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Diphenyliodonium Ion/Et_3N Promoted Csp2-H Radical Phosphorylation of Enamides

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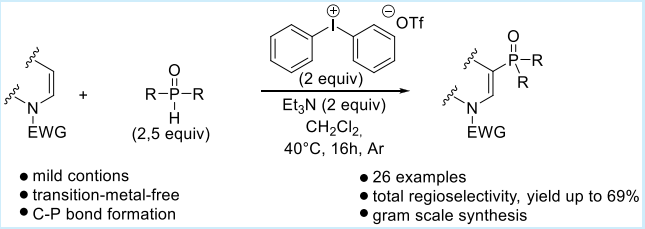
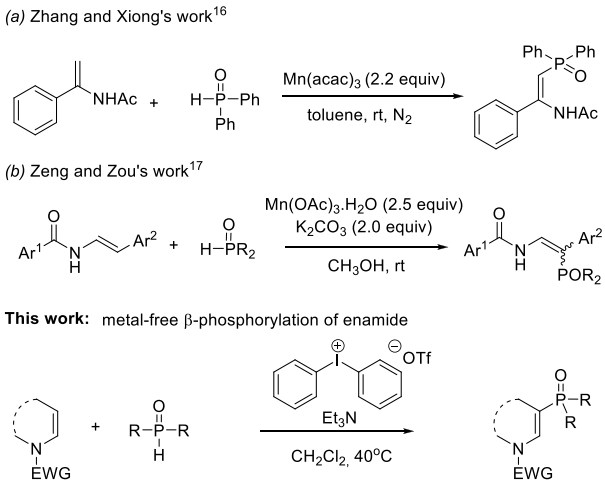
Supporting Information

ABSTRACT: This work reports a simple and efficient method for the direct phosphorylation of enamide under metal-free conditions. The P-centered radicals, derived from secondary phosphine oxides, are generated under mild reaction conditions in the presence of diphenyliodonium salt and Et_3N and are introduced onto a range of enamides in good isolated yields. The method features broad substrate scope, good functional group tolerance, and efficient scale-up.



The addition of radicals onto olefins is undoubtedly one of the most useful organic transformations in organic synthesis.[1] The impressive progress accomplished in this field due to the discovery of practically simple and environmentally benign approaches for the generation of radical species.[2] Among them, P-centered radicals have recently attracted increasing attention.[3] Phosphorus-containing compounds exhibit a broad range of applications in organic,[4] material,[5] and medicinal chemistry,[6] triggering the development of many methods for their preparation. Conventionally, C−P bond formation was achieved using metal catalysis;[7] however, most of the reported procedures show drawbacks, which include the use of noble metal catalysts (i.e., Pd, Rh, Ir) and precious ligands and/or drastic conditions. Recent studies demonstrate that radical mediated C−P bond formation can interestingly emerge as a very useful tool to synthesize organophosphorus compounds. The P-centered radicals can be obtained from the cleavage of the H−P bond generated by various radical initiators such as Ag(I),[8] Mn(III),[9] Cu(II),[10] peroxides,[11] or under visible-light photocatalytic conditions.[12] In addition, although great progress has been made on C(sp_2)-P bond formation,[13] the direct construction of a radical-mediated C(sp_2)-P bond from an enamide C−H bond is scarce. One of our current research interests deals with the direct functionalization of enamide C−H bonds. Enamides are stable enamine surrogates and provide key intermediates for the synthesis of small but complex nitrogen-containing compounds.[14] The π-donating ability of the nitrogen atom renders enamides more electron-rich than simple alkenes, and they afford a means of activating carbon−carbon double bonds.[15] To the best of our knowledge, only two examples for the synthesis of β-phosphorylated enamides have been reported to date. Liu et al. showed that β-phosphorylated acyclic enamides can be obtained through manganese(III) mediated oxidative coupling (Scheme 1);[16] a *Z*-selectivity was observed. During the preparation of this communication, Zeng et al. reported a manganese(III) mediated method for the preparation of β-phosphorylated enamides through the radical oxidative phosphorylation of *N*-styrylamides.[17] Despite these recent advances, the development of a novel approach to access β-phosphorylated enamides that proceeds under mild and metal-free conditions is highly appealing.

Scheme 1. Manganese-Mediated (a) and (b) and Metal-Free β-Phosphorylation of Enamides



Although the photophysical properties of EDA complexes have been extensively studied,[18,19] their use to allow organic transformations is even less explored as electron transfers from donors to acceptors are fast and reversible.[20] A highly anticipated application of this complex is the photochemical

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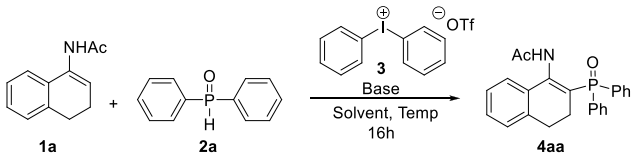
or thermal generation of reactive aryl radicals.[12c,21] Indeed, Kita et al. suggested the ability of diaryliodonium salts[22] to form EDA complexes with rich electron arenes and confirmed the generation of aryl radicals by EPR spectroscopy.[23]

Although this strategy has been frequently used in the radical arylation reaction, its use as a hydrogen abstractor to generate phosphinoyl radical from related phosphine oxides is scarce. Prior to this work, we developed the synthesis of 6-phosphorylated phenanthridines in the presence of phosphinoyl radicals from the combination of diphenyliodonium salt ($Ph_2I^+,^-OTf$), triethylamine (Et_3N), and secondary phosphine oxides.[24] We consequently aimed at extending this approach to consider the unprecedented transition-metal-free phosphinoyl-functionalization of enamides. To the best of our knowledge, the use of diphenyl iodonium ion/Et_3N as radical initiator system to promote Csp2-H phosphorylation of enamide, otherwise inaccessible via conventional radical conditions, is unprecedented. The phosphinoylation of enamides was first investigated starting from **1a** and diphenylphosphine oxide **2a**, selected as model substrates (Table 1). We surveyed the

Table 1. Optimization of the Reaction Conditions for the Phosphorylation[a]



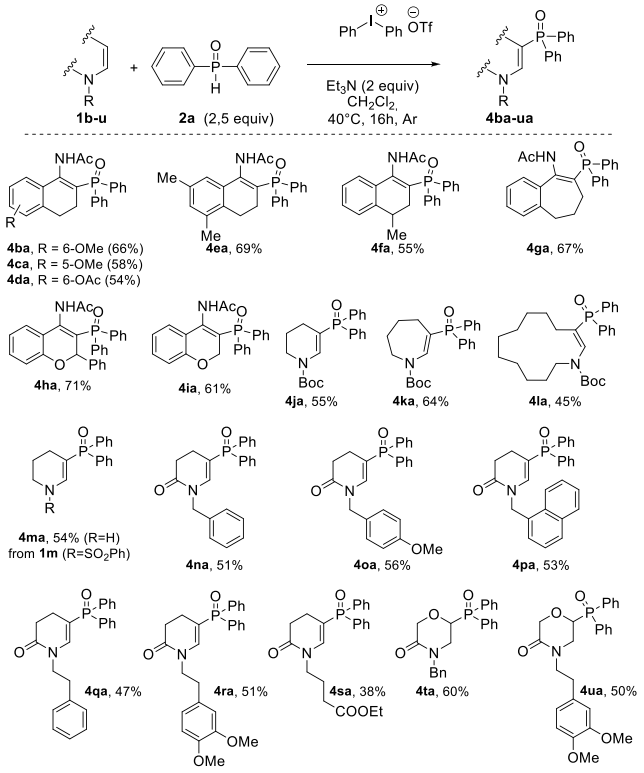
entry	base (equiv)	solvent	temp (°C)	yield[b] (%)
1	Et_3N (2.0)	CH_3CN	40	66
2	Et_3N (2.0)	CH_3CN	90	65
3	Et_3N (4.0)	CH_3CN	40	58
4[c]	Et_3N (2.0)	CH_3CN	40	NR
5	Et_3N (2.0)	CH_2Cl_2	40	70
6	Et_3N (2.5)	CH_2Cl_2	40	68
7	Et_3N (1.5)	CH_2Cl_2	40	15
8[d]	Et_3N (2.0)	CH_2Cl_2	40	46
9[e]	Et_3N (2.0)	CH_2Cl_2	40	35
10	Et_3N (2.0)	EtOAc	90	46
11	Et_3N (2.0)	DMF	90	57
12	Et_3N (2.0)	MeOH	60	53
13	piperidine (2.0)	CH_3CN	90	60
14	morpholine (2.0)	CH_3CN	90	51
15	Cs_2CO_3 (2.0)	CH_3CN	90	37
16	K_2CO_3 (2.0)	CH_3CN	90	44
17		CH_3CN	90	NR
18[f]	Et_3N (2.0)	CH_2Cl_2	40	50

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), **3** (0.4 mmol), base, solvent (1.0 mL) under Ar. [b]Isolated yields. [c]Reaction performed in the absence of iodonium salt **3**. [d]Reaction performed with 2 equiv of diphenylphosphine oxide **2a**. [e]Reaction performed with 1.5 equiv of Ph_2I^+,OTf^- **3**. [f]In the presence of air.

reaction parameters by using the diphenyliodonium salt **3** (2 equiv) and Et_3N (2 equiv), as a sacrificial electron donor, at 40 °C in CH_3CN under argon atmosphere. Fortunately, trapping of the phosphinoyl radical by enamide **1a** delivered the phosphorylated product **4aa** in 66% of isolated yield (Table 1, entry 1). NMR and mass spectroscopy unambiguously confirmed the structure of **4aa**. No obvious improvement on the reaction outcome was observed when the amount of base or the reaction temperature was increased (entries 2–3). Control experiments revealed the essential role of the base (entry 17) and of the iodonium salt (entry 4) in the reaction. Attempts to reduce the amount of base, diphenylphosphine oxide, or iodonium salt led to lower the yield significantly (entries 6–9). A series of common solvents was next examined, revealing that CH_2Cl_2 is best suited to the reaction (entries 1, 5, 10–12). Other organic or inorganic bases also worked well to deliver **4aa**, albeit in lower yields (entries 13–16). Incomplete conversion was observed with a shorter reaction time or in the presence of air (entry 18).

With the optimized conditions in hand, we first explored the scope of the reaction with respect to the enamide derivative **1b–u** (Scheme 2). The reaction proceeded smoothly with a

Scheme 2. Scope of Enamides 1[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.75 mmol), **3** (0.6 mmol), base (0.6 mmol), CH_2Cl_2 (1.5 mL), 40 °C, 16 h under Ar.

wide functional group tolerance. The reaction of diphenylphosphine oxide **2a** with cyclic enamide **1b–e** containing an aryl group bearing strong electron donating (6-OMe, 5-OMe, 5,7-diMe) or withdrawing groups (7-F, 6-OAc) with different substitution patterns afforded the corresponding phosphorylated products **4ba–4ea** in moderate to good yields. In addition, cyclic enamide bearing a methyl group at C4 position reacted smoothly with **2a**, leading to the hindered phosphorylated product **4fa** in 55% yield. Similarly, 1-benzosuberone and chromanone derived cyclic enamides were easily transformed to the corresponding products **4ga–4ia** in good to excellent yields. Next, our method also proved to be applicable to the 6-, 7-, and 13-membered cyclic enecarbamates **4ja–ma**. Interestingly, enesulfonamide **1m** led after N–S bond cleavage[25] to the *β*-phosphorylated secondary enamine **4ma** isolated as a stable product in 54% yield after purification on silica gel. This method appears thus as a valuable alternative to the known reported procedures.[26] Our strategy was also amenable to the

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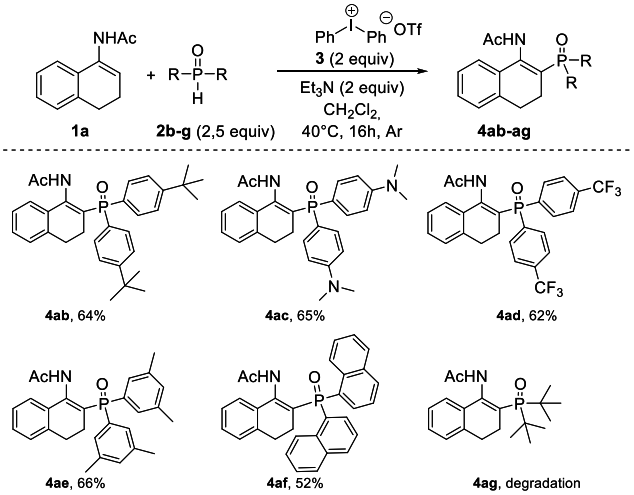
phosphinoyl-functionalization of *endo*-enamides bearing terminal aryl (**4na−ra**) or ester (**4sa**) functional groups. In addition, the electron-rich morpholinone-derived enamides **1t,u** led to the formation of the unexpected hydrophosphorylation products **4ta−ua**. While the hydrophosphorylation of an electron-rich olefin such as glycal is already known,[27] to the best of our knowledge, in the case of enamide, this reaction has been described only once as side traces.[17] The formation of the phosphinoyl morpholinones **4ta−ua** can be rationally explained as follows: the phosphinoyl radical **7** formed added to **1t** or **1u**, giving the alkylradical **8** (see Scheme 5), which subsequently abstracts a hydrogen atom from a hydrogen donor such as **2a** and affords the corresponding adduct **4ta−ua**.

These phosphinoyl lactams **4ta−ua** can then be envisaged as precursors of more complex compounds based on the reactivity of the lactam or the phosphinoyl moiety. A variety of phosphinoyl functionalized enamides was thus readily furnished in synthetically useful yields. It is worth noting that a complex mixture was unfortunately observed starting from acyclic enamide.

Subsequently, we investigated furthermore the reactions of enamide **1a** with different secondary phosphine oxides (Scheme 3). Various electronic properties and steric bulks

Scheme 3. Scope of Pentavalent Phosphorus Derivatives 2[a]

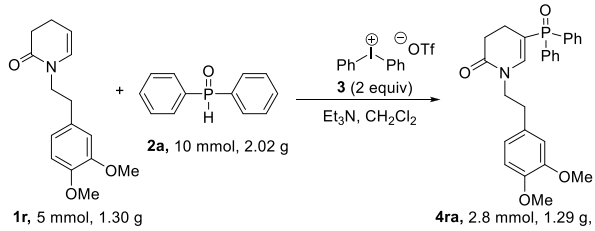


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.75 mmol), **3** (0.6 mmol), base (0.6 mmol), CH_2Cl_2 (1.5 mL), 40 °C, 16 h under Ar.

were tolerated. Diarylphosphine oxides bearing a *t*-Bu, NMe_2, or CF_3 group at the C_4 position of the aryl rings provided the enamide adduct with good yields (**4ab−ad**). Diarylphosphine oxides bearing a 3,5 disubstituted methyl group on the aryl ring afforded the product (**4ae**) in 66% isolated yield. Unfortunately, *tert*-butyl phosphine oxide proved to be unsuccessful in our methodology. Then, we examined the scalability of the process to demonstrate its practicability (Scheme 4). In this context, more than 1 g of **1r** and **2a** was treated under similar reaction conditions, and the corresponding product **4ra** was isolated in 56% yield (1.29 g, 2.8 mmol).

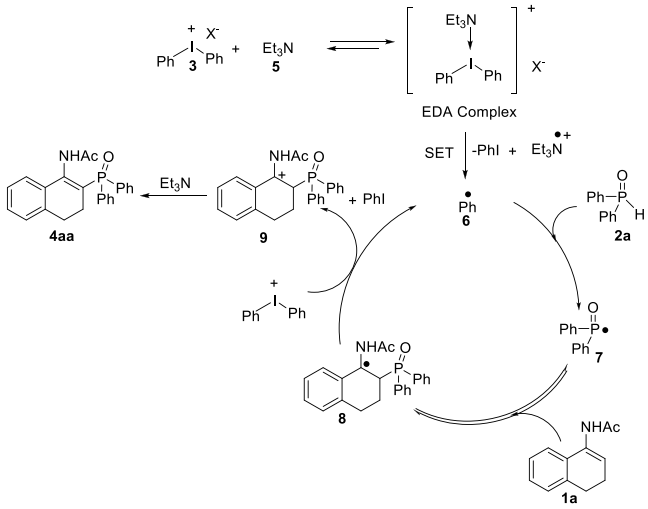
Radical trapping experiments using TEMPO or BHT were conducted, confirming the free radical process for the mechanism (see Supporting Information). On the basis of these experiments and our previous mechanistic investigations, a tentative reaction mechanism for this phosphorylation

Scheme 4. Gram-Scale Synthesis



reaction is depicted in Scheme 5. It starts with formation of the electron donor−acceptor (EDA) complex between Et_3N **5**

Scheme 5. Postulated Reaction Mechanism for the *β*-Phosphorylation of Enamide



and $Ph_2I^+,^-OTf$ **3**. Consequently, a single electron transfer process is initiated to generate the phenyl radical **6**. This radical abstracts a hydrogen from the secondary phosphine oxide **2a** to form the phosphinoyl radical **7**. The latter adds reversibly to the enamide **1a**, generating the radical **8**. The oxidation of **8** with the diphenylidonium **3** give rise to the radical cation **9**, which yield the phosphorylated product **4aa** after deprotonation with Et_3N.

In conclusion, we have successfully developed a novel and new transition-metal-free C−P bond formation method allowing the regioselective *β*-phosphorylation of cyclic and acyclic enamides via a phosphinoyl radical. The transformation features excellent functional group tolerance, simple operation, and mild conditions. The scope of enamide and phosphine oxide derivatives is broad. This strategy is anticipated to be an important approach for the transition-metal-free functionalization of enamides, precursors of more complex nitrogen-containing molecules. Further studies to apply this strategy to other reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01963.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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