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Selective P–C(sp^3) Bond Cleavage and Radical Alkynylation of α-Phosphorus Alcohols by Photoredox Catalysis

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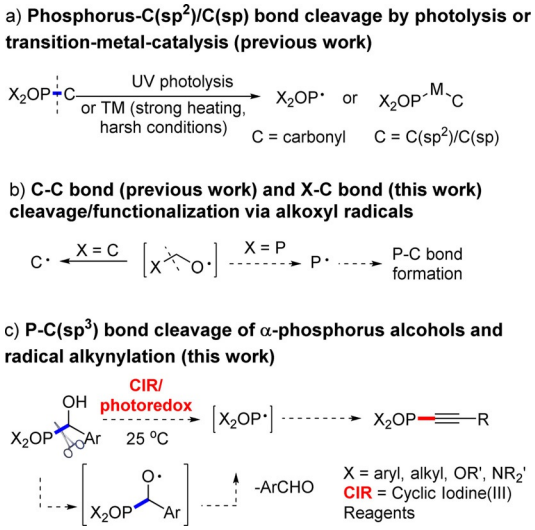
Abstract: Herein the first P–C(sp^3) bond cleavage and radical alkynylation of α-phosphorus alcohols to construct phosphonoalkynes is reported. The phosphorus radical is generated upon P–C bond cleavage reaction via the alkoxyl radical through photoredox catalysis with cyclic iodine(III) reagents. Various arylphosphinoyl-, alkylphosphinoyl-, phosphonate-, and phosphonic amide alcohols serve as radical phosphorus precursors to construct phosphonoalkynes for the first time.

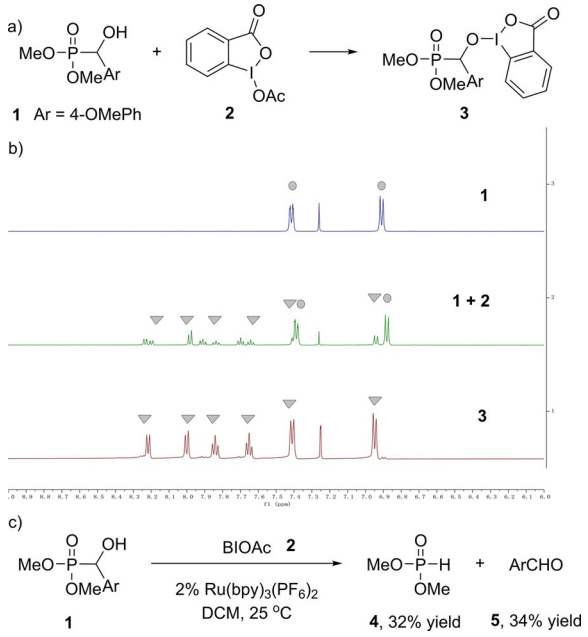
The cleavage and construction of phosphorus–carbon bonds are useful for the synthesis of organophosphorus compounds, representing widely-used organic ligands and bioactive molecules.[1] Although P–C bond construction methods are well developed, P–C bond cleavage reactions are difficult and limited.[2] Acylphosphine oxides undergo homolytic P–C bond cleavage reaction by photolysis, however only the P–carbonyl bond can be cleaved and UV light irradiation is required (Scheme 1 a).[3] Transition metals engage in P–C(sp^2) and P–C(sp) cleavage reactions through oxidative addition, however strong heating/harsh reaction conditions are required and P–C(sp^3) bonds are inaccessible.[2,4]

Phosphorus radicals are versatile reactive intermediates for organophosphorus syntheses, in which the phosphorus–hydrogen, phosphorus–heteroatom and phosphorus–carbonyl compounds are used as P-radical precursors.[1a–d] α-Phosphorus alcohols are important structural motifs in organic synthesis,[1b,f] which can be prepared easily by the Pudovik reaction and represent an attractive phosphorus radical precursor.[5] The alkoxyl radical is known for C–C bond cleavage reactions,[6] however the counterpart P–C bond cleavage from α-phosphorus alcohols is unknown and further functionalization is elusive (Scheme 1 b).[7,8] Herein, we report the first P–C(sp^3) bond cleavage reaction of α-phosphorus alcohols to generate phosphorus radicals, giving phosphonoalkynes by radical alkynylation for the first time (Scheme 1 c).



Scheme 1. P–C bond cleavage and phosphorus radical alkynylation.

We started the investigation by mixing α-phosphonate alcohol **1** with acetoxylbenziodoxole (BIOAc) **2** (Scheme 2 a),[9] which was reported to undergo ligand exchange with alco-



Scheme 2. a) Reaction of α-phosphonate alcohol **1** with CIR **2** giving alcohol/benziodoxole complex **3**. b) ^{1}H NMR spectra displaying signals for **1** (circles) and **3** (triangles). c) Reaction of **1** with **2** catalyzed by $Ru(bpy)_3(PF_6)_2$.

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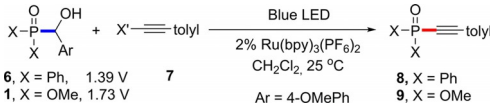
hols.[10] The ^{1}H NMR spectrum is shown in Scheme 2b, where signals of the product appear. The α-phosphonate alcohol/benziodoxole complex **3** was isolated as an air-stable colorless solid.[10,11] We next measured the oxidation potential of complex **3** [$E_p = 1.09$ V vs. saturated calomel electrode (SCE) in MeCN] where the oxidation potential was significantly decreased compared to α-phosphonate alcohol **1** ($E_p = 1.73$ V vs. SCE in MeCN).[12] We then treated **1** with BIOAc **2** under blue LED ($\lambda_{max} = 468 \pm 25$ nm) irradiation using $[Ru(bpy)_3](PF_6)_2$ ($E^0_{1/2}{}^{III/II} = 1.26$ V vs. SCE in MeCN) as the photocatalyst. The formation of H-phosphonate **4** and 4-methoxylbenzaldehyde **5** confirmed that alkoxyl radical generation and P–C(sp^3) bond cleavage (Scheme 2c) took place.[8]

Phosphonoalkynes are important structural motifs for heterocycle synthesis and are typically prepared from nucleophilic or electrophilic alkynylation reactions.[13] We next ascertained if the phosphorus radical from the P–C(sp^3) bond cleavage reaction could engage in hitherto unknown radical alkynylations.[1b,d] With α-diarylphosphinoyl alcohol **6** ($E_p = 1.39$ V vs. SCE in MeCN) as the model substrate, the widely-used bromoalkyne and alkynylsulfone acceptors were ineffective (entries 1–2 in Table 1). In contrast, alkynyl benziodoxole (BI-alkyne) gave phosphonoalkyne **8** in 81% yield (78% isolated yield, entry 3).[10,11b,c,14] Different acetoxylbenziodoxole derivatives all promoted the reaction with 3,4-dimethoxy acetoxylbenziodoxole (3,4-OMe-BIOAc) **10** affording the best yield of 87% (83% isolated yield, entries 4–6). We next tested α-phosphonate alcohol **1** ($E_p = 1.73$ V vs. SCE in MeCN) and found tetrafluoro hydroxylbenziodoxole 2,3,4,5-F-BIOH **12** gave the 74% yield of phosphonoalkyne **9** (72% isolated yield, entries 7–10).[10b,15] We hypothesize that electron-deficient benziodoxole **12** improved the reaction from: 1) the decreased oxidation potential of the cyclic iodine(III) reagent (CIR)–phosphorus alcohol complex, and 2) the increased oxidative quenching efficiency on photoexcited Ru^{II*}.[16] Both photocatalyst and light irradiation were required for the reaction (entries 11–12).[17]

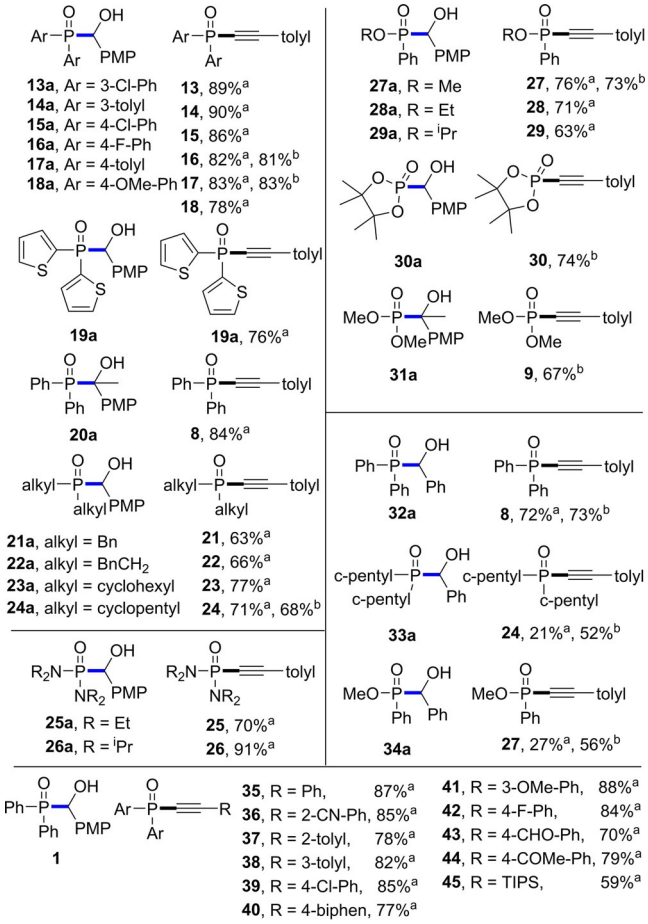
Table 1. Study of the P–C(sp^3) bond cleavage and alkynylation reaction.



Entry	Conditions[a]	Conv. [%][b]	Yield [%][b]
1	X′ = Br, **6**, BIOAc **2**	> 95	< 5
2	X′ = SO_2Ph, **6**, BIOAc **2**	76	27
3	X′ = BI, **6**, BIOAc **2**	> 95	81 (78)
4	entry 3, 3,4-OMe-BIOAc **10**	> 95	87 (83)
5	entry 3, 3,4-F-BIOAc **11**	81	68
6	entry 3, 2,3,4,5-F-BIOH **12**	> 95	83 (79)
7	X′ = BI, **1**, BIOAc **2**	83	57
8	entry 7, 3,4-OMe-BIOAc **10**	56	34
9	entry 7, 3,4-F-BIOAc **11**	78	69
10	entry 7, 2,3,4,5-F-BIOH **12**	> 95	74 (72)
11	entry 10, no [Ru]	< 5	< 5
12	entry 10, no hν	< 5	< 5

[a] Reaction conditions: **6** or **1** (0.15 mmol, 1.5 equiv), **7** (0.10 mmol, 1 equiv), BI derivatives (0.15 mmol, 1.5 equiv), and $Ru(bpy)_3(PF_6)_2$ (0.002 mmol, 0.02 equiv) in 2.0 mL DCM under nitrogen with 4 W blue LED irradiation at 25 °C for 6–24 h, unless otherwise noted. [b] Conversions and yields determined by ^{1}H NMR analysis; isolated yields in parentheses. BI = benziodoxole.

The substrate scope of the P–C(sp^3) bond cleavage/alkynylation reaction was next tested. Electron-rich or electron-withdrawing aryl substituents on α-diarylphosphinoyl alcohols **13a**–**18a** did not affect the reaction and gave **13**–**18** in 78–90% yields (Scheme 3). The reaction was compatible with thiophene, giving phosphonoalkyne **19** in 76% yield. Tertiary α-di-



[a]entry 4 in table 1, [b]entry 10 in table 1

Scheme 3. Substrate scope for P–C(sp^3) cleavage/alkynylation.

arylphosphinoyl alcohol **20a** gave **8** in 84% yield. α-Dialkylphosphinoyl alcohols **21a**–**24a**, including benzyl or cycloalkyl substituents, all reacted smoothly to give phosphonoalkynes **21**–**24** in 63–77% yields. α-Phosphonic diamide alcohols **25a** and **26a** gave **25** and **26** in 70 and 91% yields, respectively. Alkynyl phosphonic diamides were not previously synthesized and the phosphonic diamide radicals are inaccessible through other methods.[1d,18]

α-Phosphinate alcohols with mixed aryl and alkoxyl substituents were also tested, and the 3,4-OMe-BIOAc or 2,3,4,5-F-BIOH conditions gave similar 63–76% yields of **27**–**29**. Cyclic α-phosphonate alcohol **30a** gave the cyclic phosphonate alkyne **30** in 74% yield and the tertiary α-phosphonate alcohol **31a** gave **9** in 67% yield. We lastly tested α-phosphorus alcohols that

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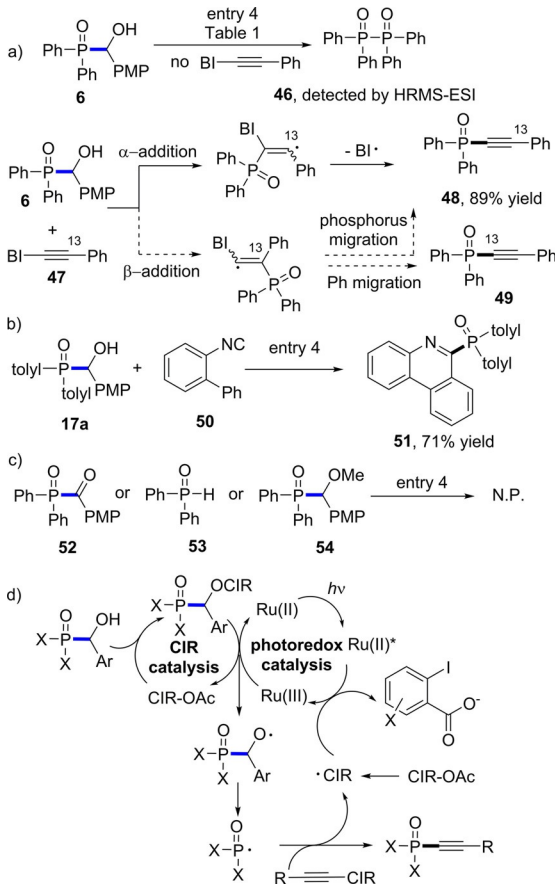
lacked electron-rich 4-methoxylphenyl groups, which bear significantly higher oxidation potentials ($E_p = 2.06–2.10$ V vs. SCE in MeCN). Under the 2,3,4,5-F-BIOH conditions (entry 10 in Table 1), the α-diarylphosphinoyl, α-dialkylphosphinoyl, and α-phosphonate alcohols **32**–**34a** reacted smoothly to give 52–73% yields.

Various *ortho*-, *meta*-, or *para*-aryl substituents appended to BI-alkynes were tolerated in the phosphorus radical alkynylation reactions, including both electron-rich and electron-deficient functional groups (Scheme 3). Methoxy, fluoride, chloride, ketone, aldehyde, and nitrile groups did not affect the reactions, which gave phosphonoalkynes **35**–**44** in 70–88% yields. Triisopropylsilane (TIPS)-substituted BI-alkyne reacted smoothly to give TIPS protected phosphonoalkyne **45** in 59% yield, which can be readily deprotected to yield the terminal phosphonoalkyne quantitatively.[12,19]

To gain mechanistic insight on this P–C(sp^3) bond cleavage/alkynylation reaction, we added radical quenchers (2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl (TEMPO) or butylated hydroxytoluene (BHT) to the reaction and observed inhibition of the reaction.[12,20] We also observed the formation of diphosphorus compound **46** in the absence of radical acceptors using high-resolution mass spectrometry (HRMS), which additionally suggested the formation of phosphorus radical intermediates (Scheme 4a). As heteroatom radical addition to alkynyl benziodoxoles was previously unknown, we performed isotope labeling experiments (Scheme 4a). Retention of C13 in the phosphonoalkyne **48** suggested the α-addition of phosphorus radicals to alkynyl benziodoxoles owing to the unlikely migration of the phosphorus group.[21] We also tested the isocyanide radical acceptor **50** and obtained 71% yield of **51** through a phosphorus radical addition/cyclization reaction, which confirmed the postulated phosphorus radical intermediate (Scheme 4b).[22]

We lastly subjected acylphosphine oxide **52** or H-phosphonate **53** to the reaction and observed no conversion, which suggested that these played no part in the reaction (Scheme 4c). In addition, the hydroxyl-protected α-diarylphosphinoyl alcohol **54** was unreactive in the reaction, suggesting that the free hydroxyl group is critical for the reaction. Based on mechanistic investigations described above, we propose that the reaction is initiated by the formation of a benziodoxole/α-phosphorus alcohol complex in situ, which yields the alkoxyl radical upon oxidation with $Ru(bpy)_3^{3+}$ (Scheme 4d). $Ru(bpy)_3^{3+}$ was in turn generated from the oxidative quenching of the photoexcited $Ru(bpy)_3^{2+}$* by benziodoxole derivatives.[14e] The alkoxyl radical then undergoes P–C(sp^3) bond cleavage to yield the phosphorus radical, and further radical α-addition to the alkynyl benziodoxole to yield the phosphonoalkyne.[23]

In conclusion, we have developed the first P–C(sp^3) bond cleavage/alkynylation reaction by photoredox catalysis with cyclic iodine(III) reagents. The reaction is applicable to various α-phosphorus alcohols to construct phosphonoalkynes by phosphorus radical alkynylation. We envision that this novel heteroatom–carbon bond cleavage/functionalization reaction that takes place under mild photoredox conditions will be beneficial for chemoselective heteroatom–carbon bond manipulation and chemical biology studies, which are currently underway.



Scheme 4. Mechanistic investigations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynylation · P–C(sp^3) bond cleavage · phosphorus · photochemistry · radicals

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[23] The quantum yields of phosphinoyl alcohol 6 with 3,4-OMe-BIOAc and 2,3,4,5-F-BIOH were 5.3% and 10%, respectively. In combination with the light-dependence results, the radical chain mechanism was unlikely. See supporting information for details.

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