Organic LETTERS

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Silver-Catalyzed Radical-Involved Cascade Cyclization of Diphenylphosphine with Cinnamamides: Access to 2-Phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles

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Supporting Information

ABSTRACT: A Ag-catalyzed phosphorus radical promoted cyclization of cinnamamides to give exclusively 2-phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles derivatives via a 5-endo-trig manner is described. This novel reaction leads to the simultaneous formation of C−C and C−P bonds in one step with excellent chemo- (only 5-endo) and diastereoselectivity (dr >20:1) under mild conditions in moderate to good yields.

Radical cascade reactions have emerged as a powerful strategy for the synthesis of versatile heteroatom compounds.[1] In this field, significant progress has been achieved in the chemistry of phosphorus radicals.[2] The advantage of this strategy lies in easily prepared starting materials, simple reactions conditions, and complex phosphorus-containing heterocyclic compounds which have potential applications in medicine, synthesis, and material science.[3] This protocol usually starts from a P-centered radical (which is usually generated from P(O)H compounds under oxidative condition) attacking unsaturated moieties, rendering a carbon radical intermediate, which is subsequently intramolecularly trapped by a nucleophile[4] or aromatic rings.[5] By means of this protocol, various novel phosphorus compounds which are difficultly synthesized by traditional methods could be easily achieved. For instance, Yang reported a silver-catalyzed difunctionalization of alkenes for the preparation of diphenylphosphoryl oxindoles in 2013.[6] Studer reported a reaction between phosphorus radicals and 2-isocyanobiphenyls, affording corresponding 6-phosphorylated phenanthridines.[7] Duan[8a] and Miura[8b] independently developed a Ag- or Mn-mediated phosphorus radicals addition to internal alkynes, furnishing an alkenyl radical, which was then trapped by the aromatic ring of diphenylphosphine oxide affording benzophosphole oxides scaffolds. Although phosphorus radical cascade reactions have been well developed and widely utilized in various transformations, challenges still remain in this area. Among them, finding appropriate radical initiators[9] and the design of new radical acceptors might be the key aspects.

On the other hand, the pyrrolo[1,2-*a*]indoles framework is a distinctive structure which widely exists in numerous natural products and bioactive drugs. Some representatives containing the pyrrolo[1,2-*a*]indoles core are listed in Figure 1.[10] Therefore, developing an efficient and versatile strategy to afford pyrrolo[1,2-*a*]indoles is highly desirable,[11] especially via a cascade radical approach because of the feasibility of building up the pyrrolo[1,2-*a*] indoles rings and introducing a new functional group in a one-pot strategy.[12]

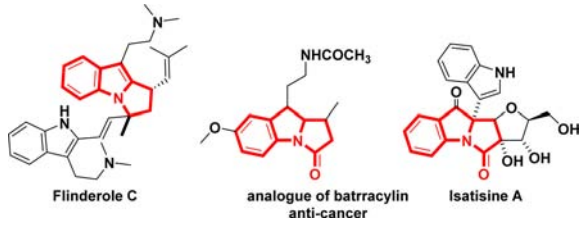


Figure 1. Representative examples of biologically active pyrrolo[1,2-*a*]indole derivatives.

A recent study suggests that when a radical reacts with α,β-unsaturated systems, attack at the α-position would be preferable compared to the β-position,[13] and a 6-membered ring was formed via a tandem intermolecular 6-endo-trig cyclization process.[14] Unlike previous results, herein we report a Ag-catalyzed highly selective phosphorus radical promoted synthesis of P-containing pyrrolo[1,2-*a*]indoles through 5-endo-trig cyclization; most remarkably, no any 6-endo-trig cyclization product was observed in our system (Scheme 1).

Our study was initiated by employing (*E*)-3-phenyl-1-(3-phenyl-1*H*-indol-1-yl)prop-2-en-1-one (**1a**) and diphenylphosphine oxide (**2a**) as model substrates (**1a**:**2a** = 2.5:1). When $AgNO_3$ (100 mol %) was chosen as the oxidant with CH_3CN as the solvent, **3a** was obtained in 60% yield at 100 °C under argon (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis, and only trans isomers were observed (Figure 2; also see Supporting Information (SI) for details). Encouraged by this result, we decreased the amount of $AgNO_3$ to 20 mol % and added $Mg(NO_3)_2{\cdot}6H_2O$ as an oxidant, which also afforded **3a** in 62% yield. Subsequently,

Received: December 14, 2016
Published: February 16, 2017

DOI: 10.1021/acs.orglett.6b03713
Org. Lett. 2017, 19, 980−983

Scheme 1. Radical Promoted Cyclization of Cinnamamides

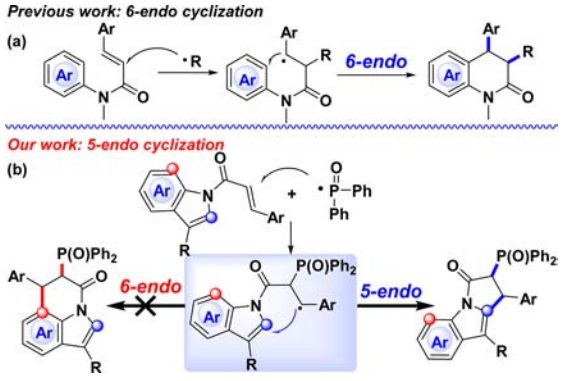
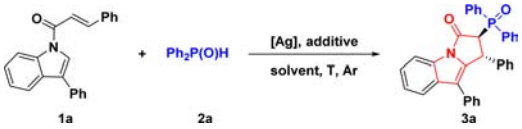


Table 1. Optimization of Reaction Conditions[a]



entry	cat. (mol %)	additive	solvent	yield (%)
1	$AgNO_3$ (100)	–	CH_3CN	60
2	$AgNO_3$ (20)	$Mg(NO_3)_2{\cdot}6H_2O$	CH_3CN	62
3	$AgNO_3$ (20)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	67
4	Ag_2CO_3 (20)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	55
5	Ag_2O (20)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	60
6	AgOAc (20)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	74
7	AgOAc (10)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	78
8	AgOAc (15)	$Zn(NO_3)_2{\cdot}6H_2O$	CH_3CN	72

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.75 mmol), additive (0.15 mmol) in solvent (2 mL) stirring at 100 °C under argon for 20 h. Yields of the isolated products.

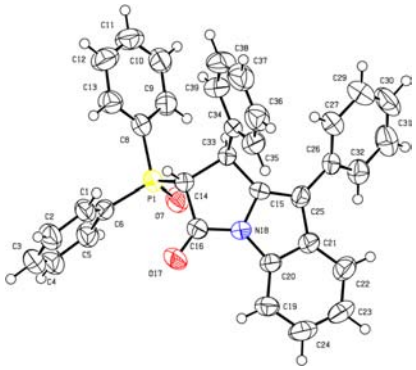
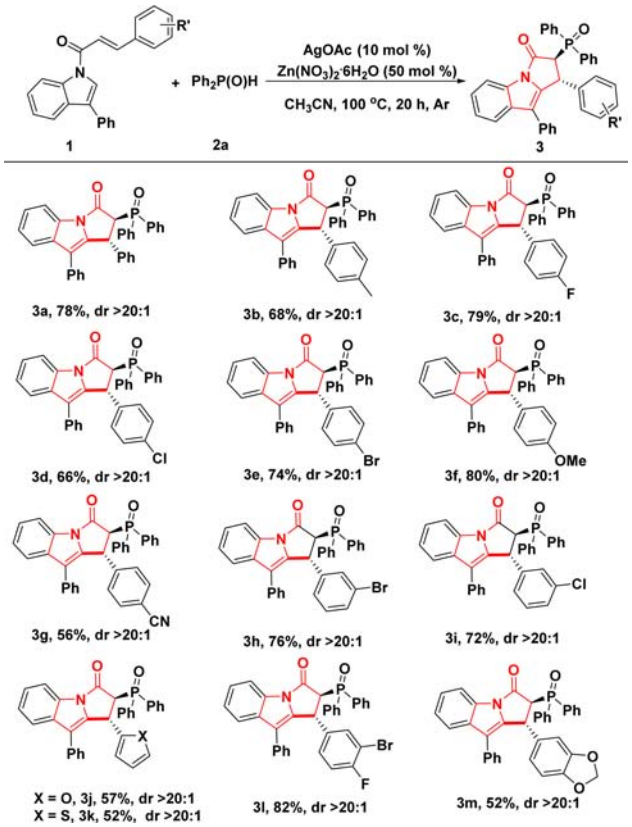


Figure 2. X-ray structure of **3a**.

different oxidants were investigated and $Zn(NO_3)_2{\cdot}6H_2O$ was found to be the most efficient one. Later, a variety of Ag salts, including Ag_2CO_3, Ag_2O, and AgOAc (Table 1, entries 4–6) were examined carefully, and AgOAc gave the best yield (74%). To our delight, the yield was increased to 78% when the catalyst loading was reduced to 10 mol % (Table 1, entry 7). Further solvent optimization showed that CH_3CN was the optimal solvent among THF, dioxane, and DCE (see SI for details). Increasing or decreasing the temperature just led to slightly decreased yields (see SI for details).

With the optimized reaction conditions in hand, a wide range of cinnamamides **1b**–**1m** were then examined with diphenylphosphine oxide (**2a**), and the results are summarized in Scheme 2.

Scheme 2. Scope of Cinnamamides[a]



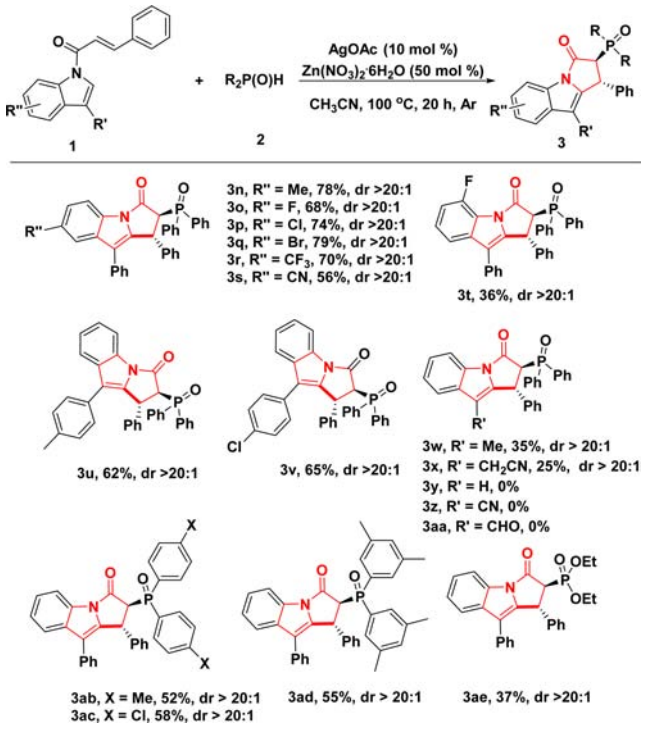
[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.75 mmol), AgOAc (10 mol %), $Zn(NO_3)_2{\cdot}6H_2O$ (0.15 mmol) in CH_3CN (2 mL) stirring under argon in 100 °C for 20 h.

In general, different substituents such as methyl, fluoro, chloro, bromo, and methoxy on *para* or *meta* or on both positions of phenyl rings proceeded smoothly, affording corresponding desired products in moderate to good yields (**3b**–**3f**, **3h**, **3i**, **3l**, and **3m**, 52%–82%) with high *dr* values. This result indicates that most substituents did not greatly affect the reaction. However, only a moderate yield (**3g**, 56%) was achieved when an electron-withdrawing substituent was utilized. In addition, compounds with furyl and thiophenyl could also react smoothly with **2a** to afford the desired products **3j** and **3k** in 57% and 52% yield.

The scope of indoles and diarylphosphine oxide was subsequently investigated as shown in Scheme 3. Aromatic rings of indoles bearing various substitutents such as Me, Fe, Cl, Br, CF_3 and CN were well tolerated to give the desired products (**3n**–**3v**) in 56–79% yields except for the 7-F substituent, which gave **3t** in 36% yield. It is of note that alkyl groups on the 3-position of indoles were also compatible under the standard conditions albeit with lower isolated yields (**3w** and **3x**). However, there was no desired product detected when R′ in **1** was H, which might be attributed to the less stable carbon radical intermediate. Similarly, indoles with electron-withdrawing substituents (e.g., CN, CHO) at the 3-position failed to afford the desired products. These results suggested that a carbocation intermediate may be involved in this reaction. Different P(O)H compounds were also examined; diphenylphosphine oxides bearing substituents such as *p*-Me, *p*-Cl, and 3,5-di-Me on the phenyl ring gave the corresponding pyrrolo-[1,2-*a*]indoles **3ab**–**3ad** in satisfactory yields. However, diethyl H-phosphonate reacted with **1a** to afford **3ae** only in 37% yield.

DOI: 10.1021/acs.orglett.6b03713
Org. Lett. 2017, 19, 980–983

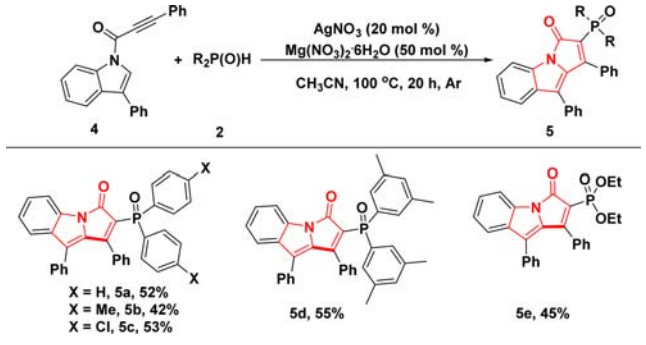
Scheme 3. Scope of Indoles and Diphenylphosphine Oxides[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.75 mmol), AgOAc (10 mol %), $Zn(NO_3)_2{\cdot}6H_2O$ (0.15 mmol) in CH_3CN (2 mL) stirring under argon in 100 °C for 20 h.

To our delight, propynamides were also competent substrates in this reaction. With a slight change in the conditions, the corresponding pyrrolo[1,2-*a*] indoles were obtained in acceptable yields (Scheme 4, **5a**−**5e**, 42%−55%).

Scheme 4. Reaction of Propynamide with 2[a]

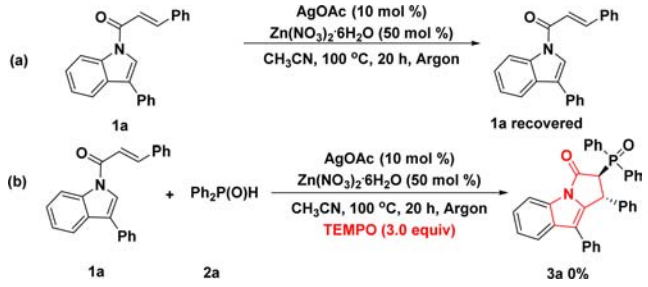


[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.75 mmol), $AgNO_3$ (20 mol %), $Mg(NO_3)_2{\cdot}6H_2O$ (0.15 mmol) in CH_3CN (2 mL) stirring under argon in 100 °C for 20 h.

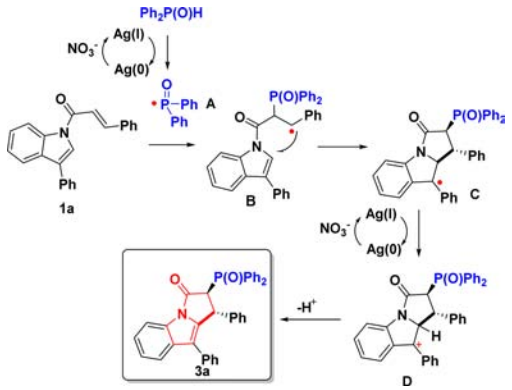
To gain mechanistic insights into the reaction, a series of control experiments were conducted (Scheme 5). When the reaction was carried out in the absence of diphenylphosphine oxide (**2a**), **1a** was almost completely recovered. When the radical scavenger TEMPO was added, none of **3a** was observed, indicating that the reaction might proceed through a radical pathway.

Based on all of the above-mentioned results and previous reports, a possible reaction pathway is described in Scheme 6. Initially, oxidation of diphenylphosphine oxide (**2a**) is catalyzed

Scheme 5. Control Experiments



Scheme 6. Proposed Mechanism



by Ag(I) via a single-electron transfer to afford the phosphorus-centered radical **A**. Subsequently, the addition of **A** across a C−C double bond in cinnamamide **1a** produces the radical intermediate **B**, which is further transformed to the radical intermediate **C** via intramolecular cyclization on C2 of the indole ring. After oxidation, carbocation intermediate **D** is obtained. Final deprotonation delivers the product **3a**.

In conclusion, we have successfully developed a Ag-catalyzed radical-involved cascade reaction between diphenylphosphine oxide and indole-based cinnamamides, providing direct access to various phosphorus-containing pyrrolo[1,2-*a*]indoles. This new tandem cyclization proceeds via a 5-endo-trig pathway instead of the well-known 6-endo-trig pathway. Additionally, this novel reaction leads to the simultaneous formation of C−C and C−P bonds in one step with excellent chemo- (only 5-endo)- and diastereoselectivity (dr >20:1) under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03713.

Experimental procedure, characterization data, copies of ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b03713
Org. Lett. 2017, 19, 980−983

■ ACKNOWLEDGMENTS

Global Experts (1000 Talents Plan), the Natural Science Foundation of Fujian Province (2016J01064), Fujian Hundred Talents Plan and Program of Innovative Research Team of Huaqiao University (Z14X0047), and China Postdoctoral Science Foundation (163633) are gratefully acknowledged. We also thank Instrumental Analysis Center of Huaqiao University for analysis support.

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DOI: 10.1021/acs.orglett.6b03713
Org. Lett. 2017, 19, 980−983