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Silver-Catalyzed Cascade Radical Cyclization for Stereoselective Synthesis of Exocyclic Phosphine Oxides

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A silver-catalyzed phosphorylation/cyclization radical cascade of 1,6-dienes has been developed. The reaction process involves in a one-pot operation described as an autotandem catalytic process with a cascading radical cyclization for the construction of C—P and C—C bond with high stereoselectivity. Moreover, it also affords an efficient method for the synthesis of valuable exocyclic phosphine oxides compounds with broad substrate applicability, mild reaction condition and succinct reaction system.

Keywords silver-catalyzed, cascade radical cyclization, 1,6-dienes, exocyclic phosphine oxides

Introduction

Organophosphorus compounds belong to an extremely important class of molecules that are increasingly gaining attention because of their unique bioactivities and inherent chemical properties. So they have been widely used in the fields of organic synthesis,[1] medicinal chemistry,[2] ligand synthesis,[3] and materials science.[4] In the past decades, research for the construction of C—P bond has attracted great attention, and considerable effort has been made.[5] The traditional methods for constructing C—P bond include various reactions involving in different electrophilic phosphorus reagents.[6] Transition-metal-catalyzed cross-coupling reactions of aryl halides, tosylates, triflates, boronic acids, or diazonium salts with H-phosphonates have also promised the most frequently used method.[7] However, general requirements on a specifically functionalized precursor or harsh reaction conditions often limit their applications. Recently, the cascade radical cyclization of olefin derivatives discloses a novel and efficient strategy for the synthesis of various heterocyclic compounds.[8] Thereinto, P-radical participating cascade cyclization reaction has been recognized as a powerful tool for rapidly constructing cyclic organophosphorus compounds and attracted considerable attention.[9] In general, an ideal P-radical which is often initiated from $HP(O)R^1R^2$ with Cu, Ag, Mn, and other oxidants exhibits high reactivity and provides direct means for C—P and C—X (X =C, N, O) bonds formation simultaneously with unsaturated bonds as starting materials characterized by high atom economy, excellent functional groups compatibility, and mild reaction conditions. Recently, our group firstly applied the P-radical to the cascade cyclization of olefin and has achieved the synthesis of the biologically active phosphorylated oxindoles and phosphorated indolines successfully.[10] Subsequently, Liang, Zhao, Zou, Cui, Wu and Zhu groups enlarge the P-radical to different intramolecular cascade cyclizations with alkenes and alkynes, respectively.[11] Moreover, Duan, Miura, Zhao, and Lakhdar groups have also adopted this strategy for the intermolecular cascade cyclizations to synthesize benzo[*b*]phosphole oxides.[12] In the meanwhile, our group and Studer *et al*. extend this tactic to the synthesis of α-phosphoryl quinolines by employing isocyanide as a radical acceptor.[13] But so far, cascade P-radical cyclization of 1,6-dienes has rarely been reported, possibly because the radical can be trapped or scavenged easily and resulted in poor reaction selectivity. Thus, stereoselective addition with 1,6-dienes accompanied by radical cyclization still has been considered a challenge. Herein, we wish to report a process with a cascade radical cyclization for the synthesis of valuable exocyclic phosphine oxides via C—P and C—C bond formation with high stereoselectivity (Scheme 1).

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker advance III 400 spectrometer in $CDCl_3$ with TMS as internal standard. ^{31}P NMR was recorded on the same

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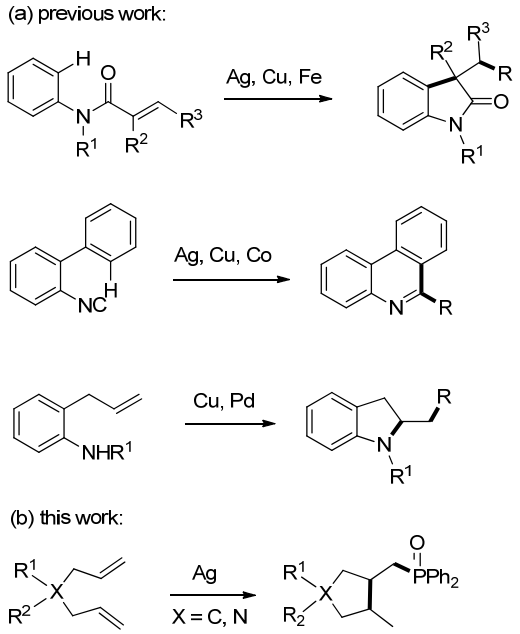
Scheme 1 Phosphorus radical participating in cascade cyclization reaction



instrument. Mass spectra were mearsured using Bruker microTOF-Q II MS and measured in EI or ESI mode. Solvents were dried and purified according to the procedure from "Purification of Laboratory Chemicals Book". Column chromatography was carried out on silica gel (particle size 200－400 mesh ASTM).

General procedure for the synthesis of exocyclic phosphine oxides (3aa－3qa, 3ab－3aj)

In a reaction tube, $Mg(NO_3)_2$•$6H_2O$ (0.1 mmol, 0.5 equiv.), and Ag_2CO_3 (0.02 mmol, 10 mol%), H-phosphine oxides **2** (0.40 mmol) were added and charged with Ar three times. Then, diethyl 2,2-diallylmalonate **1** (0.20 mmol) and DCE (1.5 mL) were added. The mixture was stirred at 40 ℃ for 6 h, after completion of the reaction, solvent was evaporated under rotary evaporators. The crude product was purified by flash chromatography on silica gel to give the desired products **3** (PE∶Isopropanol＝20∶1).

Diethyl 3-((diphenylphosphoryl)methyl)-4-methyl-cyclopentane-1,1-dicarboxylate (3aa) (90%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89－7.65 (m, 4H), 7.60－7.38 (m, 6H), 4.26－3.94 (m, 4H), 2.46－2.29 (m, 4H), 2.29－2.15 (m, 2H), 2.14－2.04 (m, 1H), 1.97 (dd, J＝13.8, 5.0 Hz, 1H), 1.19 (dt, J＝14.0, 7.1 Hz, 6H), 0.87 (d, J＝7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.5, 172.3, 133.9, 133.7, 132.9, 132.7, 131.5, 130.6, 130.5, 128.5, 128.4, 61.2, 61.1, 58.6, 40.8, 38.9, 38.8, 36.9, 36.8, 36.5, 36.4, 30.7, 29.8 (d, J＝71.9 Hz), 14.9, 13.8, 13.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.00. HRMS (ESI): m/z calculated for $C_{25}H_{31}O_5P$ $[M+H]^+$: 443.1982, found 443.1984.

1,1'-(3-((Diphenylphosphoryl)methyl)-4-methylcyclopentane-1,1-diyl)diethanone (3ba) (61%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85－7.64 (m, 4H), 7.59－7.36 (m, 6H), 2.39 (dd, J＝13.6, 6.4 Hz, 1H), 2.35－2.21 (m, 2H), 2.20－2.06 (m, 3H), 2.06－1.89 (m, 8H), 0.80 (d, J＝6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 205.1, 204.4, 134.0, 133.5, 133.0, 132.5, 131.7, 131.6, 130.8, 130.7, 130.6, 130.5, 128.7, 128.5, 74.1, 37.3, 37.1, 37.0, 36.7, 36.6, 35.4, 35.3, 29.9 (d, J＝71.8 Hz), 26.7, 26.3, 25.9, 14.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.07, 30.49. HRMS (ESI): m/z calculated for $C_{23}H_{27}O_3P$ $[M+H]^+$: 383.1771, found 383.1780.

((3-Methylspiro[cyclopentane-1,9'-fluoren]-4-yl)-methyl)diphenylphosphine oxide (3ca) (52%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84－7.71 (m, 4H), 7.63 (dd, J＝6.5, 1.9 Hz, 2H), 7.57－7.40 (m, 6H), 7.38 (dt, J＝7.6, 3.5 Hz, 1H), 7.32－7.22 (m, 3H), 7.22－7.13 (m, 2H), 3.12－2.86 (m, 1H), 2.73－2.52 (m, 2H), 2.47－2.26 (m, 2H), 2.11 (dd, J＝27.4, 15.4 Hz, 1H), 2.00－1.81 (m, 2H), 1.20 (d, J＝7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.3, 153.1, 139.7, 138.9, 134.1, 133.1, 131.7, 131.6, 130.8, 130.7, 128.7, 128.6, 127.5, 127.4, 126.7, 126.6, 122.9, 122.8, 119.4, 119.3, 56.5, 46.7, 45.5, 45.4, 37.9, 37.8, 37.2, 37.1, 31.5, 30.8, 16.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.33, 30.60. HRMS (ESI): m/z calculated for $C_{31}H_{29}OP$ $[M+H]^+$: 449.2029, found 449.2030.

2-((Diphenylphosphoryl)methyl)-3,8,8-trimethyl-7,9-dioxaspiro[4.5]decane-6,10-dione (3da) (79%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88－7.69 (m, 4H), 7.64－7.38 (m, 6H), 2.75 (m, 1H), 2.63－2.46 (m, 2H), 2.45－2.27 (m, 4H), 2.18－2.01 (m, 1H), 1.67 (d, J＝22.6 Hz, 6H), 1.06 (d, J＝7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.4, 171.3, 133.9, 133.3, 133.0, 132.3, 131.8, 131.7, 131.6, 131.5, 130.8, 130.7, 128.7, 128.6, 128.6, 128.5, 104.7, 52.4, 45.4, 44.3, 44.2, 39.0, 38.9, 38.1, 38.0, 28.8, 28.7, 28.1, 14.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.63, 30.48. HRMS (ESI): m/z calculated for $C_{24}H_{27}O_5P$ $[M+H]^+$: 427.1669, found 427.1668.

2-((Diphenylphosphoryl)methyl)-3,8,8-*tri*-methyl-spiro[4.5]decane-6,10-dione (3ea) (85%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94－7.64 (m, 4H), 7.61－7.37 (m, 6H), 2.78－2.55 (m, 2H), 2.55－2.40 (m, 2H), 2.40－2.23 (m, 2H), 2.23－2.09 (m, 5H), 1.99－1.87 (m, 1H), 1.05－0.95 (m, 3H), 0.90 (t, J＝6.2 Hz, 3H), 0.85 (d, J＝7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.9, 207.3, 134.2, 133.3, 133.2, 132.3, 131.6, 131.6, 131.5, 131.4, 130.7, 130.6, 130.5, 130.4, 130.3, 128.7, 128.6, 128.5, 128.4, 70.5, 51.8, 51.1, 39.4, 39.3, 38.0, 37.9, 37.4, 37.4, 35.6, 30.3, 29.0, 28.7 (d, J＝72.0 Hz), 27.5, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.76, 30.96. HRMS (ESI): m/z calculated for $C_{26}H_{31}O_3P$ $[M+H]^+$: 423.2084, found 423.2082.

3-((Diphenylphosphoryl)methyl)-4-methylspiro-[cyclopentane-1,2'-indene]-1',3'-dione (3fa) (76%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (m, 2H), 7.86－7.69 (m, 6H), 7.62－7.35 (m, 6H), 2.85－2.64 (m, 1H), 2.63－2.45 (m, 2H), 2.38 (m, 1H), 2.07 (m, 2H), 1.93 (dd, J＝13.4, 7.0 Hz, 1H), 1.69 (dd, J＝13.2, 6.9 Hz, 1H), 1.06 (t, J＝6.2 Hz, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ: 204.2, 203.9, 141.5, 141.2, 135.5, 135.4, 134.1, 133.6, 133.1, 132.6, 131.6, 131.5, 131.4, 131.3, 130.9, 130.8, 130.7, 130.6, 130.5, 130.4, 128.6, 128.5, 128.5, 128.4, 123.3, 123.2, 59.2, 41.0, 40.1, 40.0, 39.2, 39.1, 38.2, 38.1, 28.8 (d, J=72.0 Hz), 14.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.80, 30.72. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{25}O_3P$ $[M+H]^+$: 429.1614, found 429.1616.

2-((Diphenylphosphoryl)methyl)-3-methylspiro-[4.5]decane-6,10-dione (3ga) (80%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82−7.64 (m, 4H), 7.60−7.34 (m, 6H), 2.75−2.43 (m, 4H), 2.41−2.29 (m, 1H), 2.28−2.02 (m, 6H), 2.00−1.87 (m, 2H), 1.87−1.70 (m, 1H), 0.90 (d, J=6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.4, 207.6, 134.1, 133.4, 133.1, 132.4, 131.7, 131.6, 131.5, 130.8, 130.7, 130.6, 130.5, 128.7, 128.6, 128.6, 128.5, 71.8, 38.9, 38.9, 38.2, 38.1, 37.9, 37.5, 37.4, 37.3, 36.1, 28.8 (d, J=72.1 Hz), 17.5, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.94, 31.16. HRMS (ESI): *m*/*z* calculated for $C_{24}H_{27}O_3P$ $[M+H]^+$: 395.1771, found 395.1770.

Dibenzyl-3-((diphenylphosphoryl)methyl)-4-methyl-cyclopentane-1,1-dicarboxylate (3ha) (66%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84−7.64 (m, 4H), 7.46 (m, 6H), 7.34−7.24 (m, 6H), 7.23−7.09 (m, 4H), 5.18−4.90 (m, 4H), 2.39 (m, 3H), 2.33−2.27 (m, 1H), 2.19 (m, *3*H), 2.01 (dd, J=13.8, 5.0 Hz, 1H), 0.84 (d, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.2, 172.0, 135.4, 133.8, 132.8, 131.5, 130.7, 130.6, 130.5, 130.4, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 67.0, 67.0, 58.8, 41.0, 39.1, 39.0, 37.0, 36.9, 36.6, 36.5, 30.2, 29.5, 14.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 30.97. HRMS (ESI): *m*/*z* calculated for $C_{35}H_{35}O_5P$ $[M+H]^+$: 567.2295, found 567.2299.

3'-((Diphenylphosphoryl)methyl)-4'-methyl-2*H*-spiro[benzofuran-3,1'-cyclopentan]-2-one (3ia) (45%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91−7.70 (m, 4H), 7.63−7.38 (m, 6H), 7.26−7.15 (m, 1H), 7.05 (m, 3H), 3.07−2.75 (m, 1H), 2.67−2.31 (m, 3H), 2.21−2.00 (m, 3H), 1.94 (dd, J=13.4, 6.6 Hz, 1H), 1.10 (d, J=7.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 181.9, 152.1, 135.2, 134.0, 133.6, 133.0, 132.6, 131.8, 130.9, 130.8, 130.7, 130.6, 128.7, 128.6, 128.2, 124.6, 122.5, 110.3, 51.1, 46.7, 44.6, 44.5, 38.8, 38.7, 38.1, 38.0, 29.8, 29.1, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.17, 30.27. HRMS (ESI): *m*/*z* calculated for $C_{26}H_{25}O_3P$ $[M+H]^+$: 417.1614, found 417.1617.

1-(1-Benzoyl-3-((diphenylphosphoryl)methyl)-4-methylcyclopentyl)ethanone (3ja) (56%): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83−7.69 (m, 6H), 7.59−7.41 (m, 7H), 7.37 (m, 2H), 2.50 (ddd, J=28.0, 13.3, 6.6 Hz, 2H), 2.29 (m, 3H), 2.20−2.12 (m, 2H), 2.09 (dd, J=13.3, 5.7 Hz, 1H), 1.92 (s, 3H), 0.89 (d, J=6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 205.9, 196.6, 134.8, 134.0, 133.7, 133.1, 133.0, 132.7, 131.7, 131.6, 131.5, 130.9, 130.8, 130.7, 130.6, 129.3, 128.7, 128.6, 128.5, 128.4, 71.4, 39.0, 37.7, 37.6, 37.5, 37.4, 36.9, 36.9, 29.9, 29.2, 27.4, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.47, 30.68. HRMS (ESI): *m*/*z* calculated for $C_{28}H_{29}O_3P$ $[M+H]^+$: 445.1927, found 445.1930.

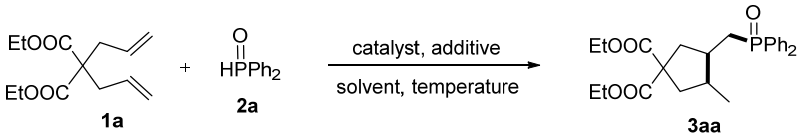
((4-Methyl-1-tosylpyrrolidin-3-yl)methyl)diphenylphosphine oxide (3ka) (79%) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75−7.66 (m, 4H), 7.62 (t, J=9.0 Hz, 2H), 7.58−7.41 (m, 6H), 7.30−7.24 (m, 2H), 3.36 (m, 2H), 3.11−2.60 (m, 2H), 2.49−2.36 (m, 3H), 2.30−2.12 (m, 2H), 2.11−1.91 (m, 2H), 0.82 (dd, J=49.8, 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.3, 133.7, 133.1, 132.2, 132.0, 131.9, 130.6, 130.5, 129.6, 128.8, 128.7, 128.6, 128.5, 127.4, 127.4, 54.1, 53.7, 53.5, 51.4, 51.3, 40.2, 39.7, 36.2, 36.1, 35.8, 35.7, 32.6, 28.4, 27.7, 21.5, 15.7, 13.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 30.45, 29.90. MS (ESI) *m*/*z* calculated for $C_{25}H_{28}NO_3PS$ $[M+H]^+$: 454.1600, found 454.1.

Diethyl 3-((diethoxyphosphoryl)methyl)-4-methyl-cyclopentane-1,1-dicarboxylate (3ab) Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.17 (dd, J=14.2, 7.1 Hz, 4H), 4.14−4.01 (m, 4H), 2.59−2.32 (m, 2H), 2.25 (m, 1H), 2.13 (dd, J=13.6, 9.8 Hz, 1H), 2.05−1.94 (m, 1H), 1.88 (d, J=16.6 Hz, 1H), 1.84−1.54 (m, 2H), 1.38−1.28 (m, 6H), 1.24 (t, J=7.1 Hz, 6H), 0.93−0.75 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.7, 61.5, 61.4, 58.7, 41.0, 38.8, 38.7, 37.0, 36.9, 36.6, 36.5, 26.7, 25.3, 16.5, 16.4, 14.8, 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.62, 30.89. MS (ESI) *m*/*z* calculated for $C_{17}H_{31}O_7P$ $[M+H]^+$: 379.1880, found 379.1.

Results and Discussion

At the onset of our studies, we chose diethyl 2,2-diallylmalonate (**1a**) and diphenylphosphine oxide (**2a**) as our model substrates. Firstly, the reaction was investigated in the presence of Ag_2CO_3 (10 mol%) and $Mg(NO_3)_2$•$6H_2O$ (1.0 equiv.) in $CHCl_3$ at 60 ℃ for 6 h. To our delight, the desired product **3aa** was isolated in 40% yield with good stereoselectivity (*trans*/*cis*=11∶1) (Table 1, Entry 1). Motivated by this result, other nitrate additives such as $Zr(NO_3)_4$•$5H_2O$, $Y(NO_3)_3$•$6H_2O$, $Bi(NO_3)_2$•$5H_2O$, $La(NO_3)_3$•$6H_2O$, $AgNO_3$, and $Cu(NO_3)_2$•$3H_2O$ were also examined and performed with moderate to good stereoselectivity in this reaction except $Cu(NO_3)_2$•$3H_2O$ (Table 1, Entries 2−7). Then, the screening of different solvents (MeCN, DMF, toluene, DCE, dioxane, DME) and silver salts (AgOAc, Ag_2O, $AgClO_4$, AgCl, AgTFA) illustrated that DCE and Ag_2CO_3 were optimal with an improved yield of 65% with excellent stereoselectivity (*trans*/*cis*=10∶1) (Table 1, Entries 8−18). Moreover, as the changing of the **1a**∶**2a**=1∶2, the yield of the target product **3aa** increased to 79% (Table 1, Entry 19). Also, when the temperature was dropped to 40 ℃, the yield increased to 85% and was improved further to 90% with reducing the loading of $Mg(NO_3)_2$•$6H_2O$ to 0.5 equiv. (Table 1, Entries 20−21). The yield of **3aa** decreased to 77% when the reaction was carried out under air (Table 1, Entry 22). Finally, with 10 mmol% Ag_2CO_3, 0.5 equiv. $Mg(NO_3)_2$•$6H_2O$, we got the product in the best yield of

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Additive	Yield/%	*trans*/*cis*[b]	Entry	Catalyst	Solvent	Additive	Yield/%	*trans*/*cis*[b]
1	Ag_2CO_3	$CHCl_3$	$Mg(NO_3)_2$•$6H_2O$	40	11∶1	12	Ag_2CO_3	Dioxane	$Mg(NO_3)_2$•$6H_2O$	51	7∶1
2	Ag_2CO_3	$CHCl_3$	$Zr(NO_3)_4$•$5H_2O$	25	8∶1	13	Ag_2CO_3	DME	$Mg(NO_3)_2$•$6H_2O$	43	10∶1
3	Ag_2CO_3	$CHCl_3$	$Y(NO_3)_3$•$6H_2O$	9	4∶1	14	AgOAc	DCE	$Mg(NO_3)_2$•$6H_2O$	61	8∶1
4	Ag_2CO_3	$CHCl_3$	$Bi(NO_3)_2$•$5H_2O$	*trace*	—	15	Ag_2O	DCE	$Mg(NO_3)_2$•$6H_2O$	64	9∶1
5	Ag_2CO_3	$CHCl_3$	$La(NO_3)_3$•$6H_2O$	16	10∶1	16	$AgClO_4$	DCE	$Mg(NO_3)_2$•$6H_2O$	62	9∶1
6	Ag_2CO_3	$CHCl_3$	$Y(NO_3)_3$•$6H_2O$	36	7∶1	17	AgCl	DCE	$Mg(NO_3)_2$•$6H_2O$	36	7∶1
7	Ag_2CO_3	$CHCl_3$	$AgNO_3$	n.r.	—	18	AgTFA	DCE	$Mg(NO_3)_2$•$6H_2O$	65	8∶1
8	Ag_2CO_3	MeCN	$Cu(NO_3)_2$•$3H_2O$	51	9∶1	19[c]	Ag_2CO_3	DCE	$Mg(NO_3)_2$•$6H_2O$	79	10∶1
9	Ag_2CO_3	DMF	$Mg(NO_3)_2$•$6H_2O$	*trace*	—	20[c,d]	Ag_2CO_3	DCE	$Mg(NO_3)_2$•$6H_2O$	85	10∶1
10	Ag_2CO_3	Tolucne	$Mg(NO_3)_2$•$6H_2O$	61	10∶1	**21**[c,d,e]	**Ag_2CO_3**	**DCE**	**$Mg(NO_3)_2$•$6H_2O$**	**90**	**10∶1 (>20∶1)[f]**
11	Ag_2CO_3	DCE	$Mg(NO_3)_2$•$6H_2O$	65	10∶1	22[c,d,e,g]	Ag_2CO_3	DCE	$Mg(NO_3)_2$•$6H_2O$	77	10∶1

[a] The reaction was carried out with catalyst (10 mol%), additive (1.0 equiv.), **1a** (1.5 equiv.), and **2a** (0.2 mmol) in solvent (2.0 mL) at 60 ℃ under argon for 6 h, unless otherwise noted. [b] Detected by ^{31}P NMR. [c] **1a**/**2a**=1/2. [d] 40 ℃. [e] $Mg(NO_3)_2$•$6H_2O$ (0.5 equiv.). [f] Recrystallization by ether. [g] Under air.

90% with excellent stereoselectivity (*trans*/*cis*=10∶1) in DCE at 40 ℃ under Ar.

With the optimized reaction conditions in hand (Table 1, Entry 21), various substrated 1,6-dienes were examined and the results were summarized in Scheme 2. With symmetrical 1,6-dienes (Scheme 2, **3aa**—**3ha**), the corresponding exocyclic phosphine oxides were produced in moderate to good yields with excellent stereoselectivities (*trans*/*cis*=8∶1 to 12∶1), the value of *trans*/*cis* would be >20∶1 after recrystallization by diethyl ether. The electronic and steric effect is unconspicuous in this reaction. However, the substrates containing *N*-heteroatom worked smoothly while with lower stereoselectivity, due to the smaller resistance of the substrates (**3ka**, **3la**). With unsymmetrical 1,6-dienes (**3ia**, **3ja**, **3ma**—**3oa**), the corresponding exocyclic phosphine oxides which have multi-stereoisomers were produced with moderate yields and good stereoselectivities. As the substrate is an internal 1,6-dienes, only a trace amount of **3pa** was observed. Moreover, to enrich the style of ring structure, an ester group was inserted into 1,6-dienes. But unfortunately, we obtained a simple product **3qa** without further cyclization, which may have been due to the ester group decreasing the eletrophilicity of carbon-carbon double bond of **1q**.

We next examined the scope of different phosphate sources (Scheme 3). Both diethyl phosphite and diisopropyl phosphite could be used as substrates and generated the corresponding products in 52% and 44% yields with the value of diastereoselectivity ratio 8∶1 and 6∶1, respectively (**3ab**—**3ac**). For disubstituted diphenylphosphine oxides, the electron-donating groups gave the desired products in moderate to good yields with excellent stereoselectivities (**3ad**—**3ae**, **3ag**—**3ah**). But due to the lower nucleophilicity of the P-radical toward 1,6-dienes, an electron-withdrawing group such as *para*-CF_3 gave a relatively lower yield (**3af**). For unsymmetrical phosphate sources, such as **2i**, **2j**, the corresponding exocyclic phosphine oxides which have multi-stereoisomers were obtained in 76% and 56% yields with great stereoselectivity after recrystallization by diethyl ether (**2ai**, **2aj**).

To gain more insight into the silver-catalyzed cascade radical cyclization, radical capture experiments were conducted by employing TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and 1,1-diphenylethylene. No desired product **3aa** was obtained when these radical trapping reagents were added in the reaction under the standard conditions (Scheme 4, a). Interestingly, product **4** was obtained in 28% yield when 1.0 equiv. of 1,1-diphenylethylene was added to the reaction. We speculate that 1,1-diphenylethylene could produce more stable free radical intermediates **A** with the addition of the P-centre radical. These results would reveal that a free radical might be involved in this cyclization. Moreover, **2A** [$Ph_2(O)PAg$] instead of Ag_2CO_3 to be tested under the optimized reaction conditions gave **3aa** in 76% yield (Scheme 4, b). Thus, we conclude that the first step is phosphorylation with Ag_2CO_3 and the formation of **2A** is the key step in this transformation.

According to the previously reported literatures and our research on 1,6-dienes cyclization,[10,11] a plausible

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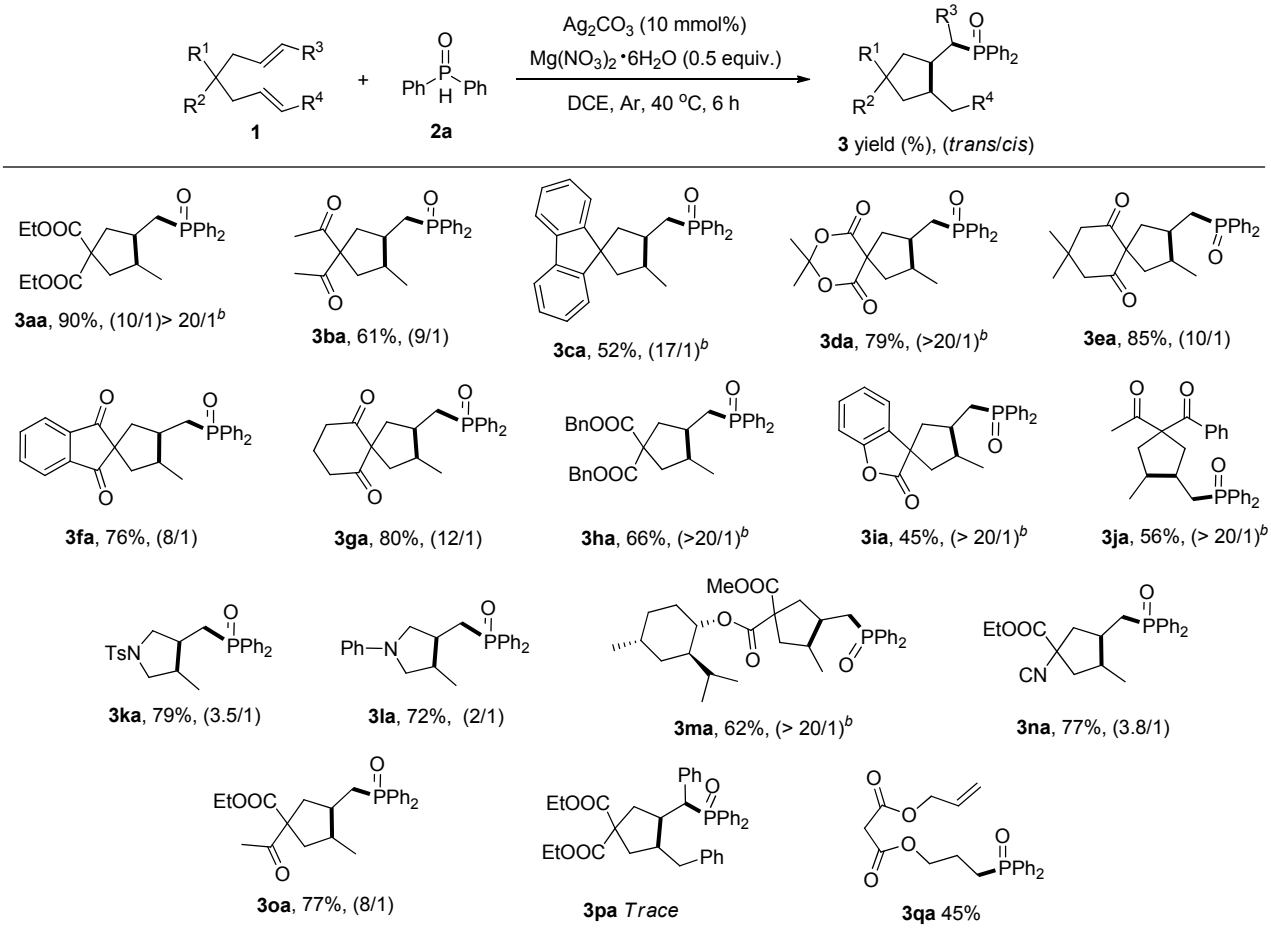
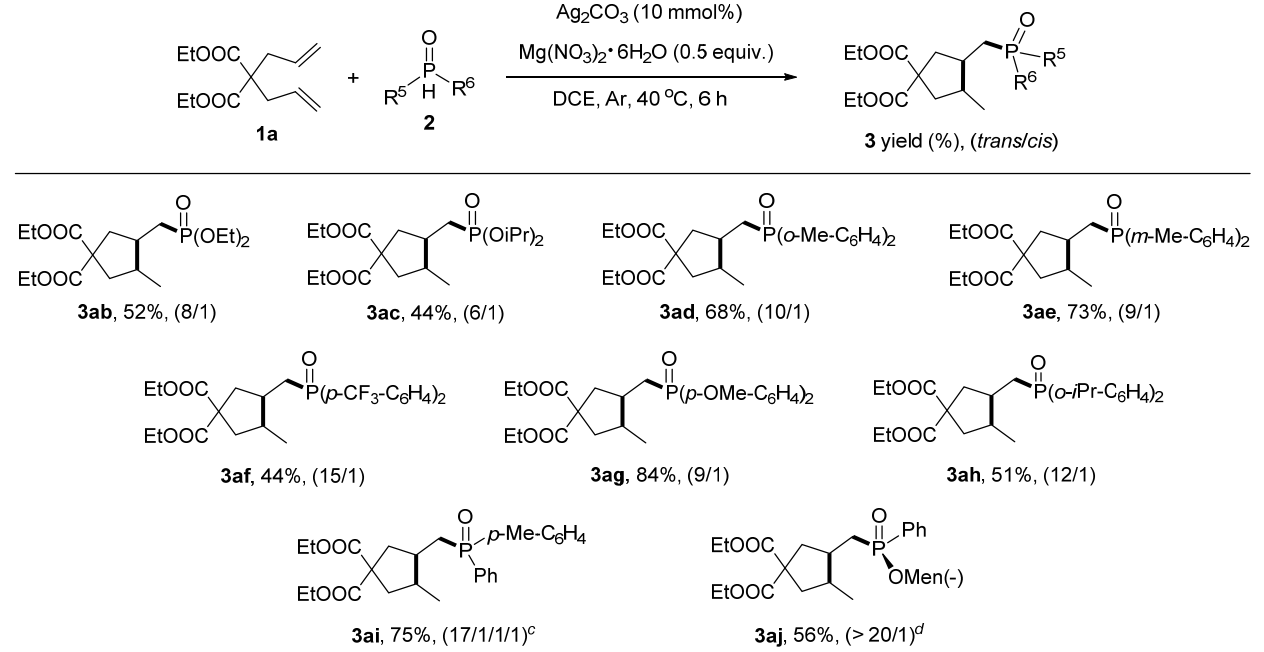
Scheme 2 Cascade cyclization with different 1,6-dienes[a,c]



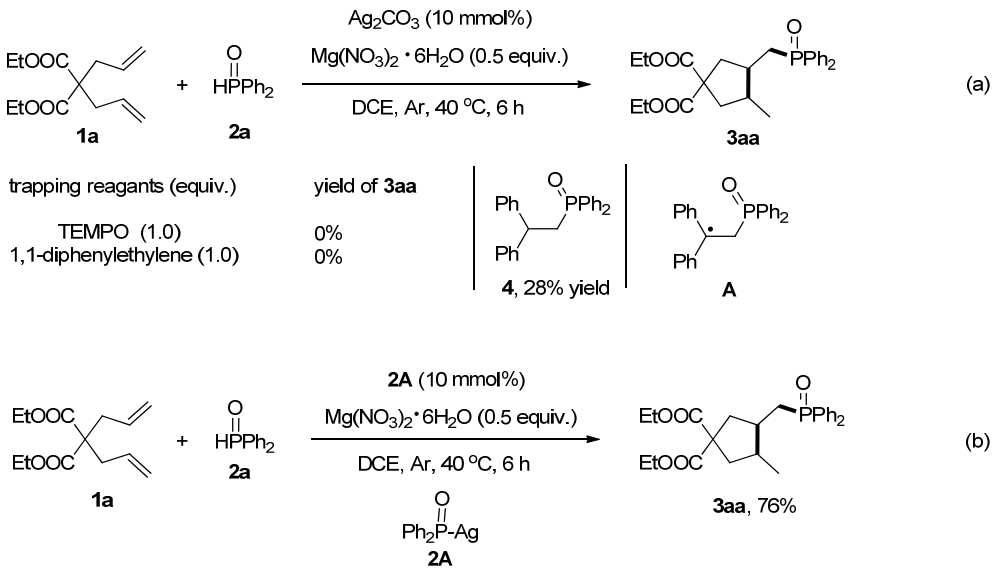
[a] All reactions were carried out in the presence of Ag_2CO_3 (10 mol%), $Mg(NO_3)_2$•$6H_2O$ (0.5 equiv.), **1a**—**1p** (0.2 mmol) and **2a** (0.4 mmol) in 2.0 mL DCE at 40 ℃, detected by ^{31}P NMR. [b] Recrystallization by ether. [c] Isolated yield before recrystallization.

Scheme 3 Different phosphate sources[a b]

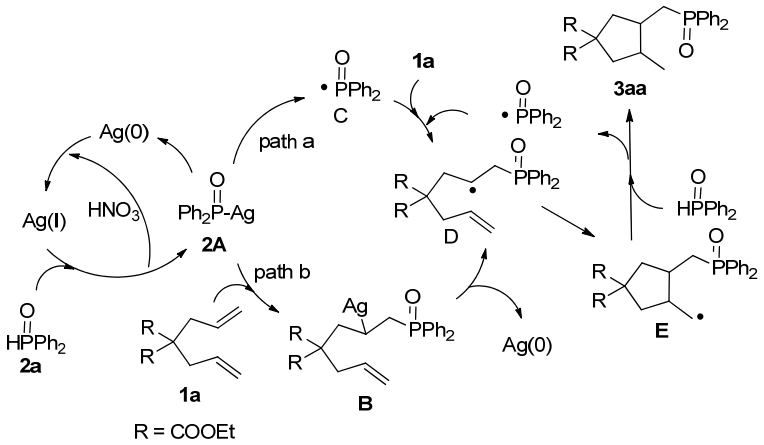


[a] All reactions were carried out in the presence of Ag_2CO_3 (10 mol%), $Mg(NO_3)_2$•$6H_2O$ (0.5 equiv.), **1a** (0.2 mmol), **2a**—**2j** (0.4 mmol) in 2.0 mL DCE at 40 ℃, detected by ^{31}P NMR. [b] Isolated yield. [c] Multi-stereoisomer. [d] Recrystallization by ether.

Scheme 4 Exploring experiments of mechanism



Scheme 5 Plausible mechanism



mechanism is depicted in Scheme 5. Firstly, diphenylphosphine oxide reacts with Ag(I) salt to form the intermediate **2A** under the reaction conditions. It may also proceed by two pathways: a) the pathway involving a silver-promoted generation of the P-radical **C**, which then adds to **1a** to give the alkyl radical **D** (Scheme 5, path a); b) homolysis of the C—Ag bond which is the addition of **2A** to **1a** to form the intermediate **B**, that generates the radical intermediate **D** (Scheme 5, path b). Then, radical **D** participates in an intramolecular radical substitution reaction. Addition of the radical to the alkene to generate the intermediate **E** with a subsequent hydrogen transfer from **E** to **2a** would release the product along with **C**.

Conclusions

In summary, we have developed a concise and effective protocol for the synthesis of various valuable exocyclic phosphine oxides via phosphorylation/cascade cyclization of various 1,6-dienes involving C—P and C—C bonds formation with good stereoselectivity.

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