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Synthesis of 3-phosphinyl chromones *via in situ* iodination mediated C–H phosphination and the tunable synthesis of 2-phosphoryl chromanones

Yongli Zhao[a], Dingsheng Cao[a], Jie-Ping Wan[a,b,*], Yunyun Liu[a,*]

[a] *Jiangxi Province Key Laboratory of Natural and Biomimetic Drugs Research, College of Chemistry and Materials, Jiangxi Normal University, Nanchang 330022, China*

[b] *International Innovation Center for Forest Chemicals and Materials, Nanjing Forestry University, Nanjing 210037, China*

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ABSTRACT

By means the *in situ* halogenation of the vinyl C–H bond in o-hydroxyphenyl enaminones, the step efficient synthesis of 3-diphenylphosphinyl chromones has been realized through the challenging construction of C-P(III) bond by using diphenyl phosphine as reaction partner. In addition, the tunable synthesis of 2-phosphoryl chromanones has been achieved *via* hydrophosphorylation by simply modifying reaction conditions without using metal reagent.

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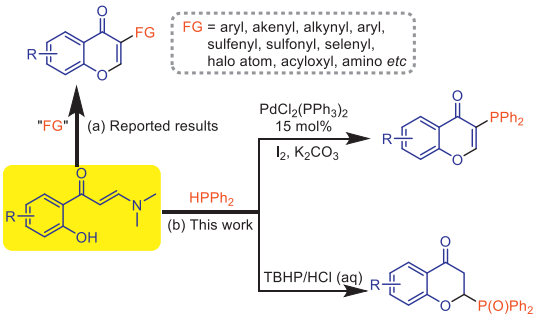
Organophosphine compounds, especially tertiary organophosphines, are indispensable chemicals in modern organic synthesis by acting as ligands in numerous catalytic reactions owing to their extraordinary excellent ability of coordination with different metal species and other electron deficient structures [1–5]. In addition, the organic molecules containing phosphorus also have found attractive application in pharmaceuticals, materials and food industry, *etc.* [6–11]. However, comparing with the plenty of methods for the synthesis of P(V) containing molecules such as phosphorylated compounds and phosphates, the synthesis of organophosphines remains as challenge because of the sensitivity of P(III) toward oxidation. Therefore, many reactions starting from the P(III) reagents result in P(V) centered products [12–15]. Currently, the synthesis of organophosphines relies mainly on the reduction of P(V) precursors such as phosphine oxides [16–18]. The nucleophilic substitution [19–21], the cross coupling of the P-H phosphines [22–26], and reactions with heteroatom functionalized phosphines [27–31] could also be employed for the synthesis of tertiary phosphines, but require usually either pre-functionalized & sensitive substrates, multi-step operation or harsh reaction conditions. In this context, developing more facile synthetic methods such as direct phosphination of C–H bonds with easily accessible starting materials is urgent for organophosphines.

On the other hand, since chromone is a typical heterocyclic moiety in many natural products and pharmaceuticals [32–35], the synthesis of chromones by employing the cascade vinyl C–H functionalization and chromone annulation of *o*-hydroxyaryl enaminones has received splendid advances [36,37]. By using proper reaction partners, numerous chromones with functional structure in the C3-site have been practically accessed *via* the formation of C–C [38–43], C-halogen [44,45], C–N [46,47], C-S/Se [48–52], C–O [53] and C-P [54] bonds as a typical transformation (Scheme 1a). Extensive efforts have also been made to realize the synthesis of chromones with other functionalization modes by such chromone annulation [55,56]. However, like the challenge in most known methods for tertiary phosphine synthesis, the synthesis of 3-phosphinylated chromones *via* such cascade reactions involving C–H bond functionalization and annulation remains inapplicable. During our longstanding efforts in devising step-economical coupling reactions [57–60], we have proven that the *in situ* halogenation of a raw C–H bond could be practical for a series of challenging coupling reaction via much simpler operation without relying on the application of prior prepared C-halogen substrates [61,62]. Under the inspiration of the previous works as

* Corresponding authors at: Jiangxi Province Key Laboratory of Natural and Biomimetic Drugs Research, College of Chemistry and Materials, Jiangxi Normal University, Nanchang 330022, China.

E-mail addresses: wanjieping@jxnu.edu.cn (J.-P. Wan), chemliuyunyun@jxnu.edu.cn (Y. Liu).

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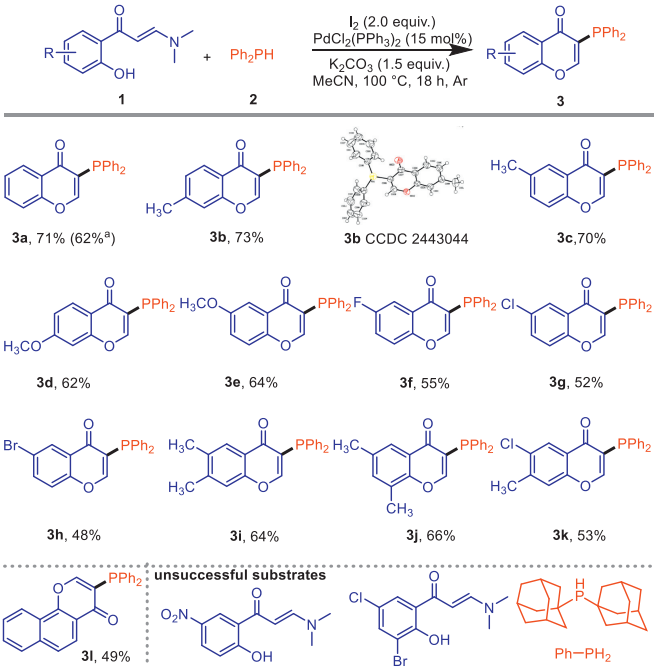
Scheme 1. Known and the current works for chromone and chromanone synthesis.

well as the notable application of enaminone C–H activation or functionalization [63–67], we envision that the *in situ* halogenation tactic may also be applicable for the C-P(III) bond formation *via* cross coupling process based on the *in situ* generated C-halogen bonds. Herein, we report the first method on the synthesis of 3-phosphinyl chromones *via* the reactions of *o*-hydroxyaryl enaminones and diaryl phosphine wherein the *in situ* C–H iodination plays the key role in mediating the subsequent C-P coupling. In addition, by modifying reaction conditions, the reaction pathway could be completely switched for the synthesis of novel 2-phosphoryl chromanones without using any metal reagent, enriching the enaminone-based synthetic diversity of chromones and their derivatives (Scheme 1b).

To start the work, the reaction of *o*-hydroxyphenyl enaminone **1a** and diphenyl phosphine **2a** was selected to probe applicable conditions. After systematic optimization on reaction parameters, including reaction medium, palladium catalyst species, base species, the loading of reagents, the reaction temperature, as well as reaction time, it was observed that running the reaction in MeCN in the presence of $PdCl_2(PPh_3)_2$, molecular iodine, K_2CO_3 at 100 °C gave the target product 3-diphenylphosphinyl chromone **3a** with optimal yield of 71 % (Table S1 in the Supporting Information).

After optimization, the application scope of this method in the synthesis of 3-phosphinyl chromones was investigated by employing different *o*-hydroxyaryl enaminones to react with diphenyl phosphine under the optimal conditions. As outlined in Scheme 2, the current method displayed good tolerance to the synthesis of products **3** by tolerating a series of different functional groups in the enaminone component. For example, the alkyl (**3b**, **3c**, **3i** and **3j**), alkoxy (**3d** and **3e**), halo atoms (**3f**-**3h**) substituted enaminones reacted with **2** to give diphenyl phosphinylated products with moderate to good yields. In addition, the reactions employing enaminone bearing two different groups in the phenyl ring as well as the naphthyl derived enaminone were also practical substrates in the titled synthesis (**3k** and **3l**). Some strong electron withdrawing group functionalized phenyl enaminones, such as nitro- and Cl-, Br-disubstituted phenyl enaminones were found inapplicable. Subsequently, the reactions using diadamantanyl phospine and phenyl phosphine were also performed, respectively. However, no target chromone products was observed (Scheme 2). Primary attempt by subjecting the reaction residue under oxygen (1 atm) after the completion of **3a** formation did not provide 3-phosphoryl chromone. Moreover, no visible new product was observed by running the reaction of diphenyl phosphine oxide with enaminone **1a** under the current conditions.

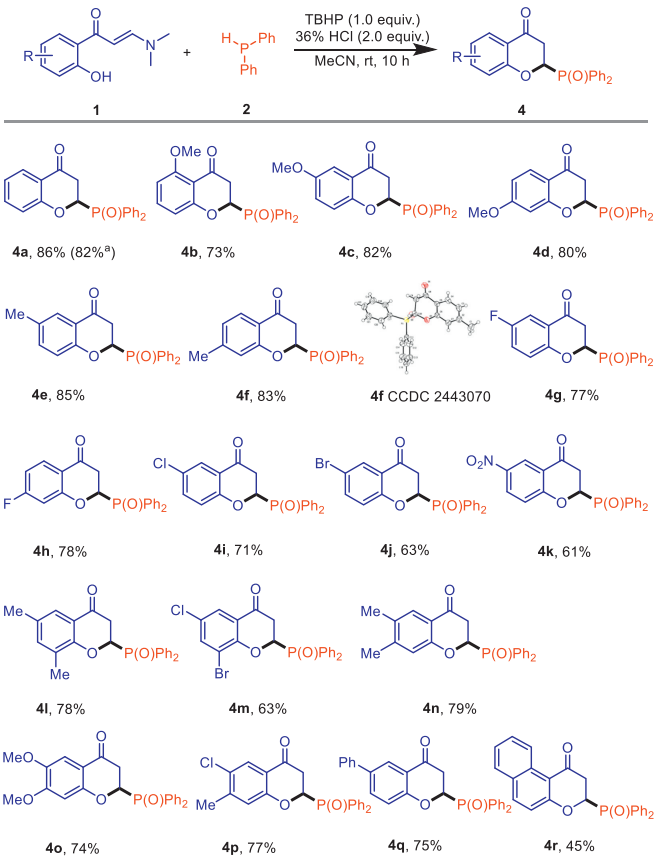
After the synthesis of 3-phosphinyl chromones **3**, further efforts in switching the reaction pathways with identical substrates were continuously executed. Interestingly, after extensive attempts in probing reaction conditions (Table S2 in Supporting information), we successfully achieved the selective synthesis of 2-phosphoryl chromanones by running the reaction at room temperature in the



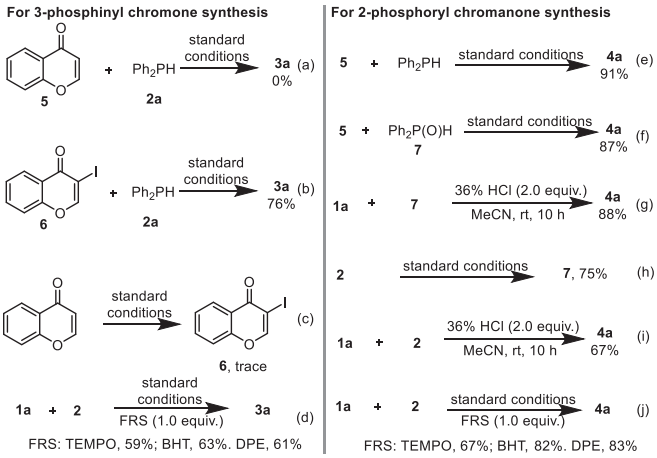
Scheme 2. Scope on the synthesis of 3-phosphinyl chromones. [a] Yield from 1 mmol-scale reaction.

presence hydrochloric acid and TBHP. Under the mild and simple conditions, the chromonone products resulting from the novel selective transformations were acquired with generally good to excellent yields (Scheme 3). Besides the reaction with enaminone **1a**, typical functional groups in the form of single (**4b**-**4k**, **4q**) and dual substitution (**4l**-**4p**) in the phenyl ring of enaminone substrates were proven generally applicable for the synthesis. Further, the naphthyl derived *o*-hydroxyaryl enaminone reacted with **2** to provide product **4r** with moderated yield (Scheme 3). It should be noted that the synthesis of such phosphoryl chromanones has not be previously accessed by the *o*-hydroxyaryl enaminone annulation reactions. Afterwards, the product **4a** was employed with stoichiometric zinc powder in MeCN at room temperature, but no 2-phosphinyl chromone was observed. Further, the reaction using enaminone without hydroxyl group in the phenyl ring, the (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one with **2** was performed under the standard conditions in Schemes 2 and 3, respectively. Neither the C–H phosphinylation, nor the phosphorylation of the enaminone was observed.

For the sake of investigating reaction mechanisms, a plethora of control experiments were designed and performed. For the reaction providing 3-phosphinyl chromone, employing the chromone **5** and diphenyl phosphine **2** to the standard reaction conditions did not provide **3a** (Scheme 4a), confirming that the C–H bond in chromone was inactive for the phosphination. Analyzing the model reaction mixture at the stage of 2 h confirmed the formation of 3-iodochromone (see Supporting information for details). In addition, the reaction using 3-iodochromone **6** and **2** gave the product **3a** with high yield (Scheme 4b), suggesting that 3-iodochromone was a key intermediate in the formation of **3**. Further explore by subjecting chromone **5** alone to the standard conditions did not provide **6** (Scheme 4c), indicating that chromone **5** could not be the intermediate in the formation of **6**. In addition, running the reaction in the presence of free radical scavenger (FRS), including TEMPO, BHT and DEP led to no evident inhibition to the synthesis of **3a** (Scheme 4d). On the other hand, for the mechanism toward the selective synthesis of 2-phosphoryl chromanones **4**, the reaction of **5** with **2** gave product **4a** with excellent yield (Scheme 4e),

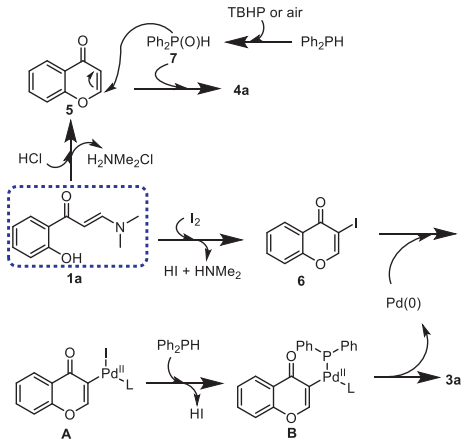


Scheme 3. Scope on the synthesis of 2-phosphoryl chromanones. [a] Yield from 1 mmol-scale reaction.



Scheme 4. Control experiments.

and analogous results was observed by using diphenyl phosphine oxide **7** as alternative reaction partner (Scheme 4f), implying that the phosphine **2** might first undergo oxidation to generate phosphine oxide **7** to participate the **4a** production. Indeed, the reaction of enaminone **1a** with **7** could provide **4a** with 88 % yield in the absence of TBHP (Scheme 4g), further supporting this hypothesis. Employing diphenyl phosphine alone to the conditions led to the formation of diphenyl phosphine oxide **7** with 75 % yield (Scheme 4h), and running the model reaction under air allowed the synthesis of product **4a** with 67 % yield (Scheme 4i). The results suggested that the diphenyl phosphine could be oxidized into corresponding phosphine oxide both by TBHP and air. Finally, the



Scheme 5. Plausible reaction mechanisms.

reaction under FRS was also run wherein no inhibition to the formation of **4a** was observed, either (Scheme 4j).

Following these information, the mechanisms for the two selective reactions are proposed (Scheme 5). For the formation of 3-phosphinyl chromones, enaminone **1a** couples molecular iodine to provide 3-iodochromone **6** *via* chromone annulation and electrophilic iodination. In the presence of palladium catalyst, the *in situ* generated C(sp^2)-I bond then undergoes oxidative addition to afford Pd(II) inserted intermediated **A**. The substitution of diphenyl phosphine to the iodine anion leads to intermediate **B**. After that, a typical reductive elimination of **B** gave target product **3a** and releases Pd(II) for continuous catalysis. On the other hand, under the conditions with only hydrochloric acid and TBHP, the enaminone **1a** proceeds to chromone **5** *via* typical acid promoted chromone annulation. Meanwhile, the oxidation of diphenyl phosphine **2** by TBHP or air gives diphenyl phosphine oxide **7**. Subsequently, the typical nucleophilic addition of $Ph_2P(O)H$ to the polar enone fragment in chromone affords 2-phosphoryl chromonone **4a**.

In conclusion, by making use of the *in situ* halogenation as the key tactic, we have designed and successfully achieved the first synthesis of 3-phosphinyl chromones involving the challenging C-P(III) bond formation. In addition, to expande the diversity of functionalized chromone derivatives, we also have realized the selective synthesis of 2-phosphoryl chromanones by modifying the reaction conditions. The step economy of the C-P(III) cross coupling without prior preparation of halogenated intermediate for the synthesis of phosphinyl chromones, as well as the metal-free selective synthesis of 2-phosphorylated chromanones provide practical accesses to divergent phosphorus functionalized chromones and chromanones.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yongli Zhao: Methodology, Investigation. **Dingsheng Cao:** Methodology. **Jie-Ping Wan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Yunyun Liu:** Writing – original draft, Supervision, Methodology.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111740.

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