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Metal-free synthesis of phosphinoylchroman-4-ones via phosphinoylation/cyclization cascade mediated by $K_2S_2O_8$

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Abstract

A variety of chroman-4-ones bearing phosphine oxide motifs were conveniently synthesized from readily available diphenylphosphine oxide and alkenyl aldehydes via a metal-free tandem phosphinoylation/cyclization protocol. The reaction utilizes $K_2S_2O_8$ as oxidant and proceeds in DMSO-H_2O at environmentally benign conditions with broad substrate scope and afforded the title compounds in moderate yields.

Keywords

chroman-4-ones; diphenylphosphine oxide; potassium persulfate; metal-free; radical cyclization

Introduction

The chroman-4-one scaffolds are important structural motifs owing to their presence in many natural products and pharmaceuticals with extraordinary biological and pharmaceutical activities (Figure 1) [1-3]. For instance, Liriopein B and Silibinin have shown significant anti-cancer activities and some chroman-4-one-containing compounds even have anti-HIV activity (Figure 1). Therefore, the preparation of functionalized chroman-4-ones and their related derivatives have received considerable attention over the last few years [1, 4, 5]. In general, the synthesis of chroman-4-ones can be achieved via a polarity reversal strategy enabled by the N-heterocyclic carbine (NHC) catalyzed intramolecular Stetter reaction [6-8]. Besides, other methods for the synthesis of chroman-4-ones were achieved by intramolecular oxo-Michael addition of 2'-hydroxychalcone catalyzed [9, 10], or condensation cyclization of o-hydroxyacetophenones with ketones/aldehydes [11, 12], or other alternative transformation [13, 14]. Moreover, the radical cascade cyclization of o-allyloxybenzaldehydes, by employing appropriate radical precursors through visible-light promoted systems [15, 16], transition-metal-catalyzed systems [17, 18], or transition-metal-free systems [19, 20], is a hot topic, which has emerged as a powerful strategy for the synthesis of diversely functionalized chroman-4-ones derivatives.

It is well known that organophosphorus compounds, with their medicinal, biological or specific material-relating properties, have found wide applications in pharmaceutical chemistry, biochemistry and material science [21-23]. There are also excellent ligands for many metals and have been used in catalyzing a huge of significant organic reactions [21-23]. Due to the importance of the chroman-4-one scaffolds and the organophosphorus compounds, the development of concise and

efficient approaches for the synthesis of the chroman-4-one derivatives containing phosphorus functionality frameworks [24, 25] that combine both characteristics together may find useful application. By far, there are only few ways to prepare such compounds. For example, in 2008 Rovis group [24] reported an intramolecular Stetter reaction of alkenyl aldehydes to synthesize a series of phosphine oxide and phosphonate functionalized chroman-4-ones, but preparation of the substrates involved Rh-catalyzed hydrophosphinylation of a protected functional alkyne and subsequent deprotection with $Hg(O_2CCF_3)_2$, which is not environmentally benign (Scheme 1a). Besides, in 2016 Li's group [25] reported a silver catalyzed straightforward approach to synthesize phosphonate chroman-4-ones via a phosphoryl-radical-initiated cascade cyclization of 2-(allyloxy)arylaldehydes using $K_2S_2O_8$ as an oxidant, however, diphenylphosphine oxide (DPPO) was not suitable for the transformation (Scheme 1b). So the development of metal-free and greener methods to approach chroman-4-ones bearing phosphine oxide moiety is still highly desirable. Herein, we present a transition-metal-free radical cascade cyclization to access the above chroman-4-ones in one pot under environmentally benign conditions (Scheme 1c).

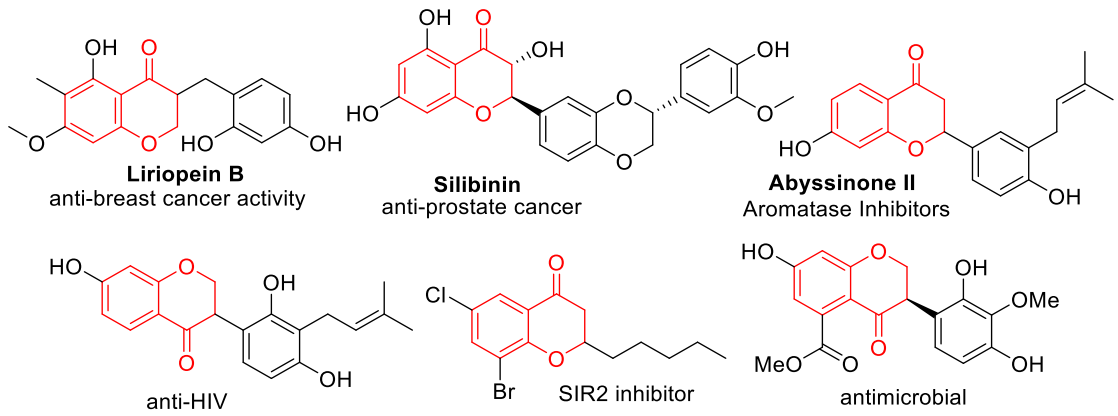
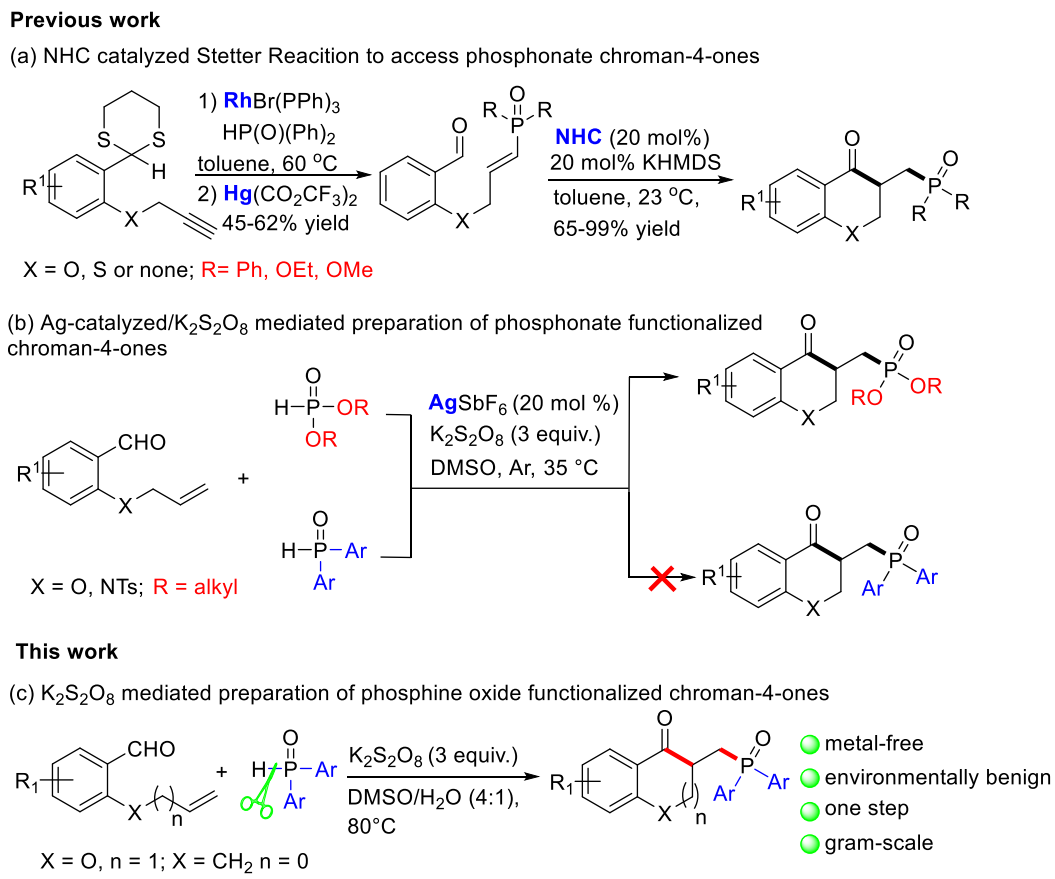


Figure 1: Biologically active compounds featuring chroman-4-one framework..



Scheme 1: Methods to produce phosphonate chroman-4-ones

Results and Discussion

Motivated by the desire to develop a metal-free and environmentally benign protocol for the construction of phosphine oxide functionalized chroman-4-ones, we focused on the cascade cyclization employing 2-(allyloxy)benzaldehyde **1a** and diphenylphosphine oxide (DPPO) **2a** as model substrates with $K_2S_2O_8$ as an oxidant, which is cheap, readily available, and versatile oxidant. On the basis of the literature reports [26, 27] and our continuing interest in green chemistry [28, 29], we set the temperature as 70 °C based on the fact $K_2S_2O_8$ thermally decomposes to form sulfate radical ($SO4^{\bullet-}$) [26, 27], which may react with the substrates to finish such a cascade cyclization. To our delight, the anticipated product **3aa** was obtained in 42% yield in DMSO/H_2O (4:1) system in one pot (Table 1, entry 1). The structure of **3aa**

was unambiguously confirmed by X-ray diffraction analysis of a single crystal (Figure 2) and NMR spectroscopy (see ESI) [30]. Then the increase of the amount of $K_2S_2O_8$ to 3 equiv. resulted in the improvement of the yield of **3aa** to 52% (Table 1, entry 2). Adjusting the amount of the oxidant $K_2S_2O_8$ to 4 equiv. (Table 1, entry 3) did not improve the yield. By further screening of a few solvents, such as MeCN/H_2O, DMF/H_2O, DMA/H_2O, dioxane/H_2O, THF/H_2O, EtOH/H_2O, DCE/H_2O and NMP/H_2O, it turned out that the highest yield was still provided in DMSO/H_2O (4:1) system (Table 1, entries 4-13). It is notable that product **3aa** was not observed at room temperature or in the absence of $K_2S_2O_8$, indicating that the reaction was mainly mediated by $K_2S_2O_8$ (Table 1, entries 14, 15). Adjusting the reaction temperature to 80 °C bring about better yields as compared with the reaction temperature of 70 °C or 90 °C (Table 1, entries 2, 16, 17). Then, a various oxidants such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, TBHP (tert-butyl hydroperoxide) and DTBP (di-tert-butyl peroxide) were tested and the results showed that $K_2S_2O_8$ exhibited the best efficiency (Table 1, entries 18-21).

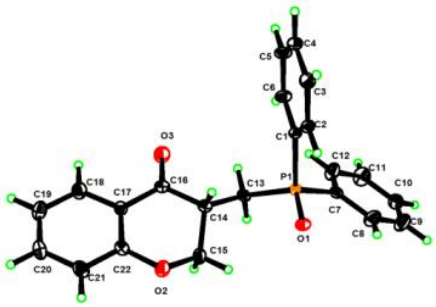
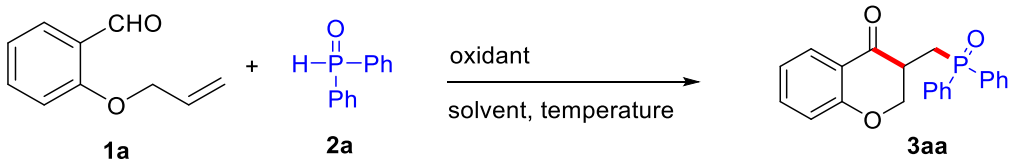


Figure 2: X-ray structure of compound 3aa (CCDC 2002878)

Table 2: Optimization of the reaction condition[a].

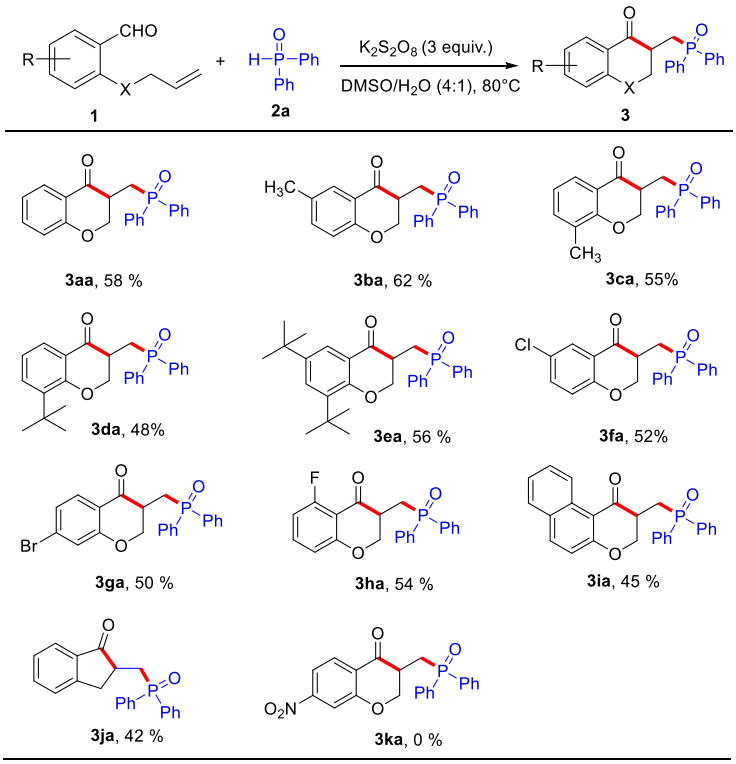


Entry	Oxidant	Solvent	Temp.(°C)	Yield (%)[b]
1	$K_2S_2O_8$ (2.0 eq.)	DMSO-H_2O(4:1 v/v)	70	42%
2	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(4:1v/v)	70	52%
3	$K_2S_2O_8$ (4.0 eq.)	DMSO-H_2O(4:1v/v)	70	50%
4	$K_2S_2O_8$ (3.0 eq.)	MeCN-H_2O(4:1 v/v)	70	32%
5	$K_2S_2O_8$ (3.0 eq.)	DMF-H_2O(4:1 v/v)	70	24%
6	$K_2S_2O_8$ (3.0 eq.)	DMA-H_2O(4:1 v/v)	70	21%
7	$K_2S_2O_8$ (3.0 eq.)	Dioxane-H_2O(4:1 v/v)	70	Trace
8	$K_2S_2O_8$ (3.0 eq.)	THF- H_2O(4:1 v/v)	70	Trace
9	$K_2S_2O_8$ (3.0 eq.)	EtOH-H_2O(4:1 v/v)	70	Trace
10	$K_2S_2O_8$ (3.0 eq.)	DCE-H_2O(4:1 v/v)	70	Trace
11	$K_2S_2O_8$ (3.0 eq.)	NMP-H_2O(4:1 v/v)	70	18%
12	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(1:1 v/v)	70	32%
13	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(8:1 v/v)	70	44%
14	-	DMSO-H_2O(4:1 v/v)	70	0
15	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(4:1 v/v)	r.t. [c]	0
16	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(4:1v/v)	80	58%
17	$K_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(4:1v/v)	90	54%
18	$(NH_4)_2S_2O_8$(3.0 eq.)	DMSO-H_2O(4:1 v/v)	80	40%
19	$Na_2S_2O_8$ (3.0 eq.)	DMSO-H_2O(4:1v/v)	80	50%
20	DTBP (3.0 eq.)	DMSO-H_2O(4:1 v/v)	80	0
21	TBHP (3.0 eq.)	DMSO-H_2O(4:1 v/v)	80	0

[a]Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (1.5 equiv.), solvent (v/v, 5 mL), N_2 atmosphere, 18 h. [b]Isolated yields. [c]Room temperature.

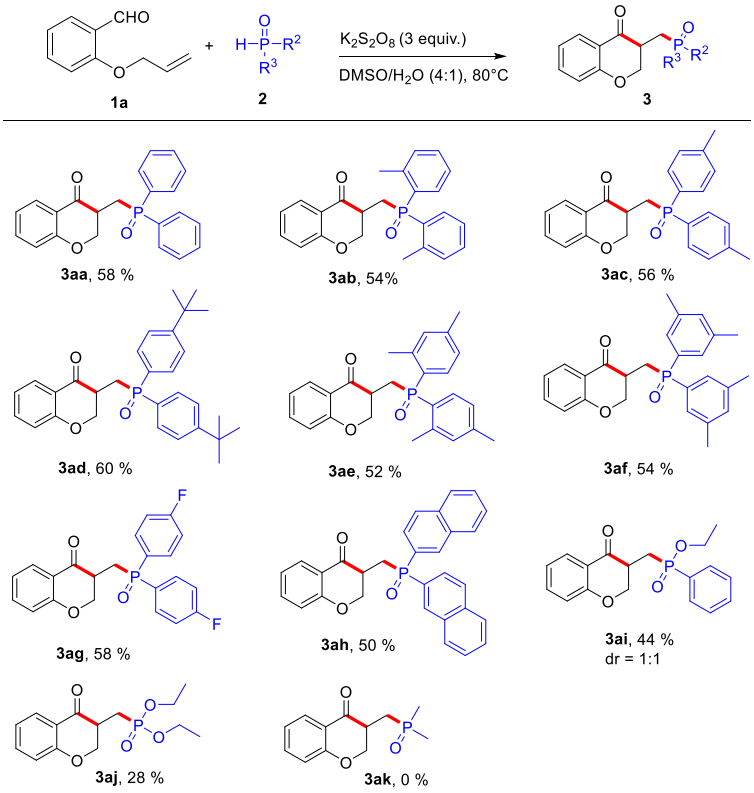
With the optimal reaction conditions in hand (Table 1, entry 16), we next sought to explore the scope and generality of this protocol using various 2-(allyloxy)arylaldehydes **1** with diphenylphosphine oxide (DPPO) **2a**. As shown in Table 2, substrates **1** with a range of functional groups, such as electron-donating

groups Me- (**1b** and **1c**), t-Bu- (**1d** and **1e**), electron-withdrawing groups Cl- (**1f**), Br- (**1g**), F- (**1h**) were well tolerated in this transformation, providing the desired products (**3aa**-**3ha**) in 48–62% yields. Furthermore, the transformation can also proceed when there is a naphthyl ring in the substrate (**1i**) giving the desired product **3ia** in 45% yields. Notably, when the substrate is 2-allylbenzaldehyde **1j**, this protocol is also compatible affording the product **3ja** as an indanone derivative. The indanone derivatives are also privileged structural motifs found in numerous natural products and pharmaceuticals with extraordinary biological and pharmaceutical activities [31, 32]. However, no desired product (**3ka**) was obtained when there was an NO2- group in the substrate (**1k**).



Scheme 2: Scope of 2-(allyloxy)arylaldehydes. Reaction conditions: **1** (0.3 mmol, 1 equiv.), **2a** (1.5 equiv.), DMSO/H_2O (v/v, 5 mL), $K_2S_2O_8$ (3.0 equiv.), N_2 atmosphere, 18 h. Isolated yields.

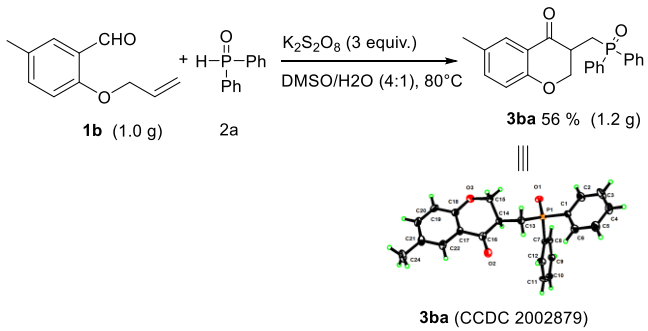
Next, to further demonstrate the generality of this strategy, the scope of different diphenylphosphine oxide (DPPO) **2** was examined as shown in Scheme 3. Simple diphenylphosphine oxide (DPPO), such as 2-Me-DPPO (**2b**), 4-Me-DPPO (**2c**) and 4-tBu-DPPO (**2d**) furnished the corresponding products in good yields. Multi-substituted diarylphosphine oxides (**2e** and **2f**) were also well tolerated under these reaction conditions. Gratifyingly, diphenylphosphine oxides bearing F- groups (**2g**) reacted smoothly to furnish the anticipated products **3ag** in 58% yield. Furthermore, 1-Naphthyl-DPPO (**2h**) was suitable for this transformation, to give the product **3ah** in 50% yield. The reaction between diethyl phosphonate **2j** and **1a** proceeded less efficiently under the conditions and low yield of **3aj** was obtained. Dimethylphosphine



oxide **2k** did not participate in the reaction, perhaps because of its high oxidation potential and poor ability to undergo tautomerization [33].

Scheme 3: Scope of diphenylphosphine oxides. Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2** (1.5 equiv.), DMSO/H_2O (v/v, 5 mL), $K_2S_2O_8$ (3.0 equiv.), N_2 atmosphere, 18 h. Isolated yields.

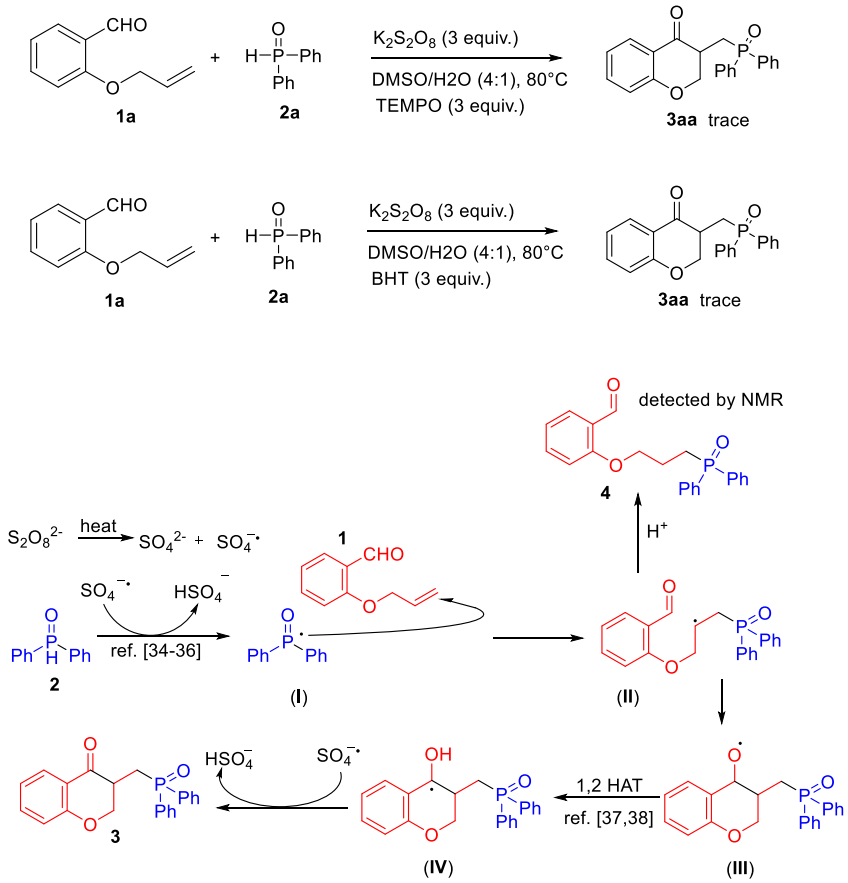
To demonstrate the practicability of this methodology, a gram-scale experiment was then performed, employing **1b** and **2a** as substrates under optimized conditions (Scheme 4). The reaction afforded the desired product **3ba** in a good yield of 56%, and the structure was also confirmed by X-ray diffraction (see ESI) [30].



Scheme 4: Gram-scale reaction.

To gain an insight into the reaction mechanism, some control experiments were carried out (Scheme 5). When the reaction was conducted in the presence of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and butylated hydroxytoluene (BHT), the reactions were completely shut down. Also, we successfully separated a little by-product **4** which was identified by NMR spectroscopy. These experiments clearly support the phosphorus centered radical reaction pathway. It has been reported that phosphorus centered radicals can be generated from phosphine oxides in the presence of potassium persulfate [34-36]. Based on literature precedent [26, 27, 34-38] and preliminary mechanistic experiments, a plausible mechanism was proposed in Scheme 5, which should be different from the predominant mechanism with Ag-catalyzed radical cascade for the

preparation of phosphonate functionalized chroman-4-ones [25]. Initially, $K_2S_2O_8$ thermally decomposes to form sulfate radical anion ($SO4^{\bullet-}$) [26, 27], which reacts with the diphenylphosphine oxide (DPPO) **2** to give a phosphorus centered radical **I** [34-36]. Then **I** undergoes an intermolecular addition to the C-C double bond of **1**, leading to the formation of a new radical intermediate **II**. Sequential radical **II** attack on the aldehyde moiety, and an oxygen radical **III** is generated and then a formal 1,2-H shift occurred to deliver the benzyl radical **IV** [37, 38]. Finally, the sulfate radical anion ($SO4^{\bullet-}$) abstract a hydrogen from the benzyl radical **IV** to give the final products **3** [37, 38].



Scheme 5: Control experiments and proposed mechanism

Conclusion

In conclusion, we have developed an environmentally benign and practical protocol for the synthesis of phosphonate chroman-4-ones from 2-(allyloxy)benzaldehydes and diphenylphosphine oxide under metal-free conditions. The efficiency of this protocol was further enhanced by using $K_2S_2O_8$ as oxidant. This transformation proceeded through a tandem C–P and C–C bond formation with easy-handing and good functional-group compatibility.

Supporting Information

Supporting Information File 1: Experimental procedures, spectroscopic and X-ray data and copies of NMR spectra.

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