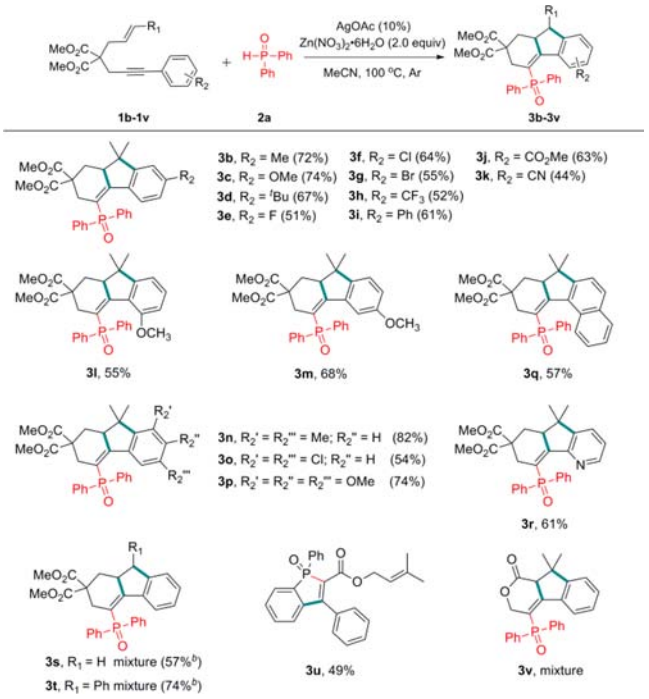
entry	oxidant (equiv)	additive (equiv)	yield[b] (%)
1	$AgNO_3$ (2.0)	–	51
2	Ag_2O (3.0)	–	62
3	AgOAc (3.0)	–	71
4	$CuSO_4$ (3.0)	–	55
5	CuF_2 (3.0)	–	44
6	$Fe_2(SO_4)_3$ (3.0)	–	46
7	AgOAc (0.2)	$Mg(NO_3)_2{\cdot}6H_2O$ (2.0)	52
8	AgOAc (0.2)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	81
9	AgOAc (0.2)	$K_2S_2O_8$ (2.0)	21
10	AgOAc (0.2)	BPO (2.0)	26
11	AgOAc (0.2)	TBHP (2.0)	trace
12	**AgOAc (0.1)**	**$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)**	**81**
13	AgOAc (0.05)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	64
14	AgOAc (0.1)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	54[c]
15	AgOAc (0.1)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	76[d]
16	AgOAc (0.1)	$Zn(NO_3)_2{\cdot}6H_2O$ (1.5)	61
17	AgOAc (0.1)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	47[e]
18	AgOAc (0.1)	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	67[f]
19	–	–	trace
20	–	$Zn(NO_3)_2{\cdot}6H_2O$ (2.0)	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), oxidant, and additive in anhydrous CH_3CN (3 mL) with stirring at 100 °C under argon for 24 h. [b]Isolated yield. [c]Under 110 °C. [d]Under 90 °C. [e]**2a** (0.45 mmol) was employed. [f]Under air.

1, entries 8–11). Contrast experiments demonstrated the reaction was subject to notable temperature and catalyst loading effects (Table 1, entries 12–15). A decrease in **2a** and nitrate negatively affected the yield (Table 1, entries 16–17). The reaction took place under air conditions as well, but the reactivity decreased significantly (Table 1, entry 18). Control experiments indicated $Zn(NO_3)_2{\cdot}6H_2O$ alone restrained the reaction completely (Table 1, entries 19–20). Finally, we confirmed the optimal conditions were AgOAc (10 mol %) and $Zn(NO_3)_2{\cdot}6H_2O$ (2.0 equiv) in 3 mL of MeCN at 100 °C under argon (Table 1, entry 12).

With the optimized reaction conditions in hand (Table 1, entry 12), we further explored the scope of substrates. As shown in Scheme 2, an investigation into different 1,6-enynes

Scheme 2. Scope of 1,6-Enynes[a]



[a]All the reactions were carried out with **1b–1v** (0.3 mmol), **2a** (0.6 mmol), AgOAc (0.03 mmol), and $Zn(NO_3)_2{\cdot}6H_2O$ (0.6 mmol) in anhydrous CH_3CN (3 mL) at 100 °C under argon for 24 h; all the yields refer to isolated product after chromatography with silica gel. [b]AgOAc (3.0 equiv) was employed without an additive.

showed that substrates with both electron-donating and -withdrawing groups on the *para*-position of the benzene ring reacted smoothly in moderate to good yields, and generally those bearing electron-donating groups were more favorable (**3b–3k**). With a substituent group at the *ortho*-position on the aromatic ring, the effect of the steric hindrance was very distinct and it produced a relatively lower yield (**3l**). To our delight, *meta*-OCH_3 substituted 1,6-enyne achieved a total regioselective reaction at the opposite position, probably because of the large obstacle posed by the terminal of vinyl (**3m**).[14] Several multisubstituted 1,6-enynes were also applied, and they all showed excellent tolerance (**3n–3p**). Other arenes such as naphthalene and pyridine proved to be good supplements (**3q–3r**). As an extension of our substrates, a variety of substituted olefins were tested. When two substituted methyls on olefin were removed or replaced by phenyl, mixture products were involved in the reaction system. To our surprise, the desired products **3s** and **3t** could be obtained in 57% and 74% yields when employing a stoichiometric amount of AgOAc. To enrich the style of ring structure, an ester group was inserted into 1,6-enyne. But unfortunately, we obtained a simple product **3u** without further cyclization, which may have been due to the ester group decreasing the eletrophilicity of the alkene. Moreover, α-vinyl esters were not an ideal choice and

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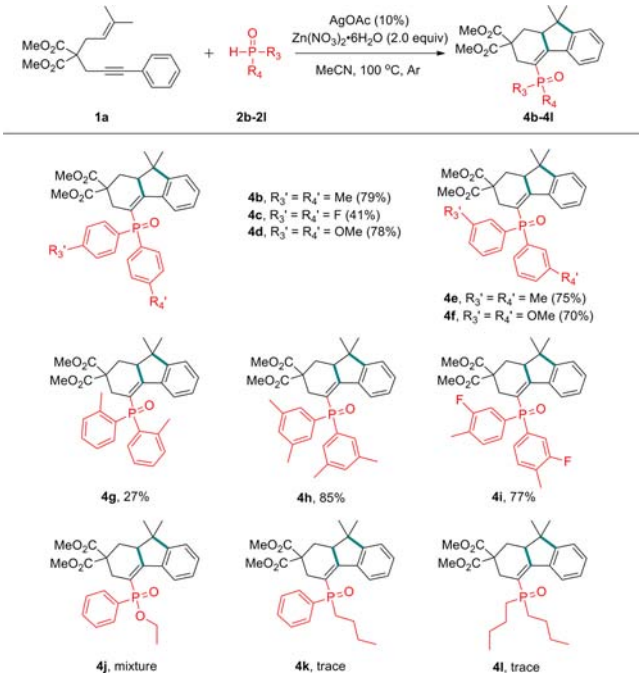
the mixture products indicated complex addition routes in this reaction system (**3v**).

The scopes of phosphonylations and phosphinylations were also examined. As shown in Scheme 3, for *para*- and *meta*-

Scheme 3. Scope of Phosphonylations and Phosphinylations[a]

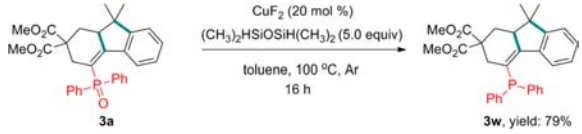


[a]All the reactions were carried out with **1a** (0.3 mmol), **2b**−**2l** (0.6 mmol), AgOAc (0.03 mmol), and $Zn(NO_3)_2{\cdot}6H_2O$ (0.6 mmol) in anhydrous CH_3CN (3 mL) at 100 °C under argon for 24 h; all the yields refer to isolated product after chromatography with silica gel.

substituted diphenylphosphine oxides, both electron-donating and -withdrawing groups gave the desired products in moderate to good yields (**4b**−**4f**). But due to the lower nucleophilicity of the phosphorus radical toward 1,6-enyne, an electron-withdrawing group such as fluorine gave a decreased yield relatively (**4c**). For *ortho*-methyl substituted diphenylphosphine oxide, it is noteworthy that the low nucleophilicity accompanying the decreased yield is somewhat relative to the degree of bend that affects the *s*-character of the phosphorus radical (**4g**).[19,20] Good yields were also obtained when two groups were present on the benzene ring (**4h**−**4i**). To clarify the relationship between the nucleophilicity of the phosphorus radical and regioselectivity, different phosphonylations and phosphinylations were applied to this reaction and the results were consistent with their nucleophilicity. Ethyoxyl-containing phosphonylation showed poor selectivity as its strong addition trend, which was determined by the electron-rich substituent and more bent *s*-character compared with diphenylphosphine oxide (**4j**), and *n*-butyl substituted phosphinylations reacted in trace amount as their nucleophilicity decreased toward alkenyl and alkynyl (**4k**−**4l**).

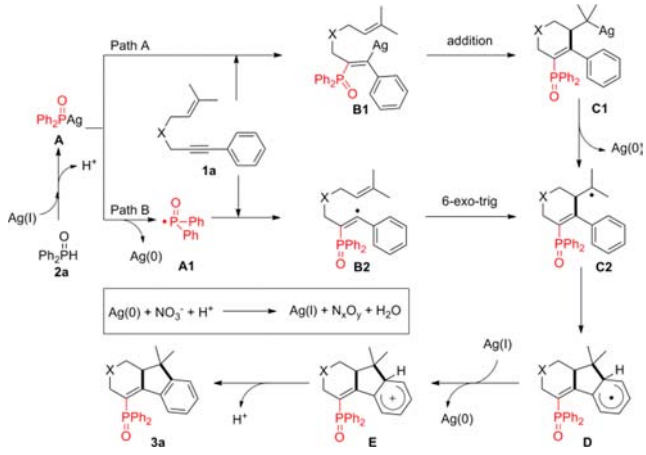
It is generally known that trivalent phosphines occupy a large part of phosphorus ligands and they are also pivotal intermediates widely employed in the synthesis of functionalized cyclic compounds.[21] Thus, it is of remarkable value to obtain trivalent phosphines from pentavalent ones. Herein, we successfully gained reductive product **3w** by using TMDS $[(CH_3)_2HSiOSiH(CH_3)_2]$ as a reductant and CuF_2 as a catalyst.[22] To our delight, the result embodied good chemoselectivity and ester groups were well retained under the strict conditions (Scheme 4).

Scheme 4. Reduction of Standard Product 3a



To gain further understanding about the reaction mechanism, inhibition experiments were carried out. When 2.2 equiv of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) were added into the reaction system, no desired product **3a** was detected. At the same time, 2.0 equiv of TEMPO could totally restrain the reaction when using 3.0 equiv of AgOAc. The above-mentioned results both indicate a SET (single electron transfer) process triggered by a free radical. According to previous reports on the phosphorus radical and our research on enyne cyclization,[23] a hypothetic mechanism is depicted in Scheme 5. First, diphenylphosphine oxide reacts with Ag(I) salt

Scheme 5. Proposed Mechanism



to form intermediate **A** under the standard conditions. After that, intramolecular addition of silver diphenylphosphine oxide to an alkyne and alkene followed by homolysis of the C−Ag bond generates the radical intermediate **C2** (Scheme 5, Path A). An alternative path is that intermediate **A** affords diphenylphosphine oxide radical **A1** directly. Next, the radical **A1** adds to 1,6-enyne **1a** regioselectively with a 6-exo-trig process to form **C2** (Scheme 5, Path B). Then its addition to the aromatic ring generates cyclohexadienyl radical **D**, and the product **3a** would be gained with a subsequent SET with Ag(I) salt as the oxidant followed by release of a proton. With the existence of NO_3^- and H^+, Ag(0) generated during the process could be oxidized to Ag(I) again in the reaction system, allowing the catalytic cycle to proceed smoothly.

Moreover, $Mn(OAc)_3$ was reported to be an appropriate oxidant that easily assists P-centered radicals to react with disubstituted phosphine oxides.[9b,14−16] Based on this reason, stoichiometric $Mn(OAc)_3{\cdot}2H_2O$ was employed in AcOH as a solvent at rt. Not surprisingly, the desired product was isolated in 58% yield (Scheme 6).

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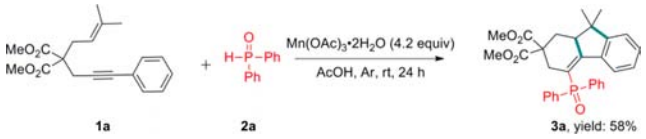
Scheme 6. Oxidative Cyclization of 1,6-Enynes Mediated by $Mn(OAc)_3 \cdot 2H_2O$



In summary, we have developed a silver(I) promoted oxidative cyclization of 1,6-enynes to regioselectively synthesize phosphorated fluorene derivatives with good yields in a simple, efficient way. The reaction was proven to proceed through an oxidative radical cyclization mechanism. Reduction toward the oxidic product led to trivalent phosphine, which implies great potential in application. Further studies of this procedure will focus on the detailed mechanism and application in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data and CIF information for **3a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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