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C−H Bonds Phosphorylation of Ketene Dithioacetals

Liping Zhu,[†] Hongmei Yu,[†] Quanping Guo,[†] Qiao Chen,[†] Zhaoqing Xu,*[,†] and Rui Wang*[,†,‡]

[†]Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China

[‡]State Key Laboratory of Chiroscience, Hong Kong, Polytechnic University, Hong Kong, China

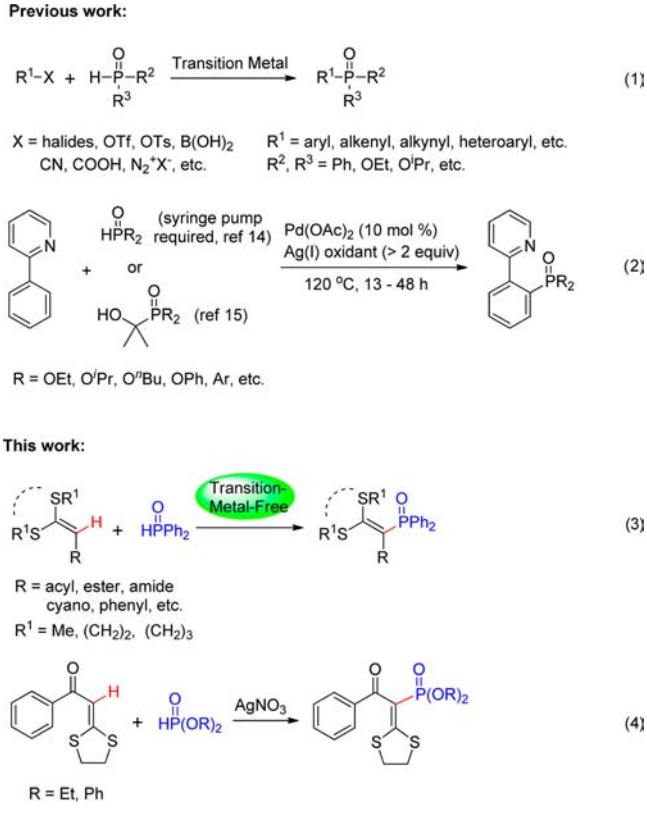
Supporting Information

ABSTRACT: C−H bond phosphorylation of ketene dithioacetals was achieved under transition-metal-free or $AgNO_3$ mediated conditions. Synthetic transformations of the coupling product provided promising methods for the construction of highly functionalized phosphorylated *N*-heterocycles and tetrasubstituted alkenes.

Phosphonates and their derivatives attracted increasing attention for their great importance in drug discovery,[1] organic synthesis,[2] photoelectric materials,[3] and catalysis.[4] Since the first report by Hirao and co-workers,[5] a wide variety of transition-metal-catalyzed cross-coupling reactions for the construction of C−P bonds have been developed, including the reaction of C(sp^2)-halides/triflates/tosylates,[6] aryl boronic acids,[7] aryl diazonium salts,[8] alkenyl/alkynyl carboxyl acids,[9] or nucleophilic heteroarenes[10] with *H*-phosphonates or *H*-phosphine oxides (Scheme 1, eq 1). In previous decades, transition-metal-catalyzed C−H functionalizations emerged as a very efficient strategy for C−C and C−heteroatom formations.[11] However, transition-metal-catalyzed direct C−H phosphorylation remains an enormous challenge. Both *H*-phosphonates and *H*-phosphine oxides are in equilibrium with the corresponding phosphinous acids and tend to form a P-bound phosphinous acid complex in the presence of a late transition metal.[12] Thus, the metal catalyst binds to the existing phosphorus rather than to the much less coordinative C−H bond, which inhibits the C−H activation step.[13] In 2013, Yu and co-workers reported a pyridine-directed aromatic C−H phosphorylation, in which a strategy involving slow addition of a *H*-phosphonate via a syringe pump was employed to avoid the deactivation of the Pd catalyst (eq 2).[14] With the same substrates and catalyst, the Murakami group recently reported another protocol for aryl C−H phosphorylation. In that reaction, α-hydroxyalkylphosphonate was used as a masked phosphonation agent which released *H*-phosphonate gradually in the reaction, thereby avoiding its coordination to Pd (eq 2).[15]

As a significant motif in organic chemistry, the C−H functionalization of alkenes has been intensively studied over the past years.[11e−g] Although the C−P coupling of aromatic C−H has been developed, the C−H phosphorylation of the alkene C−H bond has not yet been achieved due to the low reactivity of the alkene C−H bond (especially for internal alkenes) and the strong coordination of the phosphorus reagents to transition metal catalysts. In recent years, remarkable results from transition-metal-free C−H activation have been reported.[16]

Scheme 1. Phosphorylation Reaction



Encouraged by those results, we envisioned transition-metal-free conditions that could avoid the catalyst deactivation problem since no transition metals were involved in the system. To activate the inert C−H bond of the internal alkene, an electron-donating dithioalkyl group is installed in the substrates, by which

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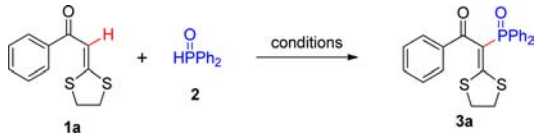
the olefin would be reactive enough for a direct functionalization.[17] In continuing with our research interest in C−H functionalization,[18] we disclose here the first example of transition-metal-free C−H phosphorylation of internal alkenes with diaryl phoshine oxides (eq 3). With modified conditions, *H*-phosphonates were also successfully coupled with internal alkenes in good yields (eq 4). Moreover, the phosphorylation product was easily cross-coupled with aryl boronic acid through Pd-catalyzed C−S cleavage and gave the tetrasubstituted alkene in moderate yield. The synthetic utilities of current methodology were further demonstrated by the synthesis of highly functionalized phosphorylated *N*-heterocycle compounds through a simple one-step operation from the C−H phosphorylation product in excellent yields.

Initially, we used alkene **1a** as the model substrate and reacted it with diphenylphosphine oxide **2** (2 equiv) in the presence of $K_2S_2O_8$ (3 equiv) in CH_3CN at 60 °C. However, after 24 h, only 11% desired product was obtained (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



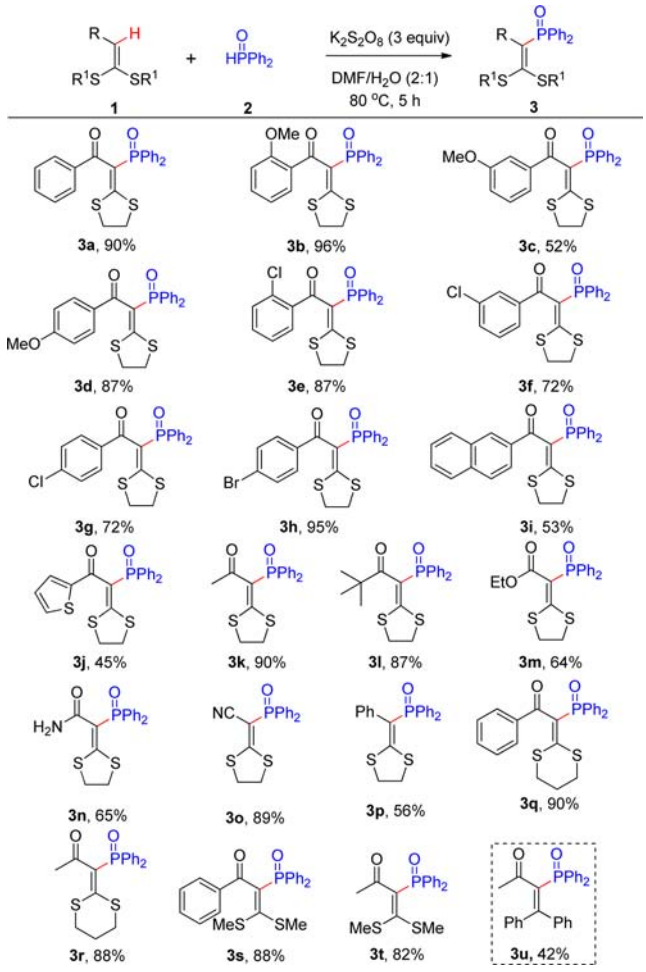
entry	oxidant	solvents (ratio)	t (°C)	yield[b] (%)
1[c]	$K_2S_2O_8$	CH_3CN	60	11
2	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	60	74
3	MnO_2	CH_3CN/H_2O (1:1)	60	20
4	$PhI(OAc)_2$	CH_3CN/H_2O (1:1)	60	<10
5	H_2O_2	CH_3CN/H_2O (1:1)	60	22
6	TBHP	CH_3CN/H_2O (1:1)	60	14
7	$K_2S_2O_8$	DMF/H_2O (1:1)	60	85
8	$K_2S_2O_8$	tol/H_2O (1:1)	60	3
9	$K_2S_2O_8$	DCE/H_2O (1:1)	60	7
10	$K_2S_2O_8$	$dioxane/H_2O$ (1:1)	60	8
11	$K_2S_2O_8$	$DMSO/H_2O$ (1:1)	60	67
12	$K_2S_2O_8$	DMF/H_2O (2:1)	60	89
13	$K_2S_2O_8$	H_2O	60	20
14	$K_2S_2O_8$	DMF/H_2O (2:1)	20	<5
15	$K_2S_2O_8$	DMF/H_2O (2:1)	40	12
16	$K_2S_2O_8$	DMF/H_2O (2:1)	80	92[d]
17	$K_2S_2O_8$	DMF/H_2O (2:1)	100	77

[a]All reactions were carried out by using 0.2 mmol of **1a**, 0.4 mmol of **2**, 0.6 mmol of oxidant, 2 mL of mixed solvents, followed by stirring for 5 h under aerobic conditions, except as noted. [b]Yields were detected by GC. [c]Reacted for 24 h. [d]Isolated yield of **3a** is 90%.

Astonishingly, a mixed solvent (CH_3CN/H_2O = 1:1) dramatically improve the yield to 74% (entry 2). Several other oxidants could also be used as an oxidant albeit less effectively compared to $K_2S_2O_8$ (entries 3−6). A solvent survey proved that high polar solvents, such as DMF and DMSO, facilitated the reaction (entries 7 and 11), whereas solvents with low polarity, namely toluene, 1,2-dichloroethane, and 1,4-dioxane, completely inhibited the reaction (entries 8−10). The variation of the solvent ratio revealed that DMF/H_2O = 2:1 was optimal (entry 12; see the Supporting Information (SI) for details) and H_2O is less efficient for this reaction (entry 13). It is worth noting that the yield of **3a** decreased significantly with reaction temperature reduction (entries 14 and 15). 80 °C was determined to be the best temperature for this reaction (entries 16 and 17). Changing the amount of solvent, oxidant, or diphenylphosphine oxide **2** resulted in negative reaction effects (see the SI for details).

With the optimized reaction conditions in hand, we next investigated the reaction generality by using various internal alkene substrates (Scheme 2). The benzoyl alkenes with the

Scheme 2. Transition-Metal-Free C−H Phosphorylation[a,b]



[a]All reactions were carried out by using 0.2 mmol of **1**, 0.4 mmol of 2, 0.6 mmol of $K_2S_2O_8$, 2 mL of solvent (DMF/H_2O = 2/1,) and 80 °C for 5 h. [b]Isolated yields.

methoxy or halogen substituent at the *o*-, *m*-, and *p*-position on the aryl ring were well tolerated (**3b**−**3h**). The substrates with the 2-naphthyl and 2-thienoyl moiety gave moderate yields (**3i**, **3j**). Gratifyingly, we found that, under optimized conditions, alkenes with other types of substituents such as alkyl acyl (**3k**, **3l**), ester (**3m**), amide (**3n**), cyano (**3o**), and phenyl (**3p**) were all reactive and gave the desired products in good yields. Furthermore, altering the dithioalkyl moiety to $-S(CH_2)_3S-$ (**3q**, **3r**) or using acyclic alkylthio (**3s**, **3t**) did not affect the outcome of the C−H phosphorylation reaction. However, under the standard conditions, the phosphorylation of diphenyl alkene only afforded **3u** in 42% yield.

In the study of using *H*-phosphonates as the coupling partners, we found that the stated reaction conditions in Scheme 2 did not work efficiently. In this context, we next explored another protocol for alkene C−H bond phosphorylation (Scheme 3; for reaction conditions optimization, see the SI). By using 3 equiv of

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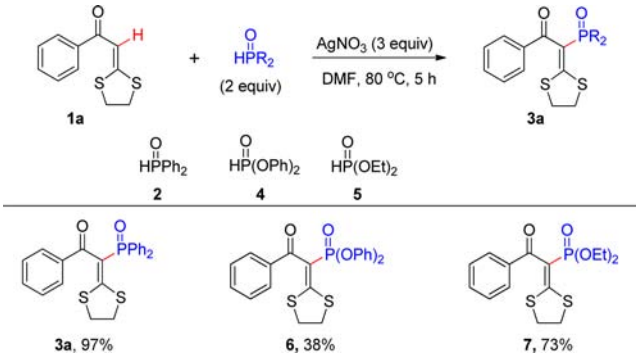
Scheme 3. Alkene C−H Phosphorylation with H-Phosphonates[a,b]

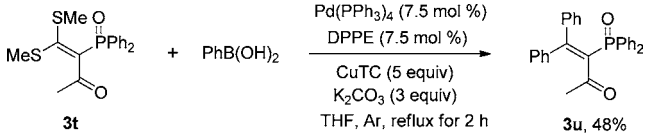


[a]All reactions were carried out by using 0.2 mmol of **1**, 0.4 mmol of **2**, 0.6 mmol of $AgNO_3$, 2 mL of DMF, at 80 °C for 5 h. [b]Isolated yields.

$AgNO_3$ as a promoter, the reactions went smoothly for both *H*-phosphine oxide (**2**) and *H*-phosphonate (**4**, **5**) with good yields.

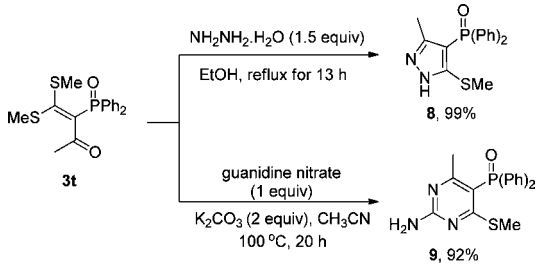
The pharmaceutical and biological utility of the phosphorylation product was demonstrated for the synthesis of phosphorylated tetrasubstituted alkenes.[19] Under the typical Liebeskind−Srogl cross-coupling reaction conditions,[18d,20] **3t** was treated with arylboronic acid in the presence of $Pd(PPh_3)_4$ and CuTC to give the alkenyl phosphine oxide **3u** in 48% yield (Scheme 4).

Scheme 4. Synthesis of Tetrasubstituted Alkenes



Following the successful building of the C−H phosphorylation reaction, its conversion into a valuable phosphorylated *N*-heterocycle structure was also found to be straightforward (Scheme 5). Compound **3t** was reacted with hydrazine hydrate

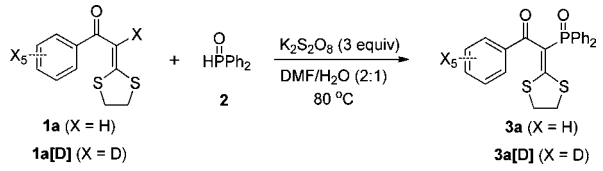
Scheme 5. Synthesis of Phosphorylated *N*-Heterocycles



smoothly and transformed into multifunctionalized pyrazole **8** in 99% yield. The six-membered *N*-heterocycle pyrimidine **9** was successfully achieved in 92% yield as well.

To gain some mechanistic insight, we performed the kinetic isotope effect (KIE) exploration by a deuterium labeling experiment (Table 2). The experimental results suggested that the rupture of the C−H bond in internal olefin was not involved in the rate-determining step of the reaction. Radical trapping experiments were also examined (Scheme 6). At the end of the reaction, GC analysis of the reaction mixture revealed formation of the target product **3a** decreased dramatically with the addition

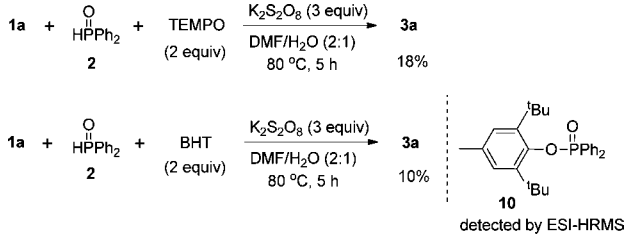
Table 2. KIE Exploration[a,b]



time	yield 3a (%)	yield 3a[D] (%)	k_H/k_D
5 min	31	32	
10 min	67	70	
15 min	81	81	1.0
2 h	86	87	
4 h	89	89	

[a]Yields were detected by GC. [b]All reactions were carried out by using **1** (0.2 mmol), **2** (0.4 mmol), and $K_2S_2O_8$ (0.6 mmol) in DMF/H_2O (2/1, 2 mL) at 80 °C for 5 h.

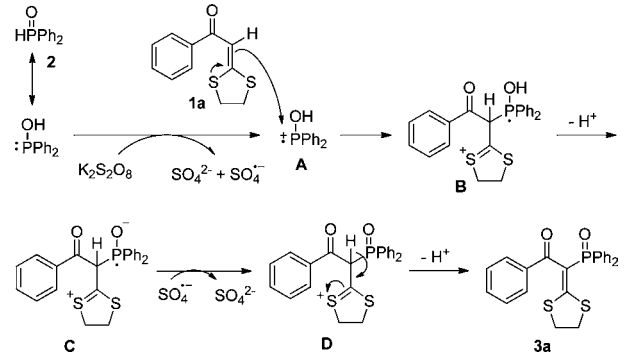
Scheme 6. Radical Trapping Study



of TEMPO or BHT. Moreover, the BHT adduct **10** was detected by ESI-HRMS measurement of the crude reaction mixture. These results indicated that a radical pathway might be involved in the transformation.

Based on previous reports and the above-mentioned experimental results, a plausible mechanism was proposed in Scheme 7.[13c,17a] Initially, diphenylphosphine oxide **2** is in

Scheme 7. Proposed Mechanism



equilibrium with the phosphinous acid, which is oxidized by $K_2S_2O_8$ to form a cation radical **A**.[21] Then, the nucleophilic attack of **1a** to **A** leads to a thionium cation radical intermediate **B**. A subsequent deprotonation followed by the second single-electron-transfer process gives the intermediate **D**. The final elimination of H^+ results in the desired C−H phosphorylation product **3a**.

In summary, we have reported the first example of alkene C−H phosphorylation under transition-metal-free conditions. A variety of internal alkenes were coupled with *H*-phosphine oxides

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using $K_2S_2O_8$ as the sole oxidant. Under modified conditions, both *H*-phosphonate and *H*-phosphine oxide were successfully employed in the phosphorylation reaction with good yields. Moreover, the synthetic utility of product was demonstrated by the one-step synthesis of highly functionalized phosphorylated *N*-heterocycles (**8**, **9**) and tetrasubstituted alkene (**3u**) in good yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zqxu@lzu.edu.cn.
*E-mail: wangrui@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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(21) As shown in the proposed mechanism, we supposed that the phosphinic acid equilibriums of *H*-phosphonates (**4** and **5**) cannot be oxidized smoothly by $K_2S_2O_8$ to form the cation radicals.

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